



VNIVERSITAT
DE VALÈNCIA

Doctorado en Biomedicina y Farmacia

**EL PAPEL DE LA SERENDIPIA EN EL DESCUBRIMIENTO DE LOS
FÁRMACOS ANTIDEPRESIVOS Y REGULADORES DEL HUMOR**

Tesis Doctoral

FRANCISCO LÓPEZ MUÑOZ

**Directora:
M^a PILAR D'OCÓN NAVAZA**

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FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

DEPARTAMENT DE FARMACOLOGIA



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Dña. Pilar D'Ocon Navaza, Catedrática de la Universitat de València,

CERTIFICA:

Que el trabajo presentado por el Dr. **FRANCISCO LÓPEZ MUÑOZ**, titulado *“El papel de la serendipia en el descubrimiento de los Fármacos antidepresivos y reguladores del humor”* para obtener el grado de Doctor por la Universitat de València dentro del Doctorado en Biomedicina y Farmacia, ha sido realizado bajo mi dirección y asesoramiento.

Concluido el trabajo experimental y bibliográfico, autorizo la presentación de la Tesis, para que sea juzgada por el tribunal correspondiente.

Lo que firmo en Valencia a 29 de abril de 2025

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*A Amparo, Isabel, Paco y Carlos.
Aunque a veces no lo parezca, son mi guía vital.*

*El descubrimiento necesita suerte, inventiva e intelecto:
ninguno puede prescindir del otro.*

Johann Wolfgang von Goethe

*El descubrimiento consiste en ver lo que todo el mundo ha visto
y pensar lo que nadie ha pensado.*

Albert Szent-Györgyi

*En el reino de la observación científica,
la suerte está reservada sólo para aquellos
que están preparados para aprovecharla.*

Louis Pasteur

AGRADECIMIENTOS

Este proyecto vio la luz en el año 2017, aunque se pergeñó un año antes, cuando conocí a la profesora M^a Pilar D'Ocón Navaza, catedrática de Farmacología de la Universitat de València, como miembro del tribunal de otra tesis doctoral que en ese momento dirigía el que suscribe a otro ilustre valenciano, el profesor Fernando Ruis Alarcó, en la Universidad de Alcalá. La tesis se enmarcaba en una de mis sub-líneas de investigación, la influencia de la serendipia en el proceso de descubrimiento e introducción clínica de los agentes psicofarmacológicos, que formaba parte de una línea de mayor envergadura como es la historia de la psicofarmacología, a la que he dedicado más de 30 años de mi vida profesional. Esa tesis estaba circunscrita a los fármacos antipsicóticos. En la comida posterior, la profesora D'Ocón me comentaba si habíamos puesto en marcha alguna otra tesis doctoral en este campo, pues le pareció muy interesante, y le contesté que no. Y en este momento parece que intervino la mismísima serendipia, pues me hizo notar que sería interesante abordar este tema en otros grupos terapéuticos. Justo en esos meses había comenzado a recopilar datos para avanzar en ese proyecto, analizando el papel de la serendipia en el descubrimiento e introducción clínica de los fármacos empleados en el tratamiento de los trastornos del estado de ánimo (antidepresivos y reguladores del humor). Cuando comenté este asunto, la profesora D'Ocón me preguntó si tenía algún doctorando trabajando en este tema y ante mi respuesta negativa, me insto a que lo buscara. Y el azar quiso, de forma un tanto irreflexiva, que me ofreciera yo mismo de candidato si ella estaba dispuesta a ejercer la dirección. En cualquier caso, yo no podía imaginar en ese momento que dicha conversación culminaría con la presentación de esta tesis doctoral, tras mi primer doctorado en Medicina y Cirugía, en la Universidad Complutense de Madrid, hace 32 años, y el segundo, en Lengua Española y Literatura,

en la Universidad de Alcalá, hace 10 años. Y de esta forma se gestó este proyecto. Por este motivo, expreso mi agradecimiento, en primer lugar, a M^a Pilar por todo el apoyo que me ha brindado en estos 7 años, en los que el trabajo se ha visto muchas veces enlentecido y disipado por las ocupaciones laborales sobrevenidas, con mi nombramiento como vicerrector de Investigación y Ciencia de la Universidad Camilo José Cela, y los efectos perniciosos de la pandemia de la covid-19. También agradezco la disposición y ayuda permanente de M^a Carmen Arce Heras, Mamen, PAS del Departamento de Farmacología de la Facultad de Farmacia de la Universitat de València.

En segundo lugar, quería mencionar al profesor Cecilio Álamo, catedrático de Farmacología, ya emérito, de la Universidad de Alcalá, al que nunca dejaré de considerar como mi “maestro” en este complicado mundo del fármaco y del medicamento. Me recibió hace 33 años en su equipo y como he comentado en algunas otras ocasiones, me enseñó (y continúa haciéndolo) muchas cosas de la ciencia, pero bastantes más de la vida, lo que es mucho más de agradecer. Su amistad es un bien preciado que procuraré conservar siempre.

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SOBRE LA ESTRUCTURA DE ESTA TESIS DOCTORAL

En la presente tesis doctoral se analiza el papel de la serendipia, entendida como circunstancia azarosa junto a la sagacidad de un investigador, en el descubrimiento de los agentes farmacológicos empleados en el tratamiento de los trastornos afectivos, del humor o del estado de ánimo.

La temática de esta tesis doctoral constituye la base de una línea de investigación viva dirigida por el doctorando, que se inició hace 26 años, en el marco de sus estudios sobre la historia de la psicofarmacología.

Fruto de esta línea de investigación específica sobre historia de los fármacos antidepresivos son 23 artículos publicados en revistas científicas (14 en revistas internacionales y 9 en revistas nacionales), 11 de ellos en revistas con índice de impacto JCR-ISI (*Journal Citation Report*), 6 publicados en revistas del primer cuartil de su sección JCR (*Journal of Affective Disorders*, *Journal of Clinical Psychopharmacology*, *Current Pharmaceutical Design*, y *Mental Illness*), uno en una revista del segundo cuartil JCR (*International Journal of Molecular Sciences*) y 4 en revistas de los cuartiles tercero y cuarto de su sección JCR (*Journal of the History of the Neurosciences*, *World Journal of Psychiatry*, *Alpha Psychiatry*, y *Actas Españolas de Psiquiatría*). De ellos, uno de los artículos fue publicado en una de las revistas más relevantes en el ámbito de estudio en el

que se enmarca la tesis doctoral (*Journal of the History of the Neurosciences*) y otro en el referente de la psiquiatría española (*Actas Españolas de Psiquiatría*). Además, se han publicado 5 artículos de divulgación científica y 2 comunicaciones en revistas. Del mismo modo, se han publicado dos libros en editoriales internacionales (CRC Press Taylor & Francis Group y NPP Books) y otros 2 en editoriales nacionales (Ediciones Eurobook, S.L. y Editorial Médica Panamericana, S.A.), además de 9 capítulos de libros en ediciones internacionales, algunos en editoriales de gran prestigio, como Springer Internacional o Elsevier Academic Press, y otros 7 capítulos de libros en ediciones nacionales. Esta línea de investigación también aporta 2 ponencias (una de ellas de clausura de un congreso nacional) y 2 comunicaciones en congresos. De estas 54 aportaciones, el doctorando es el primer firmante de 43 de los trabajos. Finalmente, el doctorando ha dictado un discurso de ingreso sobre esta materia en una Academia Asociada del Instituto de España (Academia de Ciencias, Ingenierías y Humanidades de Lanzarote). La Tabla adjunta recoge esta producción científica.

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El formato de esta tesis doctoral corresponde al denominado modelo de compendio de artículos publicados, que permite recoger la trayectoria investigadora del doctorando en este tema durante los últimos 26 años. Con el objetivo de garantizar la unidad temática, se han seleccionado, para incluir como capítulos de la tesis, 4 trabajos de investigación publicados en revistas especializadas con índices de calidad relativos (factor de impacto en JCR-ISI) durante el periodo de matriculación del doctorando en el Programa de Doctorado en Biomedicina y Farmacia de la Universitat de València, y un artículo publicado previamente, que ayudará a dar consistencia y homogeneidad a dicha unidad temática, que no se incluye en la sección de Resultados, pero constituye un apartado específico de la sección de Introducción. Estas publicaciones son las siguientes:

ARTÍCULO INTRODUCTORIO	
	López-Muñoz F, Álamo C. Monoaminergic neurotransmission: The history of the discovery of antidepressants from 1950s until today. <i>Current Pharmaceutical Design</i>, 2009; 15: 1563-1586. Factor de impacto JCR-ISI 2009 = 4.414 (29/237 Categoría Pharmacology & Pharmacy, T1/Q1).
ARTÍCULOS INTEGRANTES DE LA TESIS DOCTORAL	
1	López-Muñoz F, Shen WW, D'Ocon P, Romero A, Álamo C. A history of the pharmacological treatment of bipolar disorder. <i>International Journal of Molecular Sciences</i>, 2018; 19 (7): 2143. doi.org/10.3390/ijms19072143. Factor de impacto JCR-ISI 2018 = 4.183 (46/172 Categoría Chemistry, Multidisciplinary, T1/Q2; 78/298, Categoría Biochemistry & Molecular Biology T1/Q2).
2	López-Muñoz F, D'Ocón P, Romero A, Guerra JA, Álamo C. The role of serendipity in the discovery of classical antidepressant drugs: Applying operational criteria and patterns of discovery. <i>World Journal of Psychiatry</i>, 2022; 12: 588-602. Factor de impacto JCR-ISI 2022 = 3.100 (91/155 Categoría Psychiatry, T2/Q3).

3	López-Muñoz F, D'Ocón P, Romero A, Guerra JA, De Berardis D, Álamo C. Discovery patterns of drugs approved for treating bipolar disorder by applying operational criteria of serendipity: A historical analysis. <i>Mental Illness</i>, 2024; 8848525. doi.org/10.1155/2024/8848525. Factor de impacto JCR-ISI 2023 = 9.000 (9/276 Categoría Psychiatry, T1/Q1).
4	López-Muñoz F, D'Ocón P, Romero A, De Berardis D, Álamo C. Did serendipity contribute to the discovery of new antidepressant drugs?. Historical analysis using operational criteria. <i>Alpha Psychiatry</i>, 2025; 26 (2): 40037. doi.org/10.31083/AP40037. Factor de impacto JCR-ISI 2023 = 1.300 (205/276 Categoría Psychiatry, T3/Q3).

Este modelo de tesis doctoral incorpora las 4 publicaciones como cuerpo documental, amparadas en una Introducción General, en la que se incluye la 5ª publicación, que centra al lector en el contexto histórico del proceso de desarrollo de cada uno de los fármacos antidepresivos. Como podrá observar el lector, los documentos que integran la tesis doctoral no muestran una secuencia cronológica con respecto a su fecha de publicación, sino que han sido ordenados siguiendo un criterio estructural, para un mejor desarrollo narrativo y una organización más adecuada en la presentación de los objetivos de esta tesis doctoral. Así, en el Documento 2 se analiza el papel de la serendipia en el descubrimiento y la introducción clínica de los clásicos fármacos antidepresivos, mientras en el Documento 3 se aborda este rol de la serendipia en relación con los agentes antidepresivos modernos. El Documento 4 analiza el descubrimiento y el contexto histórico de todos los fármacos empleados en la actualidad en el tratamiento de los pacientes con trastorno bipolar y, finalmente, en el Documento 5 se estudia el papel y relevancia de la serendipia en el proceso de descubrimiento e introducción en terapéutica de estos agentes eutimizantes.

El lector apreciará que el estilo en que se presenta cada documento es diferente; esto se debe a que se han respetado las normas editoriales de las revistas donde fueron publicados y se presentan tal cual fueron remitidos en su última versión revisada. En una posterior Discusión conjunta se concretan aspectos relevantes y sustanciales de todos los documentos. Finalmente se exponen las conclusiones y se relacionan las citas bibliográficas consultadas y manejadas para la redacción de las secciones de Introducción y Discusión general. Para ello, se han aplicado las Normas Vancouver, que, en estos momentos, son las más utilizadas en el ámbito de las disciplinas biomédicas.

Aunque en este tipo de tesis doctorales por compendio de artículos publicados no suele incorporarse el clásico apartado metodológico (pues ya va inserto en cada uno de los Documentos que lo integran), en este caso sí se ha incorporado, aunque de manera breve, para contextualizar las fuentes utilizadas en los análisis realizados. En este sentido, hay que mencionar que el estudio histórico del proceso de desarrollo de cada uno de los fármacos analizados se ha basado en los artículos originales en los que se publicaron los primeros datos farmacológicos y clínicos de los mismos. Para ello se recurrió a diferentes fuentes: los artículos originales fueron, en gran medida, obtenidos mediante su búsqueda especializada en las bases de datos más relevantes en este campo, como son *EMBASE*, *SCOPUS* y *Web of Science (WoS)*. *EMBASE (Excerpta Medica dataBASE)* es una base de datos del ámbito biomédico y farmacológico propiedad de la editorial Elsevier (Ámsterdam, Holanda), que incluye más de 28 millones de referencias, pertenecientes a más de 8.400 revistas indexadas desde 1947 hasta la actualidad. *SCOPUS*, también perteneciente a Elsevier, es una base de datos bibliográfica introducida en el año 2004, que cubre unos 24.500 títulos de publicaciones periódicas de más de 5000 editoriales, incluyendo revistas científicas, libros de investigación, conferencias y libros de actas de congresos, en los campos de la ciencia, tecnología, medicina y ciencias sociales, incluyendo las artes y humanidades. Finalmente, *WoS* es un servicio en línea propiedad de Clarivate Analytics (Londres, UK; Filadelfia, USA), que incorpora una serie de bases de datos que indexan casi 10.000 revistas de las áreas de ciencia, tecnología, ciencias sociales, artes y humanidades, además de 100.000 actas de conferencias y congresos.

En relación a otro tipo de documentos (manuscritos, informes o documentos digitalizados), se han consultado los fondos de los servicios de documentación de las compañías farmacéuticas que han comercializado dichos medicamentos, así como la documentación disponible en la Red de Bibliotecas del Consejo Superior de Investigaciones Científicas (CSIC). También se ha obtenido información muy relevante de la serie de entrevistas realizadas por David Healy, publicadas en los volúmenes *The Psychopharmacologists* (Arnold – Oxford University Press, Oxford, UK) y de los textos históricos redactados por los propios investigadores y descubridores de todos estos agentes, publicados en la colección *The History of Psychopharmacology*, del International College of Neuropsychopharmacology (CINP) (Collegium Internationale Neuro-Psychopharmacologicum), coordinada por Thomas A. Ban, David Healy y

Edward Shorter y editada por Animula Publishing House (Budapest, Hungría). Finalmente, también se ha recurrido a la International Network for the History of Neuropsychopharmacology (INHNP), coordinada por Thomas A. Ban (Vanderbilt University, Nashville, Tennessee, USA), de la que el doctorando es miembro, y al fondo documental sobre historia de la psicofarmacología del profesor Francisco López-Muñoz, que inició hace 26 años cuando comenzó esta línea de investigación.

RESUMEN

Los descubrimientos vinculados al azar o a la casualidad han constituido una constante permanente a lo largo de la historia de la ciencia, ámbito en el que se ha popularizado el uso del concepto “serendipia”. El origen de este término hay que buscarlo en la correspondencia mantenida entre el escritor, político e historiador inglés Horace Walpole y su compatriota, el diplomático Horace Mann, y en concreto en una epístola en la que se hace referencia al clásico cuento de origen persa *Los tres príncipes de Serendip*, donde se recogen los dos componentes que deberían integrar el concepto de serendipia: “accidente y sagacidad”. Pero no pueden considerarse sinónimos las acepciones “descubrimiento fortuito” y “serendipia”, pues este último término, además de a la casualidad, hace referencia adicional a la sagacidad del investigador, aunque con este término se han venido refiriendo tradicionalmente los analistas a aquellos descubrimientos o hallazgos de carácter afortunado e inesperado, eventos fortuitos o coincidencias accidentales.

Sin embargo, en la presente tesis doctoral se ha postulado que existe una diferencia estructural en este planteamiento; la sagacidad siempre precede y conduce a la observación en los descubrimientos no serendípicos, pero en los descubrimientos serendípicos, la sagacidad se manifiesta después de la observación inesperada. No obstante, incluso esta apreciación arrastra problemas interpretativos, pues los científicos, una vez que ha acontecido su descubrimiento, tienden a explicarlo como consecuencia de

unas hipótesis de trabajo perfectamente planificadas, incluso cuando estos tienen lugar de una forma absolutamente azarosa.

En este sentido, el descubrimiento de la mayor parte de los agentes psicofarmacológicos que revolucionaron la asistencia psiquiátrica tampoco ha escapado a esta conceptualización. La mayor parte de estos descubrimientos han sido considerados, incluso por los propios investigadores involucrados en ellos, como consecuencia de la intervención del azar o de la serendipia. Sin embargo, el uso del concepto serendipia para caracterizar estos descubrimientos es, cuando menos, confuso y contradictorio. Precisamente estas diferencias de opinión acerca del papel de los descubrimientos fortuitos o azarosos radican básicamente en la ambigüedad semántica de este concepto.

En esta tesis doctoral se ha desglosado el papel real que desempeñó la serendipia en los hallazgos que confluyeron en el descubrimiento de los fármacos empleados durante los últimos 70 años (desde la denominada “revolución de la psicofarmacología” en la década de 1950) en el tratamiento de los trastornos del humor, fármacos antidepresivos y reguladores del humor, de acuerdo con una definición operativa y categorial de serendipia que ha sido publicada por el grupo de investigación dirigido por el doctorando.

Las afirmaciones acerca de que los descubrimientos más importantes de la psicofarmacología fueron fortuitos suelen implicar que la casualidad fue condición necesaria y suficiente en esos acontecimientos. Sin embargo, rara vez la casualidad fue una condición suficiente. En los primeros momentos de la moderna era psicofarmacológica, los descubrimientos serendípicos puros, en contra de lo que se ha venido postulando, fueron más bien escasos. La mayoría de ellos presentan un carácter mixto, en el que se mezclan hallazgos serendípicos y no serendípicos. Estos hechos pueden favorecer la existencia de las anteriormente mencionadas contradicciones entre autores, algunos de los cuales los interpretan únicamente desde la perspectiva del azar, pues estiman que los resultados de los ensayos clínicos son un mero *continuum* de los hallazgos serendípicos iniciales y todo debería ser considerado como un descubrimiento único y no como eventos separados. En cualquier caso, y excluyendo aquellos casos de diseño racional de medicamentos, casi siempre nos encontraríamos frente a un cóctel de azar e ingenio, de accidente y de perspicacia científica.

En la presente tesis se defiende la hipótesis del paulatino paso en el arquetipo del descubrimiento de agentes antidepresivos y estabilizadores del humor desde un periodo inicial en que dominaba un patrón mixto, mezcla de hallazgos serendípicos y no serendípicos, a un periodo más moderno en el que la serendipia ha perdido protagonismo y ha triunfado la política de diseño racional de los fármacos.

Para contrastar esta hipótesis, se utilizó la definición operativa de serendipia propuesta por nuestro grupo, basada en cuatro patrones diferentes de imputabilidad, que permitió reflexionar sobre el papel real que desempeñó la serendipia en los hallazgos que han configurado el descubrimiento de los agentes antidepresivos y eutimizantes. Esta definición operativa de serendipia, en relación a los descubrimientos científicos, se basa en cuatro patrones diferentes de imputabilidad: un patrón I, que englobaría a los descubrimientos serendípicos puros; el patrón II haría referencia a los descubrimientos serendípicos iniciales, en algunos casos realizados en animales de laboratorio, que conducen secundariamente a descubrimientos no serendípicos; el patrón III incluiría a los descubrimientos no serendípicos asociados secundariamente a descubrimientos de carácter serendípico; finalmente, el patrón IV hace referencia a los descubrimientos no serendípicos. En este último patrón, los fármacos surgieron, al margen de la serendipia, de programas de investigación sistemáticos diseñados específicamente para desarrollar medicamentos eficaces en diferentes trastornos psiquiátricos.

Previamente a la aplicación de los criterios de imputabilidad, se realizó un detallado estudio histórico del proceso de desarrollo de cada uno de los fármacos analizados, recurriendo a los artículos originales en los que se publicaron los primeros datos farmacológicos y clínicos de los mismos. Para ello se han empleado las bases de datos más relevantes en este campo (*EMBASE*, *SCOPUS* y *Web of Science*); los servicios de documentación de las compañías farmacéuticas que han comercializado dichos medicamentos; la serie de entrevistas realizadas por David Healy, publicadas en los volúmenes *The Psychopharmacologists* (Arnold – Oxford University Press); los textos históricos redactados por los propios investigadores y descubridores de todos estos agentes, publicados en la colección *The History of Psychopharmacology*, del International College of Neuropsychopharmacology, coordinada por Thomas A. Ban,

David Healy y Edward Shorter y editada por Animula Publishing House; la documentación disponible en la Network for the History of Neuropsychopharmacology, coordinada por Thomas A. Ban (Vanderbilt University), de la que el doctorando es miembro; y el fondo documental sobre historia de la psicofarmacología del grupo de trabajo que dirige también el doctorando, línea de investigación desarrollada durante los últimos 26 años.

Los resultados de esta tesis doctoral se presentan en 5 documentos. Así, el Documento 1 centra al lector en el contexto histórico del proceso de desarrollo de cada uno de los fármacos antidepresivos, en el Documento 2 se analiza el papel de la serendipia en el descubrimiento y la introducción clínica de los clásicos fármacos antidepresivos, mientras en el Documento 3 se aborda este rol de la serendipia en relación con los agentes antidepresivos modernos. El Documento 4 analiza el descubrimiento y el contexto histórico de todos los fármacos empleados en la actualidad en el tratamiento de los pacientes con trastorno bipolar y, finalmente, en el Documento 5 se estudia el papel y relevancia de la serendipia en el proceso de descubrimiento e introducción en terapéutica de estos agentes eutimizantes.

Los resultados obtenidos en esta tesis doctoral confirman que los hallazgos serendípicos puros (patrón tipo I) son bastante excepcionales, pudiéndose catalogar únicamente como tales los descubrimientos del efecto anticonvulsivante del ácido valproico y el posterior efecto eutimizante del valproato. Por el contrario, la mayoría de los hallazgos presentan un carácter mixto, en el que se mezclan hallazgos serendípicos y no serendípicos, y generalmente siguen un patrón consistente que parte de una observación inicial serendípica (patrón tipo II). Tal es el caso de las sales de litio, la imipramina, la iproniazida, la mianserina y la moclobemida. Mucho menos frecuentes han sido los patrones mixtos que comienzan con una apreciación no serendípica que conduce secundariamente a descubrimientos de carácter serendípico (patrón tipo III), que sólo se ha puesto de manifiesto en el caso de la lamotrigina en el tratamiento preventivo de nuevos episodios depresivos del trastorno bipolar y de la acción antidepresiva de la esketamina. Entre los descubrimientos no serendípicos (patrón tipo IV) se encuentran el desarrollo de la fluoxetina y del resto de inhibidores selectivos de la recaptación de

serotonina y otros nuevos antidepresivos de diferentes familias, así como el descubrimiento del efecto antimaníaco de los antipsicóticos atípicos.

SUMMARY

Discoveries linked to chance have been a constant throughout the history of science, a field in which the use of the concept "serendipity" has become popular. The origin of this term lies in the correspondence between the English writer, politician, and historian Horace Walpole and his compatriot, the diplomat Horace Mann, and specifically in an epistle that refers to the classic Persian tale *The Three Princes of Serendip*, which captures the two components that should comprise the concept of serendipity: "accident and sagacity". However, the terms "fortuitous discovery" and "serendipity" cannot be considered synonymous, since the latter term, in addition to coincidence, also refers to the researcher's sagacity, although analysts have traditionally used this term to refer to those discoveries or findings of a fortunate and unexpected nature, fortuitous events, or accidental coincidences.

However, this doctoral thesis has postulated that there is a structural difference in this approach; sagacity always precedes and leads to observation in non-serendipitous discoveries, but in serendipitous discoveries, sagacity manifests after the unexpected observation. Nevertheless, even this assessment entails interpretive problems, since scientists, once their discovery has occurred, tend to explain it as a consequence of perfectly planned working hypotheses, even when these occur entirely by chance.

In this sense, the discovery of most of the psychopharmacological agents that revolutionized psychiatric care has not escaped this conceptualization either. Most of these discoveries have been considered, even by the researchers involved, to be the result of chance or serendipity. However, the use of the concept of serendipity to characterize these discoveries is, at the very least, confusing and contradictory. Precisely these differences of opinion about the role of fortuitous or chance discoveries are basically based on the semantic ambiguity of this concept.

This doctoral thesis unravels the real role that serendipity played in the discoveries that led to the discovery of drugs used over the past 70 years (since the so-called “psychopharmacology revolution” in the 1950s) in the treatment of mood disorders, antidepressant drugs and mood regulators, according to an operational and categorical definition of serendipity published by the research group led by the doctoral scholar.

Claims that the most important discoveries in psychopharmacology were fortuitous often imply that serendipity was a necessary and sufficient condition for these events. However, serendipity was rarely a sufficient condition. In the early stages of the modern psychopharmacological era, purely serendipitous discoveries, contrary to what has been postulated, were rather rare. Most of them have a mixed character, combining serendipitous and non-serendipitous findings. These facts may favour the existence of the aforementioned contradictions among authors, some of whom interpret them solely from the perspective of chance, since they believe that the results of clinical trials are a mere *continuum* of initial serendipitous findings and that everything should be considered a unique discovery and not as separate events. In any case, and excluding those cases of rational drug design, we would almost always be faced with a combination of chance, accident and scientific insight.

This thesis defends the hypothesis of a gradual transition in the archetypal discovery of antidepressant and mood-stabilizing agents from an initial period dominated by a mixed pattern, a mixture of serendipitous and non-serendipitous findings, to a more modern period in which serendipity has diminished in importance and the policy of rational drug design has triumphed.

To test this hypothesis, we used the operational definition of serendipity proposed by our group, based on four different patterns of imputability. This allowed us to reflect on the real role that serendipity played in the discoveries that shaped the discovery of antidepressant and mood-stabilizing agents. This operational definition of serendipity, in relation to scientific discoveries, is based on four different patterns of imputability: Pattern I, which encompasses purely serendipitous discoveries; Pattern II refers to initial serendipitous discoveries, in some cases carried out in laboratory animals, which lead secondarily to non-serendipitous discoveries; Pattern III includes non-serendipitous discoveries secondarily associated with serendipitous discoveries; finally, Pattern IV refers to non-serendipitous discoveries. In this last pattern, drugs emerged, apart from serendipity, from systematic research programs specifically designed to develop effective medications for various psychiatric disorders.

Prior to applying the imputability criteria, a detailed historical study of the development process of each of the drugs analyzed was conducted, using the original articles in which the first pharmacological and clinical data on these drugs were published. To this end, the most relevant databases in this field (*EMBASE*, *SCOPUS*, and *Web of Science*) were used; the documentation services of the pharmaceutical companies that have marketed these drugs; the series of interviews conducted by David Healy, published in the volumes *The Psychopharmacologists* (Arnold – Oxford University Press); the historical texts written by the researchers and discoverers of all these agents, published in *The History of Psychopharmacology*, a collection published by the International College of Neuropsychopharmacology, coordinated by Thomas A. Ban, David Healy, and Edward Shorter and published by Animula Publishing House; and the documentation available on the Network for the History of Neuropsychopharmacology, coordinated by Thomas A. Ban (Vanderbilt University), of which the doctoral scholar is a member; and the documentary collection on the history of psychopharmacology of the working group also directed by the doctoral scholar, a line of research developed over the last 26 years.

The results of this doctoral thesis are presented in five documents. Document 1 focuses the reader on the historical context of the development process of each of the antidepressant drugs; Document 2 analyzes the role of serendipity in the discovery and clinical introduction of classic antidepressant drugs, while Document 3 addresses this role

of serendipity in relation to modern antidepressant agents. Document 4 analyzes the discovery and historical context of all the drugs currently used in the treatment of patients with bipolar disorder; and finally, Document 5 examines the role and relevance of serendipity in the discovery and therapeutic introduction of these mood-stabilizing agents.

The results obtained in this doctoral thesis confirm that purely serendipitous findings (Type I pattern) are quite rare, with only the discoveries of the anticonvulsant effect of valproic acid and the subsequent mood-reducing effect of valproate being categorized as such. In contrast, most findings are mixed, combining serendipitous and non-serendipitous findings, and generally follow a consistent pattern based on an initial serendipitous observation (Type II pattern). This is the case with lithium salts, imipramine, iproniazid, mianserin, and moclobemide. Much less common have been mixed patterns that begin with a non-serendipitous appraisal that leads secondarily to serendipitous discoveries (Type III pattern), which has only been demonstrated in the case of lamotrigine in the preventive treatment of new depressive episodes in bipolar disorder and the antidepressant action of esketamine. Non-serendipitous discoveries (Type IV pattern) include the development of fluoxetine and the other selective serotonin reuptake inhibitors and other new antidepressants from different families, as well as the discovery of the antimanic effect of atypical antipsychotics.

LISTADO DE ABREVIATURAS

5-HIAA: 5-hydroxyindoleacetic acid
5-HT: 5-hidroxitriptamina o serotonina
AAD: Atypical antipsychotic drug
AC: Adenilato-ciclasa
ACNP: American College of Neuropsychopharmacology
ACTH: Hormona adrenocorticotropa
ADHD: Attention-deficit/hyperactivity disorder
ADT: Antidepresivos tricíclicos
AM: Agonista melatoninérgico
AMPA: Ácido propiónico α -amino-3-hidroxi-5-metil-4-isoxazol
AMPc: Adenosina-monofosfato cíclico
AMPT: α -methylparatyrosine
AP-1: Proteína activadora 1
APA: American Psychiatric Association
ARNm: Ácido ribonucleico mensajero
AsCNP: Asian College of Neuropsychopharmacology
ATC: Anatomical Therapeutic Chemical
ATPasa: Adenosín-trifosfato sintasa
BASF: Badische Anilin und Soda Fabrik

bcl-2: B-cell lymphoma 2
BDNF: Brain-derived neurotrophic factor
BOLDER: BipOLar DEpRession
CA3: *Cornu ammonis* 3 (región del hipocampo)
CIE: Clasificación Internacional de Enfermedades
CINP: Collegium Internationale Neuro-Psychopharmacologicum
CNS: Central Nervous System
CREB: cAMP response element binding
CRF: Corticotropin releasing factor
CRH: Corticotrophin releasing hormone
CSIC: Consejo Superior de Investigaciones Científicas
DA: Dopamina
DAG: Diacil-glicerol.
d.C.: Después de Cristo
DOPA: 3,4-dihydroxy-phenylalanine
DRG: Delayed response genes
DSM: Diagnostic and Statistical Manual of Mental Disorders
ECA: Epidemiologic Catchment Area Survey
ECNP: European College of Neuropsychopharmacology
ECT: Electroconvulsivoterapia
EMA: European Medicines Agency
EMBOLDEN: Efficacy of Monotherapy Seroquel in BipOLAR DEpression
ERG: Early response genes
ERK: Extracellular signal-regulated kinase
ESEMeD: European Study of the Epidemiology of Mental Disorders
FCF-2: Factor de crecimiento fibroblástico tipo 2
FDA: Food and Drugs Administration
FGA: First-generation antipsychotic drug
FGF: Fibroblast growth factor
FI: Factor de Impacto
GABA: Ácido γ -aminobutírico
GLU: Glutamato
GSK3: Glucógeno-sintetasa-cinasa-3

JCR: Journal Citation Report
HDRS: Hamilton Depression Rating Scale
HHA: Eje hipotálamo-hipófiso-adrenal
IGF: Insulin-like growth factor
IL: Interleucina
IMAO: Inhibidores de la monoamino-oxidasa
IMPasa: Inositol-monofosfatasa
INE: Instituto Nacional de Estadística
INHN: International Network for the History of Neuropsychopharmacology
IPPasa: Inositol-polifosfato-1-fosfatasa
IRND: Inhibidor selectivo de la recaptación de noradrenalina y dopamina
IRNS: Inhibidor selectivo de la recaptación de noradrenalina y serotonina
ISRN: Inhibidor selectivo de la recaptación de noradrenalina
ISRS: Inhibidores selectivos de la recaptación de serotonina
IUPHAR: International Union of Basic and Clinical Pharmacology
LSD: Lysergic Acid Diethylamide (del alemán Lysergsäure-diethylamid)
MADRS: Montgomery-Asberg Depression Rating Scale
MAO: Monoamino-oxidasa
MAOI: Monoamine-oxidase inhibitor
MAP₂: cAMP-dependent protein associated with microtubules
MAPK: Mitogen-activated protein kinase
MG: Modulador glutamatérgico
mGlu: Receptor metabotrópico glutamatérgico
MT: Receptor melatoninérgico
mTOR: Mammalian target of rapamycin
NA: Noradrenalina
NaSSA: Antidepresivo noradrenérgico y serotoninérgico específico
NbN2: Nomenclatura basada en la neurociencia, segunda edición
NCE: New chemical entity
NCS: National Comorbidity Survey
NGF: Nerve growth factor
NIMH: Instituto Nacional de Salud Mental de Estados Unidos
NIH: National Institutes of Health (Estados Unidos)

NMDA: N-metil-D-aspartato
NO; Nitric oxide
NS: Descubrimiento no serendípico
NSRI: Noradrenaline and serotonin reuptake inhibitor
OCA: Other classical antidepressants
OMS: Organización Mundial de la Salud
p-CA: p-chloroamphetamine
PG: Proteínas G
PK: Proteincinasas
PKA: Proteincinasa A
PKC: Proteincinasa C
PKCaM: Kinase dependent on calcium and calmodulin
POW: Prisoner of war
PREVAIL: Program to Evaluate the Antidepressant Impact of Lurasidone
Pro-Enk: Proencefalina
PSD95: Postsynaptic density protein 95
Q: Cuartil
RAE: Real Academia Española
RC: Receptor corticosteroide
RIMA: Inhibidor reversible de la monoamino-oxidasa
S: Descubrimiento serendípico
SGA: Second-generation antipsychotic drug
SMIT1: Transportador de alta afinidad del miosinositol
SMS: Modulador y estimulador serotoninérgico
SNC: Sistema Nervioso Central
SNRI: Selective noradrenaline reuptake inhibitor
SR: Sustained-release
SSRI: Selective serotonin reuptake inhibitor
TCA: Tricyclic antidepressant
TDM: Trastorno depresivo mayor
TEPT: Trastorno de estrés postraumático
Tir-OH: Tirosina-hidroxilasa
TNF: Factor de necrosis tumoral

TOC: Trastorno obsesivo compulsivo

TR: Text review

TrkB: Tropomyosin receptor kinase B

UK: United Kingdom

USA: United States of America

VEGF: Vascular endothelial growth factor

WHO: World Health Organization

WHOCC: World Health Organization Collaborating Centre for Drugs Statistics
Methodology

WoS: Web of Science

WWII: World War II

XL: Extended-release

YMRS: Young Mania Rating Scale

INTRODUCCIÓN GENERAL

1. Serendipia

El azar ha jugado históricamente un destacado papel en los descubrimientos científicos, según han venido apuntando numerosos autores durante el pasado siglo XX. No obstante, en la actualidad, esta atribución parece, en cierta medida, magnificada. Dentro del ámbito de la ciencia, los procesos de descubrimiento de los agentes farmacológicos no se han quedado al margen, tal como han resaltado algunos autores (Kubinyi, 1999; Oh, 2021), aunque la trascendencia de la intervención de la fortuna en estos desarrollos ha sido evaluada desde criterios muy diversos y su importancia maximizada o minimizada según las diferentes fuentes consultadas. Estas discrepancias a la hora de juzgar el rol de los descubrimientos fortuitos o azarosos estriban posiblemente, y así lo hemos defendido en nuestras contribuciones científicas, en una ambigüedad semántica en torno al término “serendipia”, que ha generado históricamente un manifiesto entorno de confusión.

El concepto de serendipia, dentro del ámbito específico de la ciencia, se ha vinculado de forma tradicional con hallazgos y descubrimientos de carácter inesperado, con intervención de la fortuna, o eventos meramente accidentales (“accidente feliz” o “sorpresa agradable”, en opinión de algunos científicos). Del mismo modo, la serendipia

también se ha asociado etimológicamente y de forma manifiestamente errónea al concepto simple de coincidencia, casualidad o azar.

1.1. El concepto de serendipia en su contexto histórico

El término serendipia tiene su origen en la pluma del escritor e historiador inglés Horace Walpole (1717-1797), cuarto Conde de Oxford (Figura 1, izquierda) y concretamente en la amplia correspondencia manuscrita que mantuvo con su buen amigo, el diplomático de la Corona británica Sir Horace Mann (1706-1786) (Figura 1, derecha), que alcanzó la relevante cifra de 848 cartas y sus correspondientes réplicas (López-Muñoz et al., 2012).



Figura 1: Retratos de Horace Walpole, cuarto Conde de Oxford, por Rosalba Carriera (1673-1757), pintado sobre 1741 (izquierda), y Sir Horace Mann, por John Astley (1720-1787), realizado en 1751 (derecha).

Estando destinado en Italia, Mann regaló a Walpole un retrato de la aristócrata italiana del siglo XVI Bianca Cappello (1548-1587), posteriormente convertida en Gran Duquesa de Toscana (Figura 2), tras contraer matrimonio con el Gran Duque Francesco I de Médici (1541-1587). En una de las cartas de Walpole, fechada el 28 de enero de 1724, éste explicaba a Mann como, buscando el escudo de armas de los Médici para adornar el marco destinado al lienzo recibido, encontró de forma casual, en un libro veneciano de heráldica, el escudo de los Capello (Silver, 2015). Así lo refleja en su epístola manuscrita:

“... este descubrimiento es del tipo que yo llamo serendipia, una palabra muy expresiva que voy a intentar explicarle, ya que no tengo nada mejor que hacer: la comprenderá

mejor con su origen que con definiciones. Leí en una ocasión un cuentecillo titulado ‘Los tres príncipes de Serendip’: en él sus altezas realizaban continuos descubrimientos en sus viajes, descubrimientos por accidente y sagacidad de cosas que en principio no buscaban: por ejemplo, uno de ellos descubría que una mula que recorría últimamente el mismo camino era ciega del ojo derecho porque la hierba estaba más raída por el lado izquierdo - ¿comprende ahora la serendipia?” (Lewis, 1960, pp. 407-408).



Figura 2: Detalle del retrato de Bianca Cappello enviado por Mann a Walpole, realizado por un autor desconocido en Italia durante el siglo XVIII (Lewis Walpole Library).

Así pues, como se deriva de la lectura de estas letras, Horace Walpole se inspiró para la propuesta de su neologismo en un clásico relato de origen persa, incorporado al libro de poemas del erudito músico sufí Amir Khusrow o Jursan Amir (1253-1325), titulado *Hasht Bihist* (*Ocho paraísos*) (1302). En Occidente fue publicado originalmente por el autor italiano Cristoforo Armeno (n.d.) con el título *Peregrinaggio di tre giovani figliuoli del re di Serendippo* (1557) (Figura 3).



Figura 3: Frontispicio de la obra de Cristoforo Armeno *Peregrinaggio di tre giouani figliuoli del re di Serendippo*, editada en Venecia por Michele Tramezzino (1526-1571) en 1557.

Posteriormente, este cuento oriental, tras diferentes ediciones y versiones en distintos idiomas, acabaría transformándose, tal como lo conocemos en la actualidad, en *Los tres príncipes de Serendip*, y en este proceso se acabó perdiendo la autoría original, integrándose en numerosas ocasiones dentro de colecciones literarias. En este texto se describe como tres príncipes, procedentes del mítico país de Serendip (la actual isla de Ceilán, hoy denominada Sri Lanka), realizan, siguiendo las instrucciones paternas, una serie de viajes iniciáticos para conocer el mundo (López-Muñoz et al., 2012). Posiblemente la leyenda de los Tres Príncipes (Figura 4) esté inspirada en los hijos de Bahram Gur o Bahram V de Persia (421-438).



Figura 4: Los tres príncipes de Serendip, en una ilustración del poemario *Hasht Bihisht* (1302) de Amir Khusrow.

Durante estas “peregrinaciones”, los jóvenes príncipes, merced a su capacidad de observación y a su sagacidad, son capaces de descifrar misterios y analizar una serie de situaciones cotidianas, a modo detectivesco, mediante deducciones generadas de la información que consiguen y obtienen, pero que no buscan deliberadamente (Remer, 1965). A título de ejemplo, son capaces de deducir, sin observar al animal, que un camello portaba miel en una talega lateral y mantequilla en la otra, al advertir la presencia de hormigas en un lado del camino, atraídas por la mantequilla derretida, y moscas en el otro, posadas sobre la miel derramada.

Sin embargo, el término “serendipia” no volvió a aparecer en un texto escrito y publicado hasta el último cuarto del siglo XIX, cuando el químico y bibliófilo Edward Solly (1819-1886) realizó una réplica en la revista *Notes and Queries* (1875) a un estudio anónimo publicado en esta revista unas semanas antes relacionado con la historia de Walpole y los “Príncipes de Serendip”. En esta réplica, Solly escribió que “Horace Walpole utiliza la palabra *serendipity* para expresar un tipo particular de inteligencia natural” (Merton y Barber, 2004). Desde este momento, el término serendipia fue paulatinamente siendo cada vez más usado, aunque muy circunscrito, inicialmente, al entorno de los eruditos literarios.

Finalmente, la incorporación del concepto de serendipia al contexto científico se inició en la década de 1930 (Merton y Barber, 2004; Finger, 2000), con los trabajos del fisiólogo

norteamericano Walter B. Cannon (1871-1945) (véase Cannon, 1940), y se consolidó definitivamente en la década de 1950, cuando el microbiólogo de origen italiano y Premio Nobel de Fisiología y Medicina, en 1969, Salvador E. Luria (1912-1991) (Figura 5), de la Universidad de Indiana, utilizó este término en un artículo publicado en la revista *Scientific American*, en el que describió los acontecimientos casuales que sucedieron durante sus investigaciones sobre el denominado “Misterio T2”. Este “misterio” hacía referencia a un virus bacteriófago, denominado T2, que era capaz de infectar una bacteria, replicarse en su interior y finalmente destruirla (Luria, 1955). El autor lo refirió, literalmente, de la siguiente forma:

“Nuestra historia presenta como episodio crítico una de esas coincidencias que muestran como un descubrimiento depende a menudo de la oportunidad azarosa, o más bien lo que ha sido llamado 'serendipity', la posibilidad de que la observación caiga en un ojo receptivo” (Luria, 1955, p. 92).

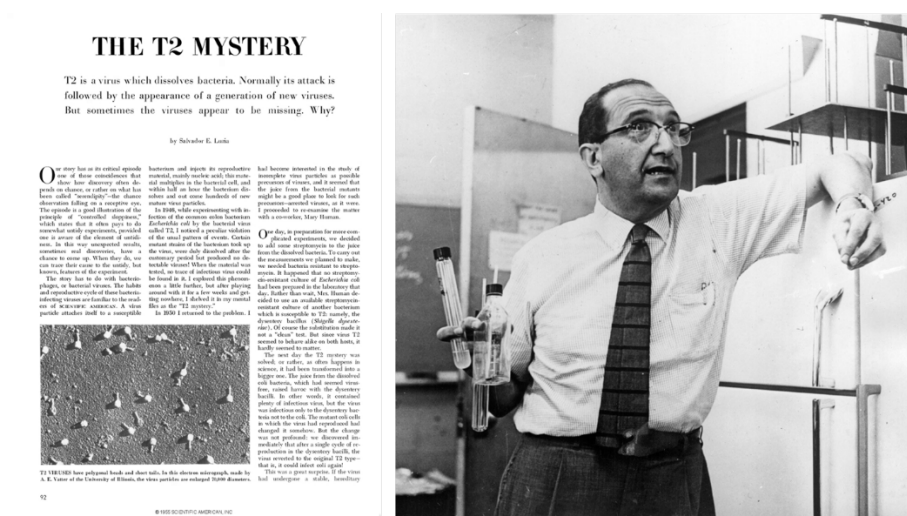


Figura 5: Primera página del artículo sobre el “Misterio T2” (*Scientific American*, 1955) del Premio Nobel Salvador E. Luria.

1.2. La interpretación semántica del término “serendipia”

El término “*serendipity*” ha adquirido, a lo largo de su corta historia, diversos significados en lengua inglesa, aunque ninguno de ellos concuerda con exactitud con la definición original propuesta por Walpole. El *Oxford English Dictionary Online* (2004) la define como “la facultad de realizar descubrimientos felices e inesperados por accidente”, y designa también “al hecho o la circunstancia en el que acontece este descubrimiento”. El

Webster's Third New International Dictionary of the English Language (2002) la define, por su parte, como “un don para el hallazgo de cosas valiosas o agradables que no se estaban buscando”, mientras el *Random House Webster's Dictionary* (2001) dice que es “una aptitud para realizar descubrimientos por accidente”. El primer diccionario en castellano donde consta, bajo la acepción de “serendipidad”, es el *Diccionario de Español Actual* de Manuel Seco, Olimpia Andrés y Gabino Ramos (2006), para quienes significa “facultad de hacer un descubrimiento o un hallazgo afortunado de manera accidental”. Finalmente, la Real Academia Española define la serendipia como un “hallazgo valioso que se produce de manera accidental o casual”. Analizando de forma conjunta todas estas definiciones, existe una característica general compartida por todas ellas: el principio de la casualidad o el accidente (lo que la RAE denomina chiripa o carambola). Empero, resulta paradójico que ninguna de estas definiciones incorpore de forma explícita el necesario componente de la sagacidad, tal como propuso expresa y literalmente Horace Walpole a la hora de concebir el término.

Por el contrario, el primer uso científico del término serendipia, atribuido, como se ha referido, a Salvador Luria, sí incorpora el componente de la sagacidad, entendido como la capacidad de discernimiento mental precisa para asumir que una determinada observación científica posee una relevante trascendencia y un significado sustancial. En este sentido, el matiz más revelador en relación al papel de los descubrimientos científicos fortuitos es el que contempla la sagacidad y la preparación mental del investigador para distinguir el alcance de las observaciones que han tenido lugar por, aparentemente, mera casualidad (Thompson y Copeland, 2023). De hecho, es mucho más frecuente en el mundo de la ciencia, como nos confirma su historia, que los investigadores realicen observaciones de gran trascendencia, pero no confirmen la relevancia del evento observado, por lo que dicha observación no se materializa en un importante descubrimiento.

Pero hay que precisar también, que la sagacidad debe constituir un elemento básico e indispensable de la propia mentalidad científica, por lo que siempre debería estar presente en el contexto de los descubrimientos científicos, independientemente de si los fenómenos observados por el investigador estaban previstos o no lo estaban (McCulloch, 2022). Esta apreciación podría dificultar el proceso de imputación serendípica de los

propios descubrimientos. No obstante, podemos afirmar que mientras en un descubrimiento puramente serendípico el factor de “sagacidad” se manifiesta después de la observación inesperada, los descubrimientos no serendípicos, se caracterizarían porque la sagacidad precede y conduce a la observación. Pero esta interpretación también está sujeta a posibles errores de apreciación, pues muchas veces los científicos suelen explicar *a posteriori* el proceso de sus descubrimientos como consecuencia de una hipótesis de trabajo perfectamente planificada con anterioridad, restando importancia al acontecimiento imprevisto, que podría mermar la calidad científica de su trabajo (López-Muñoz et al., 2012).

Dado que la sagacidad es el segundo componente del fenómeno serendípico, el primero, es decir, el “accidente”, es el que realmente establece la diferencia entre un descubrimiento serendípico y no serendípico. En este contexto, el término “accidente” puede poseer dos acepciones distintas. La primera sería el hallazgo debido al azar, que se ajusta menos al constructo de la serendipia, pues el azar o la suerte son conceptos deletéreos, vinculados al paradigma de que los fenómenos naturales están sometidos a una cierta aleatorización. La segunda acepción del término “accidente” se vincularía a la aparición, en el desarrollo del descubrimiento, de algo imprevisto, y esto, parecería más adecuado al fenómeno de la serendipia. Por este motivo, podríamos definir el descubrimiento serendípico como aquel hallazgo de algo no buscado, independientemente del proceso sistemático que condujo a la observación accidental. Y precisamente detrás de esta última propuesta se encuadra la estandarización de la acepción de serendipia en relación con los descubrimientos científicos que propuso el grupo liderado por el doctorando (Baumeister et al., 2010; López-Muñoz et al., 2012), en un planteamiento que concuerda con la definición original propuesta por Horace Walpole, y que se ha aplicado en la presente tesis doctoral.

1.3. La historia de la penicilina como ejemplo prototípico de descubrimiento serendípico

El descubrimiento de la penicilina por parte del científico escocés Alexander Fleming (1881-1955) en 1928 ha sido clásicamente considerado como el típico ejemplo de hallazgo serendípico en el ámbito de la ciencia y de la medicina. Este hecho posiblemente

constituya el más relevante descubrimiento de toda la historia de la medicina, y en su desarrollo, el “accidente” jugó un papel decisivo. Pueden consultarse, en este sentido, los trabajos de Ratcliff (1945) y MacFarlane (1984).

A finales de la década de 1920, Fleming era profesor de Bacteriología en la Universidad de Londres y realizaba su trabajo de microbiólogo en el Hospital de St. Mary (Figura 6). El laboratorio de Fleming podría considerarse como una manifestación de la personalidad un tanto desordenada de su titular, siendo habitual la presencia de placas de Petri contaminadas y otros restos orgánicos abandonados.

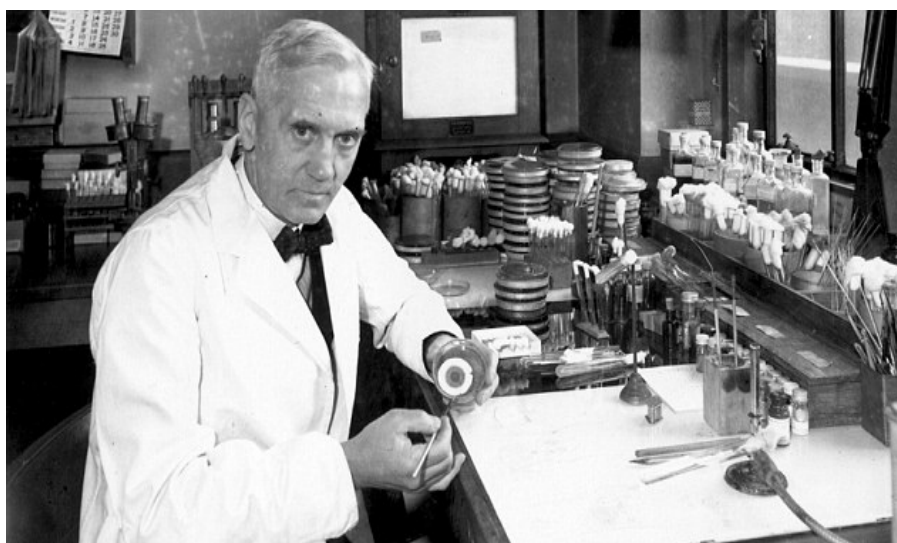


Figura 6: Sir Alexander Fleming (1881-1955) en su laboratorio del Hospital St. Mary de Londres.

Precisamente esta falta de pulcritud influyó de forma decisiva en el descubrimiento del primer agente antibiótico, pues durante el verano de 1928, una espora de un hongo cultivado en el laboratorio situado justo debajo del de Fleming fue arrastrada por el viento, depositándose en una placa de Petri que contenía agar impregnado con *Staphylococcus aureus* y que el científico escocés, como era costumbre, había dejado abierta en su mesa de trabajo durante sus vacaciones estivales. A su regreso, Fleming pudo observar que en dicha placa había crecido un hongo, pero, y esto es lo más relevante, también observó que las colonias de bacterias adyacentes prácticamente habían desaparecido. Este fue el “accidente” que activó el posterior descubrimiento. Al observar la desaparición de las colonias bacterianas, Fleming intuyó que los hongos podrían generar un agente contaminante capaz de frenar la proliferación de los microorganismos patógenos, lo que

pone de manifiesto el segundo componente del descubrimiento serendípico, la “sagacidad”. Tras recabar la ayuda del micólogo irlandés Charles J. La Touche (1904-1981), se determinó el género del hongo contaminante, *Penicillium* (“cepillo” en latín) y, por tanto, se denominó como penicilina a la nueva sustancia antibacteriana descubierta.

El descubrimiento realizado por Fleming fue publicado un año más tarde, en 1929, en la revista *British Journal of Experimental Pathology*, donde se describía como esta nueva sustancia era activa frente a estreptococos, gonococos, neumococos, meningococos y frente al bacilo causante de la difteria, pero carecía de efecto lesivo sobre otros microorganismos, como el bacilo responsable de la fiebre tifoidea o de la tuberculosis (Fleming, 1929). Pero este artículo, titulado “*On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B. Influenzae*”, apenas tuvo difusión entre la comunidad científica, en parte debido al introvertido carácter de Fleming y sus escasas relaciones con otros colegas, lo que hizo que su hallazgo fuera escasamente conocido, relegando el uso del nuevo antibiótico al de un simple antiséptico, destinado al tratamiento de infecciones superficiales, como el carbunco, infecciones nasales y oculares y úlceras cutáneas. El verdadero redescubrimiento de las propiedades antiinfecciosas de la penicilina y de su gran eficacia tras administración sistémica tuvo lugar una década después, en 1940, gracias a los trabajos de Howard W. Florey (1898-1968) y de Ernst B. Chain (1906-1979), de la Sir William Dunn School of Pathology, de la Universidad de Oxford (Abraham et al., 1949), con la ayuda de Dorothy Mary Crowfoot-Hodgkin (1910-1994), química investigadora también de la Universidad de Oxford. Finalmente, en 1945, Fleming, Florey y Chain serían reconocidos con la concesión del Premio Nobel de Fisiología y Medicina “por el descubrimiento de la penicilina y su efecto curativo en varias enfermedades infecciosas”.

En su discurso Nobel, el 10 de diciembre de 1945, Alexander Fleming destacó el papel de la “suerte, fortuna, hado o destino” en su trascendental descubrimiento (Fleming, 1964). Y lo hizo con estas palabras:

“...yo prefiero destacar la verdad, que [el descubrimiento de la penicilina] comenzó como una observación casual. Mi único mérito es que no descuidé la observación y abordé el problema con la visión de un bacteriólogo” (Fleming, 1964, p. 83).

De esta forma, el descubrimiento de la penicilina, donde la intervención del azar fue decisiva, también se benefició de la presencia de una persona curtidora en el estudio del tratamiento de las infecciones y no hubiera tenido lugar si Fleming no hubiese sido un veterano microbiólogo. Por tanto, el resultado final del descubrimiento, es decir la eficacia clínica antibiótica de la penicilina, no puede ser considerado como completamente serendípico, pues se trata de una observación intencionalmente buscada. Si se considera todo el proceso de forma global, podríamos afirmar que no nos encontramos ante un descubrimiento serendípico puro, como se ha considerado tradicionalmente, sino ante un descubrimiento serendípico de carácter mixto, según nuestra propuesta de definición operativa de serendipia (López-Muñoz et al., 2012).

Este ejemplo ilustra la controvertida adscripción que se ha dado a la serendipia en el descubrimiento de los agentes farmacológicos y es en el florido campo de la psicofarmacología donde la serendipia ha desempeñado un papel trascendental que pretendemos clarificar. Por este motivo, en la presente tesis doctoral se pretende dar luz a las controvertidas, confusas y contradictorias interpretaciones publicadas en los últimos 75 años sobre el papel real que ha desempeñado la serendipia en el proceso de descubrimiento y de introducción clínica de los fármacos antidepresivos y eutimizantes. En este análisis consideraremos los diferentes patrones de intervención serendípica, siguiendo la definición operativa de serendipia que ha publicado el grupo dirigido por el doctorando (Baumeister et al., 2010; López-Muñoz et al., 2012).

2. Trastornos del estado de ánimo

Los trastornos del humor o del estado de ánimo constituyen patologías psiquiátricas caracterizadas por la existencia de alteraciones emocionales excesivas, como depresión o euforia (hipomanía o manía), durante periodos prolongados. Tradicionalmente también se han denominado trastornos afectivos, aunque esta nomenclatura ha entrado en desuso en las modernas clasificaciones nosológicas, pues el afecto hace referencia a la expresión externa de un estado emocional puntual, mientras que el término humor o estado de ánimo viene a indicar un estado emocional sostenido en el tiempo, de mayor gravedad y en el que existe una sustancial merma de las capacidades para controlar las emociones.

Estos tipos de trastornos son conocidos desde la Antigüedad clásica, y ya Areteo de Capadocia (siglo II d.C.) describe y engloba en una misma categoría clínica a la depresión y a la manía. No obstante, es en el siglo XIX cuando tienen lugar las primeras descripciones detalladas de la “*folie circulaire*” (1854) (locura circular) por parte de Jean Pierre Falret (1794-1870) y de la “*folie à double forme*” (1854) (locura de doble forma) por Jules Baillarger (1809-1890). Posteriormente, sería el gran precursor de la psiquiatría biológica, Emil Kraepelin (1856-1926), quién definió los límites de la enfermedad y agrupó todas las formas de manía y depresión en una única entidad, que denominó “*psicosis maníaco-depresiva*” (1896), entendiéndose conceptualmente los trastornos afectivos como un “*continuum*” dentro de un mismo cuadro clínico. En la segunda mitad del siglo XX, Karl Leonhard (1904-1988) y otros autores comenzaron a hablar de dos patologías diferentes: los trastornos afectivos unipolares y los trastornos afectivos bipolares. Finalmente, con el advenimiento de sistemas clasificatorios diagnósticos internacionales y estandarizados (*Clasificación internacional de enfermedades - International Statistical Classification of Diseases and Related Health Problems -CIE- de 1948 – Organización Mundial de la Salud-; Manual diagnóstico y estadístico de los trastornos mentales - Diagnostic and Statistical Manual of Mental Disorders -DSM- de 1952 - American Psychiatric Association-*), se ha incidido más en la conceptualización de los trastornos afectivos unipolares y bipolares como dos entidades diferenciables en su presentación clínica y curso evolutivo, algo evidentemente relevante para su manejo terapéutico (López-Muñoz et al., 2023a).

La depresión y la manía podrían ser entendidos, desde una perspectiva simplista, como los extremos de las oscilaciones del estado de ánimo. Sin embargo, representan síndromes en los que la afectación del humor es muy importante y difícil de controlar y se acompañan, además, de alteraciones del pensamiento, psicomotoras, del comportamiento, de la motivación y del funcionamiento psicosocial (Álamo et al., 2009). Los estados depresivos son a menudo más fáciles de entender por la similitud que pueden mostrar con la tristeza y el duelo. Por el contrario, los estados maníacos e hipomaníacos se caracterizan por un humor exaltado, lenguaje rápido y verborreico, aceleración del pensamiento e hiperactividad física y mental, que al inicio pueden ser difíciles de diagnosticar.

2.1. Clasificación de los trastornos del estado de ánimo

El DSM-4 (APA, 2000) venía clasificando los trastornos del estado de ánimo en trastornos depresivos y episodios de tipo maníaco. Estos episodios se combinarían generando diversos patrones, constituyendo así los diferentes trastornos del estado de ánimo (trastornos depresivos, trastornos maníacos y trastornos bipolares). La Figura 7 muestra esta clasificación de los trastornos del humor y la Tabla 1 las características diferenciales de estos trastornos.

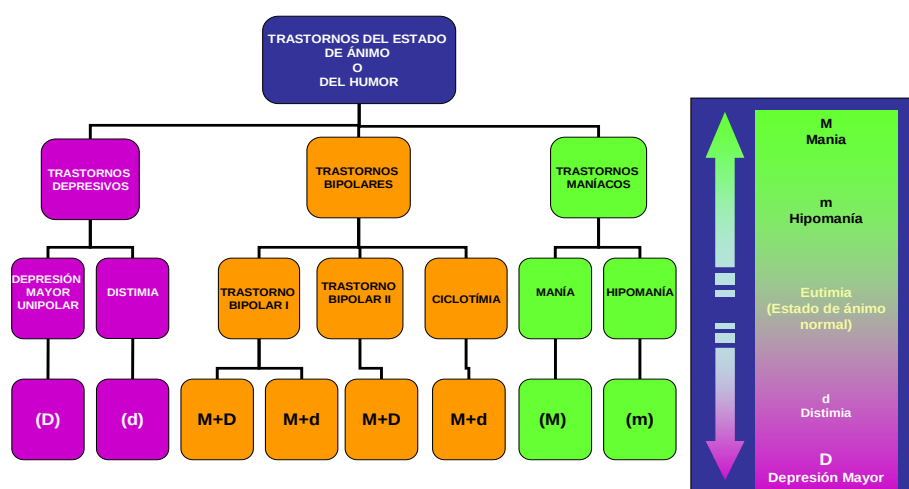


Figura 7: Clasificación de los principales trastornos del estado de ánimo o del humor, siguiendo los criterios DSM-IV.

D (depresión mayor); d (distimia); M (manía); m (hipomanía).

Tabla 1. Características de los principales trastornos del estado del ánimo.

Trastorno	Síntomas maníacos	Síntomas depresivos
Trastorno depresivo mayor	Ausencia de historia de manía o de hipomanía	Historia de episodios depresivos
Trastorno distímico	Ausencia de historia de manía o de hipomanía	Estado de ánimo depresivo leve (no cumple criterios de episodio depresivo mayor), casi todos los días, durante al menos dos años
Trastorno bipolar tipo I	Episodios maníacos o mixtos*	Episodios depresivos mayores
Trastorno bipolar tipo II	Episodios hipomaniacos (sin episodios maníacos o mixtos*)	Episodios depresivos mayores frecuentes.
Trastorno ciclotímico	Numerosos episodios hipomaniacos durante al menos dos años.	Síntomas depresivos frecuentes que no cumplen los criterios de episodio depresivo mayor

*Se entienden como “episodios mixtos” aquellos en que se presentan de forma simultánea en un mismo paciente síntomas maníacos o euforia junto con claros síntomas depresivos.

Sin embargo, el DSM-5, en su actual versión TR (APA, 2022), independiza los trastornos depresivos y los trastornos bipolares y los incluye en epígrafes separados. Dentro de los trastornos depresivos incluye el trastorno depresivo mayor (TDM), la distimia y otros trastornos del humor no especificados, y dentro de los trastornos bipolares, el de tipo I, tipo II, el trastorno ciclotímico y otros trastornos bipolares no especificados.

2.2. Trastornos depresivos

La depresión (del latín *depressus*, que significa "*abatido*", "*derribado*") es un trastorno del humor que se presenta como un estado de abatimiento e infelicidad que puede ser transitorio o permanente. El término médico "depresión" hace referencia a un conjunto de síntomas relacionados con la esfera afectiva, como son la tristeza patológica, el decaimiento, la irritabilidad, que pueden limitar el rendimiento laboral o la actividad diaria habitual, independientemente de que su causa sea conocida o desconocida. Sin embargo, la depresión también puede manifestarse mediante síntomas de tipo cognitivo (relativos al conocimiento), volitivo (relativos a la voluntad) o incluso somático (relativos a lo corporal) (Gutiérrez-Rojas et al., 2020) (Figura 8).

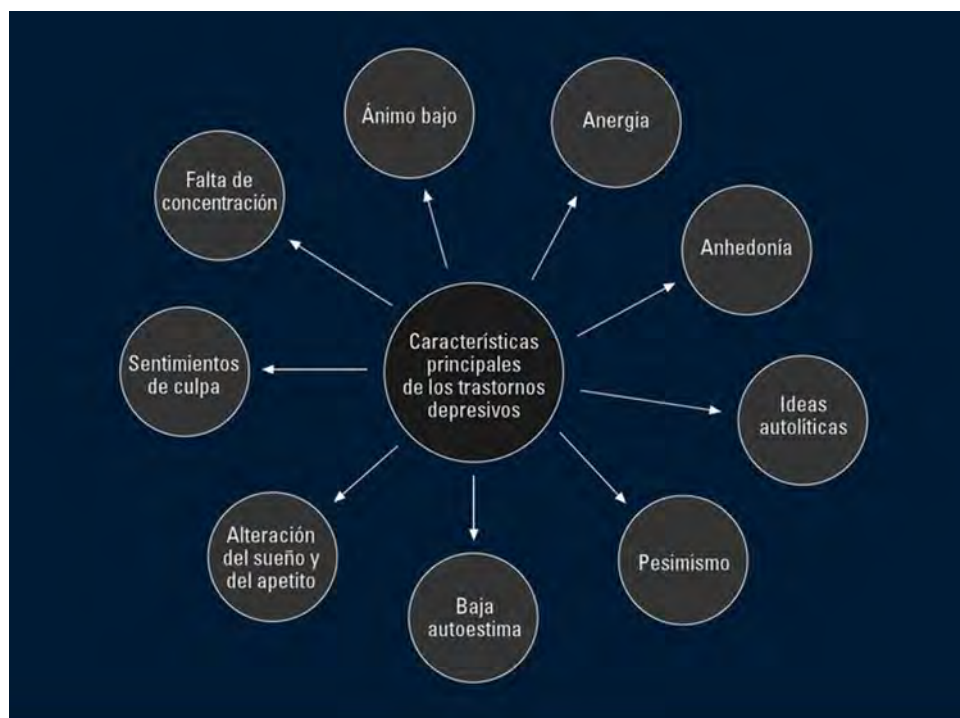


Figura 8: Características principales de los trastornos depresivos.

La depresión es una enfermedad mental grave, que afecta a más de 300 millones de personas en todo el mundo y que causa un gran sufrimiento en el paciente, alterando su actividad laboral, escolar y familiar, pudiendo llevarle incluso al suicidio (López-Muñoz y Álamo, 2009a). Según la Organización Mundial de la Salud (OMS, 2020), la depresión es la primera causa mundial de discapacidad y según los datos del Instituto Nacional de Estadística (INE) (2021) se suicidaron diariamente 11 personas en España.

La depresión es un trastorno mental muy prevalente, con una incidencia del 50% superior en mujeres. Se ha estimado que la tasa de depresión en la población mundial es del 3,8%, alcanzando el 5,7% de la población mayor de 60 años. Esto supone que, aproximadamente, entre 280 y 300 millones de personas padecen este trastorno mental (Gutiérrez-Rojas et al., 2020). Una de cada cinco personas presentará un trastorno del estado de ánimo a lo largo de su vida, que le provocará una discapacidad similar o mayor a la derivada de cualquier otra enfermedad médica crónica (Alcalá, 2006).

Los trastornos del humor ocupan el segundo grupo de trastornos psiquiátricos más frecuentes en la población general, de acuerdo con el clásico estudio ECA (*Epidemiologic Catchment Area Survey*) realizado por el NIMH (Instituto Nacional de Salud Mental de Estados Unidos) entre 1980 y 1984 en cinco ciudades norteamericanas (Bourdon et al., 1992). Los datos de este estudio revelan que entre el 10% y el 20% de los pacientes atendidos en las consultas de Atención Primaria padecerían un trastorno del estado de ánimo y sólo la mitad de los pacientes con un TDM recibirían el tratamiento adecuado, por lo que resulta fundamental el diagnóstico precoz y el tener siempre presente su elevado grado de recurrencia.

En España, en el ámbito de la Atención Primaria, la depresión es el problema de salud mental más frecuente y relevante (Baca et al., 1999), como se ha puesto de manifiesto en diversos estudios epidemiológicos, utilizando criterios diagnósticos estandarizados (Chocrón et al., 1995). La importancia clínica de esta alta prevalencia reside en el elevado grado de incapacidad y repercusión funcional que ocasiona este trastorno. El estudio más relevante sobre la epidemiología de los trastornos psiquiátricos en la población general española se enmarca en el *European Study of the Epidemiology of Mental Disorders*

(ESEMeD) (Alonso et al., 2004). Este estudio, realizado en una muestra representativa de la población general mayor de 18 años de 6 países europeos (Alemania, Bélgica, España, Francia, Holanda e Italia), confirma que un 20% de los participantes españoles había presentado algún trastorno mental en algún momento de su vida, y un 8,4% un trastorno en los últimos 12 meses. El trastorno mental más frecuente fue el TDM, con un 3,9% de prevalencia/año y un 10,5% de prevalencia-vida, mientras la prevalencia-vida de la distimia fue del 3,65% (Haro et al., 2003).

Trastorno depresivo mayor

El TDM se caracteriza por la presencia de episodios depresivos sin estados maníacos o hipomaníacos. Aunque su diagnóstico se puede plantear a partir de datos observacionales poco específicos, como el deterioro en la apariencia y en el aspecto personal, enlentecimiento psicomotriz, tono de voz bajo, facies triste, llanto fácil o espontáneo, disminución de la atención, verbalización de ideas pesimistas, ideas hipocondríacas, alteraciones del sueño o quejas somáticas inespecíficas (Gutiérrez-Rojas et al., 2020), los síntomas depresivos son susceptibles de valoración y ordenamiento según criterios diagnósticos operativos que sean homogéneos entre los diferentes profesionales.

Siguiendo los criterios diagnósticos recogidos en el *Manual Diagnóstico y Estadístico de los Trastornos Mentales* de la American Psychiatric Association, DSM-5-TR (APA, 2022), para el diagnóstico del TDM deben de estar presentes, al menos, cinco de los siguientes síntomas, incluyendo siempre el estado de ánimo depresivo o la pérdida de interés o de la capacidad para el placer (anhedonia): modificaciones del apetito y del peso (aumento o disminución), alteraciones del sueño (insomnio o hipersomnia), alteraciones psicomotoras (agitación o enlentecimiento), fatiga o pérdida de energía, sentimientos de inutilidad o de culpa excesivos o inapropiados, disminución de la capacidad para pensar o concentrarse, pensamientos recurrentes de muerte o ideación suicida recurrente. Todos estos síntomas deben ocasionar un malestar clínicamente significativo o deterioro social y laboral y no pueden ser debidos a los efectos de una sustancia (droga, medicamento) o a una enfermedad orgánica (como, por ejemplo, el hipotiroidismo) y persistir durante más de 2 semanas.

Entre los trastornos del estado de ánimo, el más frecuente es el TDM. Aproximadamente, un 10% de la población adulta lo padecerá en algún momento de su vida y un 4% lo ha padecido en el último año (Alonso et al., 2004). La incidencia anual del TDM es de un 1,5% y la prevalencia a lo largo de la vida para la mujer de un 12 a un 26%, mientras que para el varón es de un 6 a un 12% según diferentes estudios. En la Unión Europea, la prevalencia del TDM es del 6,9% (Wittchen et al., 2011) y en España, su prevalencia en Atención Primaria se ha situado en un rango del 6-15% (Chocrón et al., 1995).

Esta grave enfermedad se asocia estrechamente con la ideación suicida (Terra, 2008). El suicidio constituye la cuarta causa de muerte en el grupo etario de 15 a 29 años y cada año se suicidan más de 700.000 personas. Se estima que más del 60% de los casos de suicidios en la población general tuvo lugar durante el curso de un TDM. Del mismo modo, existen indicios de que la mortalidad por muerte natural y por otras causas (Hatcher-Kay y King, 2003) también se encuentra elevada en la población con trastornos del humor. A título de ejemplo, la mortalidad acumulada en los 6 meses tras un infarto de miocardio pasa de un 3% en el paciente eutímico hasta más del 15% cuando existe un TDM concomitante.

Distimia

La distimia o trastorno depresivo persistente es un estado de ánimo depresivo de carácter crónico, la mayor parte del día de la mayoría de los días, de intensidad leve, que perdura durante, al menos, 2 años. El diagnóstico DSM-5-TR (APA, 2022) exige la presencia de dos, o más, de los siguientes síntomas: pérdida o aumento de apetito, insomnio o hipersomnia, falta de energía o fatiga, baja autoestima, dificultades para concentrarse o para tomar decisiones y sentimientos de desesperanza. Estos síntomas suelen causar un malestar clínicamente significativo, además de deterioro social, laboral o de otras áreas importantes de la actividad del individuo. A pesar de ser considerada como un trastorno leve, por la baja intensidad de los síntomas, su respuesta al tratamiento no suele ser muy satisfactoria.

La prevalencia de la distimia en la población general oscila entre un 3% y un 5% (WHO, 2000). En España, la prevalencia de la distimia en Atención Primaria se ha situado en un

rango del 2-5% (Chocrón et al., 1995). Al igual que la mayoría de los trastornos del ánimo, la distimia es más frecuente en las mujeres que en los hombres (relación 2:1).

Episodios maníacos e hipomaníacos

Los episodios maníacos se caracterizan por un estado de ánimo anormal y persistentemente elevado, expansivo o irritable, que dura al menos 1 semana, o menos si el paciente precisa ser hospitalizado. Atendiendo a los criterios DSM-5-TR, durante el episodio deben existir, al menos, tres de los siguientes síntomas (cuatro si el estado de ánimo es sólo irritable): autoestima exagerada o grandiosidad, disminución de la necesidad de dormir, verborrea, fuga de ideas o pensamiento acelerado, distraibilidad, aumento de la actividad o agitación psicomotora, compras compulsivas, indiscreciones sexuales o inversiones económicas alocadas (APA, 2022). Esta alteración del estado de ánimo es suficientemente grave como para provocar un importante deterioro laboral, de las actividades sociales habituales o de las relaciones con los demás, pudiendo llegar a precisar hospitalización. Los síntomas no deben ser achacados a los efectos fisiológicos directos de una sustancia (droga o un medicamento), ni a una enfermedad médica (como, por ejemplo, el hipertiroidismo). El diagnóstico es más problemático cuando existe irritabilidad, ideas delirantes paranoides, agitación psicomotora y síntomas depresivos con labilidad afectiva.

Por su parte, la hipomanía es un cuadro con características similares a la manía, pero de intensidad más leve, con una duración inferior a una semana (4 días) y que no conlleva una significativa disfunción social y laboral (APA, 2022). El diagnóstico de la hipomanía puede confundirse con algunos trastornos de la personalidad, como el trastorno límite de la personalidad, histriónico, narcisista o el trastorno antisocial. En algunas circunstancias, los pacientes y sus familiares pueden considerar normal la hipomanía y no buscar tratamiento, así como no recordar episodios anteriores.

2.3. Trastornos bipolares

El trastorno bipolar es una patología mental conocida desde la Antigüedad y tiene su origen en el concepto de “manía”, término que procede del griego “μανία”, y que viene

a significar “locura” o “frenesí” (Liddell y Scott, 1940). Conocido clásicamente como enfermedad o psicosis maníaco-depresiva, es una de las entidades psiquiátricas que más atención está recibiendo en los últimos años en la literatura científica, como pusimos de manifiesto en un estudio bibliométrico (López-Muñoz et al., 2006). Se trata de un trastorno del humor grave, complejo y heterogéneo, de carácter crónico, cuyo curso tiene características variables y se caracteriza por la aparición, de forma continua o irregular, de episodios alternativos de manía/hipomanía con eutimia/episodios depresivos (Vieta, 2005): al menos, un episodio maníaco o hipomaníaco, independientemente del número de episodios depresivos que el paciente haya presentado.

Habitualmente se establecen dos tipos en el marco de este trastorno, el trastorno bipolar tipo I, caracterizado por la presencia de, al menos, un episodio de manía con episodios depresivos, y el trastorno bipolar tipo II, que requiere la presencia de algún episodio de hipomanía y, al menos, un episodio depresivo mayor (APA, 2022). En los trastornos bipolares son más frecuentes los episodios depresivos, pero son mucho más determinantes para el diagnóstico los episodios maníacos. Por su parte, la depresión unipolar y la depresión bipolar poseen una sintomatología indiferenciable y el diagnóstico diferencial se realiza gracias a la presencia de episodios de manía o hipomanía en los cuadros bipolares.

El trastorno bipolar es una patología grave y de evolución prolongada y variable, siendo habitual el diagnóstico de varios episodios depresivos, antes de diagnosticar el primer episodio maniaco. Esto condiciona que muchos pacientes sean tratados inicialmente como si presentaran una depresión unipolar. La edad de inicio de estos cuadros se sitúa entre los 15 y 19 años, existiendo muchos casos asociados al consumo de sustancias (60% de los pacientes bipolares) o vinculados a otras patologías orgánicas (Oliva, 2025).

El trastorno bipolar presenta una importante morbilidad (Bauer y Pfenning, 2005), estimándose que su prevalencia a lo largo de la vida está comprendida entre el 1-2% de la población mayor de 20 años (Goodwin y Jamison, 1990). La incidencia del trastorno bipolar tipo I es del 0,8% (0,4 a 1,6%) y la del trastorno bipolar tipo II del 0,5% de la población adulta. La prevalencia para el trastorno bipolar tipo I es similar en hombres y en mujeres, pero el trastorno bipolar tipo II es más común en mujeres. Sin embargo, en la

actualidad se considera que estos datos no son del todo correctos, y se habla del denominado “espectro bipolar”, donde se incluyen los clásicos cuadros tipo I y tipo II y el trastorno ciclotímico, que, en conjunto, podría afectar hasta el 6,5% de la población mundial (Merikangas et al., 2007; Fountoulakis et al., 2012).

Los estudios neurocognitivos han puesto de manifiesto la existencia, en este tipo de pacientes, de un déficit en tres áreas principales, atención, función ejecutiva y procesamiento emocional, lo que puede explicar algunos de los evidentes síntomas de esta patología, como la euforia y la grandilocuencia, que hacen que los pacientes, en fase maníaca, pongan en marcha proyectos excelsos, negocios incoherentes o irracionales, o se embarquen en diferentes aventuras o fantasías románticas, que generan enormes problemas personales y familiares cuando aparece la fase depresiva. De hecho, la ideación suicida está presente hasta en el 50% de los pacientes bipolares, y el suicidio consumado alcanza cifras del 9-15% de los diagnosticados de trastorno bipolar tipo I (Novick et al., 2010). En la fase depresiva se producen la mayoría de los intentos y suicidios consumados.

Trastorno ciclotímico

La ciclotimia o trastorno ciclotímico se caracteriza por oscilaciones en el estado de ánimo que no llegan a alcanzar criterios diagnósticos de trastorno bipolar I o II. Así, los pacientes experimentan síntomas hipomaniacos y en otros momentos síntomas depresivos leves o moderados, que se prolongan durante, al menos, 2 años (APA, 2022). Entre estos altibajos ciclotímicos, el paciente puede sentirse bien y estable. No obstante, a pesar de que los síntomas ciclotímicos son menos intensos que los del trastorno bipolar, es necesario recabar ayuda profesional, pues pueden interferir con las actividades habituales del paciente e, incluso, incrementar el riesgo de desarrollar un trastorno bipolar.

Entre un 3 y un 10% de los pacientes psiquiátricos tratados ambulatoriamente pueden presentar un trastorno ciclotímico. En la población general, la prevalencia en la vida del trastorno se ha estimado en un 1%, igual que con el trastorno bipolar tipo I. Entre el 15-50% de los pacientes ciclotímicos suelen progresar a trastorno bipolar tipo I y, fundamentalmente, a tipo II (Tamayo, 2011).

Finalmente, hay que hacer constar que diferentes patologías, incluyendo enfermedades neurológicas, como la epilepsia, los traumatismos craneoencefálicos o los accidentes cerebrovasculares, o enfermedades endocrinas o metabólicas, pueden generar cuadros maníacos o hipomaníacos, así como el abuso de ciertas sustancias (anfetaminas o cocaína) o en condiciones de abstinencia de alcohol o de sedantes, así como uso de numerosos fármacos (Tabla 2).

Tabla 2. Patologías, sustancias de abuso y fármacos que pueden ocasionar síntomas de manía o depresión y ser susceptibles de imitar a un cuadro bipolar.

Enfermedades	Fármacos	Substancias de abuso
<u>Neurológicas</u>	Opiáceos	Alcohol
Corea de Huntington	Salicilatos	Alucinógenos
Enfermedad de Wilson	Antidepresivos	Anfetaminas
Neoplasias cerebrales	Baclofeno	Cocaína
Talamotomía	Metilfenidato	
Esclerosis múltiple	Disulfiram	
Traumatismo cerebral	Levodopa	
Accidentes cerebrovasculares	Bromocriptina	
Epilepsia del lóbulo temporal	Anticolinérgicos	
	Teofilina	
<u>Otras</u>	Beta estimulantes	
Enfermedad de Cushing	Digital	
Hipertiroidismo	Hidralazina	
Síndrome de Klinefelter	Cimetidina	
Uremia y hemodiálisis	Isoniazida	
Demencia dialítica		
Síndrome carcinoide		
Manía postparto		
Pelagra		
Deficiencia de vitamina B12		
Lupus eritematoso sistémico		

3. Aspectos relevantes de la fisiopatología de los trastornos del humor vinculados al mecanismo de acción de los fármacos antidepresivos y reguladores del humor

3.1. Trastornos depresivos y fármacos antidepresivos

Un importante hecho diferencial en el proceso histórico del conocimiento de la fisiopatología de los trastornos del humor es la estrecha relación de este conocimiento con los efectos neurobiológicos ejercidos por los fármacos antidepresivos (Álamo et al., 1998).

Con anterioridad a la introducción clínica de estos fármacos, las herramientas terapéuticas empleadas en el manejo de los trastornos afectivos eran tremendamente escasas (López-Muñoz y Álamo, 1998; López-Muñoz et al., 2010; 2014a) y su eficacia absolutamente cuestionable desde la realidad actual. Es más, antes de la década de los 50 del siglo XX, cuando tuvo lugar la denominada “revolución de la psicofarmacología”, con el descubrimiento de los primeros agentes de las actuales grandes familias de psicofármacos (López-Muñoz et al., 2000), se pensaba que los síndromes depresivos no estaban mediados por causas biológicas y no debían ser tratados con agentes farmacológicos. Las corrientes psicoanalíticas, doctrinalmente imperantes en la psiquiatría de la época, consideraban la depresión como una manifestación sintomatológica de ciertos conflictos internos de la personalidad. Según estos planteamientos, incluso se estimaba el carácter positivo de estos cuadros, como forma de externalizar toda una serie de conflictos internos inconscientes y traumáticos, que debían ser elaborados por los pacientes. En este marco, el abordaje farmacológico de los síntomas depresivos era contemplado por gran parte de la comunidad psiquiátrica como un auténtico error, pues se impediría al paciente conocer las “verdaderas” raíces de su conflicto interno.

Sin embargo, la introducción clínica de los dos primeros antidepresivos, la imipramina y la iproniazida (López-Muñoz et al., 2008; López-Muñoz y Álamo, 2009b; 2016), desmontó estos planteamientos y la eficacia de estos agentes en el manejo clínico de los pacientes depresivos fue reconocida por toda la comunidad médica. De este modo, se abrió una nueva era en el tratamiento de la depresión, que relegó a la terapia electroconvulsiva de Ugo Cerletti, único tratamiento antidepresivo con significativas

tasas de eficacia, a unas indicaciones muy puntuales (López-Muñoz y Álamo, 2010; López-Muñoz et al., 2010).

El descubrimiento de la eficacia clínica de estos fármacos, durante la también denominada “década dorada de la psicofarmacología”, la década de 1950, estuvo condicionado por la “serendipia” (López-Muñoz et al., 2014b; López-Muñoz y Álamo, 2015), como se defiende en la presente tesis doctoral. La iproniazida, un derivado de la hidracida que se estaba estudiando como antituberculoso, mejoraba el estado de ánimo de los pacientes, independientemente de su actividad antituberculosa, surgiendo el primer antidepresivo inhibidor de la monoamino-oxidasa (IMAO) (López-Muñoz et al., 2007a; 2008; López-Muñoz, 2023a). Y explorando las propiedades antipsicóticas de un derivado de la clorpromazina, se observó que carecía de actividad antipsicótica, pero mejoraba la sintomatología afectiva en algunos pacientes psicóticos, naciendo el primer antidepresivo tricíclico (ADT) (Fangmann et al., 2008; López-Muñoz et al., 2008; López-Muñoz, 2023b).

Una de las principales consecuencias del descubrimiento de los nuevos psicofármacos en la década de 1950, junto a los simultáneos avances habidos en el conocimiento de los aspectos neuroquímicos de funcionamiento del cerebro, como el caso de los neurotransmisores (López-Muñoz y Álamo, 2009c), fue la posibilidad de postular las primeras hipótesis biológicas sobre la génesis de las enfermedades mentales, permitiendo crear los cimientos de la denominada “psiquiatría biológica” (López-Muñoz et al., 2007b). Así pues, los psicofármacos han permitido ir definiendo el proceso neuroquímico sobre el que asienta la enfermedad mental y generar una teoría fisiopatológica sobre la misma. Se trata pues de una aproximación de carácter eminentemente “farmacocéntrico”, según han postulado algunos autores (Ban, 2006).

Esta aproximación teórica, de naturaleza eminentemente farmacocéntrica, abrió las puertas, por primera vez, al conocimiento de las bases neurobiológicas de los trastornos depresivos (López-Muñoz et al., 2007; López-Muñoz y Álamo, 2014). Esta situación se constituyó como un evento singular en la historia de la medicina, pues una gran cantidad de hipótesis etiológicas se fundamentaron en la acción de una serie de fármacos, cuya aplicación a las patologías psiquiátricas fue, en muchos casos, como en el presente,

consecuencia de la intervención del azar. Con la iproniazida y la imipramina (López-Muñoz et al., 2007b), la depresión dejó de ser una enfermedad de la mente para pasar a ser una enfermedad del cerebro. De esta forma, durante la década de 1960 florecieron las teorías monoaminérgicas de la depresión, que postulaban una deficiencia funcional de la neurotransmisión noradrenérgica o serotoninérgica en determinadas áreas cerebrales como causa primordial de estas patologías (Coppen, 1967).

En la década de 1970 aparecieron nuevos antidepresivos heterocíclicos, denominados “antidepresivos atípicos” o “de segunda generación”, que dieron paso, a finales de la década de 1980, a los inhibidores selectivos de la recaptación de serotonina (ISRS), cuyo representante más popular fue la fluoxetina. Posteriormente, surgieron otras familias de agentes antidepresivos, cuya propiedad común es su capacidad para actuar mediante mecanismos monoaminérgicos, aumentando la tasa de monoaminas en la hendidura sináptica (López-Muñoz y Álamo, 2009b; 2012; 2014) (Figura 9).

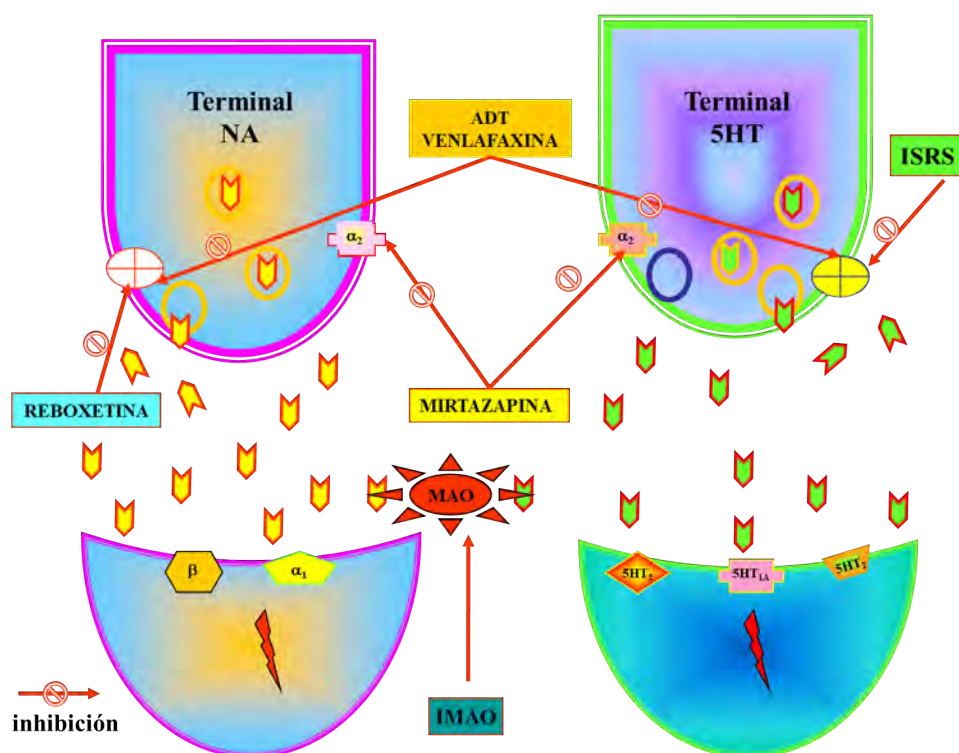


Figura 9: Representación esquemática del mecanismo de acción de los fármacos con actividad monoaminérgica.

Además, han visto la luz algunos antidepresivos que actúan sobre dianas no aminérgicas, aunque no de forma totalmente selectiva (Álamo et al., 2020; Elias et al., 2022). En la primera década del siglo XXI se comercializó la agomelatina, un agonista melatoninérgico, que además bloquea los receptores serotoninérgicos 5-HT_{2A} (Álamo et al., 2008a; 2014a; Álamo y López-Muñoz, 2010; Srinivasan et al., 2016). Más recientemente, se ha comercializado la vortioxetina, un antidepresivo denominado “multimodal” por afectar varios sistemas de neurotransmisión. También se ha introducido en clínica la tianeptina, que es el único antidepresivo considerado como “glutamatérgico” (Álamo et al., 2019). Finalmente, ha sido aprobado un enantiómero de la ketamina, la esketamina intranasal, que antagoniza los receptores glutamatérgicos N-metil-D-aspartato (NMDA) (Kawczak et al., 2024), y es considerado como el primer antidepresivo para el tratamiento de la depresión resistente con rápido inicio de acción (Ionescu et al., 2021).

En la fisiopatología de la depresión participan múltiples mecanismos fisiopatológicos, aunque su patogenia no se conoce en su totalidad (Willner et al., 2013). Sin duda, la “hipótesis monoaminérgica de la depresión” ha sido la más documentada. Según esta hipótesis, la depresión sería la consecuencia de una disfunción de las monoaminas, serotonina (5-HT), noradrenalina (NA) y dopamina (DA), en el Sistema Nervioso Central (SNC) (Álamo et al., 2007; 2014b; Nutt, 2008; López-Muñoz y Álamo, 2009b; 2012; 2014) y se apoya en el hecho de que la gran mayoría de antidepresivos aumentan las tasas de estas monoaminas, a través de diferentes mecanismos. No obstante, esta hipótesis es demasiado simple para explicar una patología tan compleja y heterogénea como es la depresión (Álamo et al., 2020). De hecho, el aumento de monoaminas por los antidepresivos, que se produce minutos tras su administración, debería mejorar la sintomatología de la depresión. Sin embargo, el efecto antidepresivo no se manifiesta hasta pasadas, como mínimo, dos o tres semanas de tratamiento. Por ello, se postula que el aumento de monoaminas en la hendidura sináptica actuaría como un “interruptor” que pondría en marcha una serie de eventos pre y postsinápticos retardados, los denominados mecanismos de transducción, que serían los responsables del efecto antidepresivo (Álamo et al., 2001; Álamo y López-Muñoz, 2012a).

En este marco, en la década de 1980, surgió la teoría de la adaptación receptorial, basada en la coincidencia temporal entre el inicio de la acción antidepresiva y la adaptación de diversos receptores en diferentes regiones del cerebro. Así, la estimulación continuada de receptores por el exceso de monoaminas provocaría la desensibilización de algunos de ellos, lo que modificaría la neurotransmisión sináptica (López-Muñoz et al., 2014a).

La mayoría de los antidepresivos poseen la capacidad de provocar una regulación a la baja (*down regulation*) de varios receptores de monoaminas, habiéndose observado que los autorreceptores presinápticos dopaminérgicos y los α_2 -adrenérgicos, así como los receptores β -adrenérgicos postsinápticos, disminuyen en densidad y sensibilidad. Estos cambios adaptativos coinciden en el tiempo con la aparición de la mejoría clínica observada con los antidepresivos. Sin embargo, la hiporregulación de los receptores β -adrenérgicos no es producida por todos los ISRS y los bloqueantes de dichos receptores carecen de efecto antidepresivo, lo que cuestiona que este mecanismo sea el único responsable del efecto terapéutico de los antidepresivos (Álamo et al., 2020). De modo similar, se observó que el inicio de la acción antidepresiva de los ISRS coincidía temporalmente con la desensibilización de los autorreceptores presinápticos 5-HT_{1A}, hecho que se acompaña de un aumento de la síntesis y la liberación de 5-HT, fundamentalmente en el hipocampo. Pero este efecto no se observa con los antidepresivos tricíclicos (ADTs). Por tanto, más que responsable del efecto terapéutico, la regulación a la baja de los receptores monoaminérgicos por diversos antidepresivos podría ser un marcador de un mecanismo de adaptación más complejo a nivel de la transducción.

Precisamente, los antidepresivos, al aumentar la tasa de monoaminas, NA y 5-HT (primeros mensajeros) en la hendidura sináptica, estimularían a sus respectivos receptores postsinápticos acoplados a proteínas G (PG) (González-Maeso et al., 2006), poniendo en marcha una cascada de eventos intracelulares. Inicialmente, un incremento de la síntesis de segundos mensajeros (AMPc, DAG, etc.) que, activarían a las proteincinasas (PK), consideradas terceros mensajeros. Estas activarían, por fosforilación, a los factores de transcripción, cuartos mensajeros, responsables de la síntesis de proteínas, como la enzima tirosina-hidroxilasa (Tir-OH), paso limitante en la síntesis de catecolaminas, la proencefalina (Pro-Enk), o las neurotrofinas BDNF (*brain-derived neurotrophic factor*) y el VEGF (*vascular endothelial growth factor*), relacionados con el efecto antidepresivo.

Así pues, se postuló que en la depresión podrían existir alteraciones de las vías de transducción (Figura 10) que, hipotéticamente, podrían ser reparadas por los antidepresivos a través de los mecanismos comentados previamente (Krishnan y Nestler, 2008).

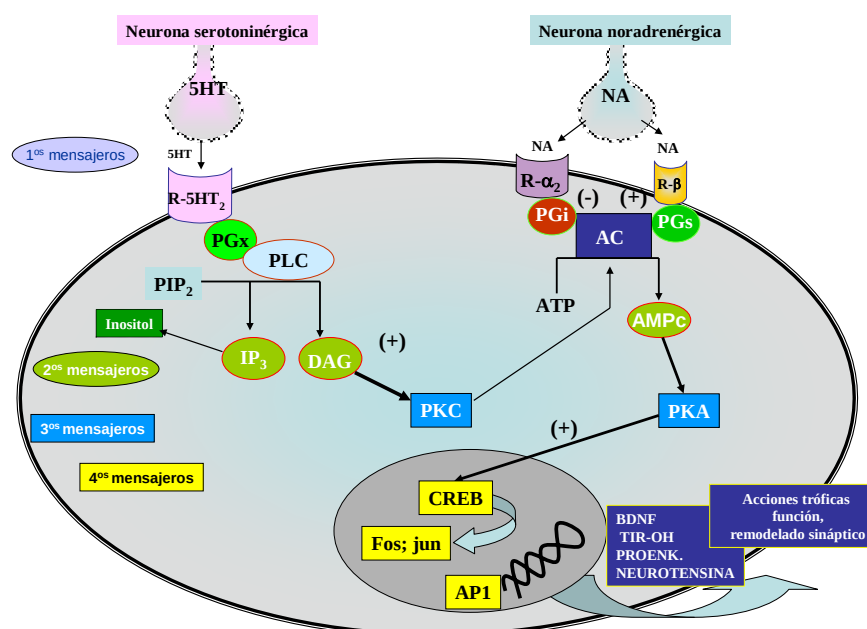


Figura 10: Mecanismos de transducción de las señales monoaminérgicas.

Las vías de transducción puestas en marcha por las distintas monoaminas no son idénticas, ya que estas actúan sobre diferentes receptores (López-Muñoz et al., 2012; 2014). Así, la 5-HT en el hipocampo actúa sobre los receptores 5-HT_{1A}, acoplados a la proteína G_i (inhibidora), que influiría en la vía de la MAPK (*mitogen-activated protein kinase*) dependiente del calcio, mientras que la NA actúa sobre los receptores β-adrenérgicos, acoplados a la proteína G_s (estimuladora), por lo que activará a la adenilato-ciclase (AC), aumentando la producción de adenosina-monofosfato cíclico (AMPc), que activa a la PKA. Las dos vías comentadas van a tener un eslabón común intranuclear que es la fosforilación del CREB (*cAMP response element binding*), que modifica la transcripción genética, facilitando la generación de una serie de proteínas, entre las que destaca el BDNF (Figura 10). El CREB parece ejercer una gran importancia en la fisiopatología y tratamiento de la depresión, encontrándose disminuido en cerebros de sujetos suicidas. El CREB, en los pacientes que responden al tratamiento, aumenta con la administración prolongada de ISRS, ADTs e IMAOs, así como con la electroconvulsivoterapia (ECT) aguda. Por tanto, operando a diferentes niveles (NA o 5-

HT), los antidepresivos pueden actuar sobre elementos comunes, como el CREB y la neurotrofina BDNF (Castren et al., 2007), que favorecen la neurogénesis y neuroplasticidad en las áreas cerebrales relacionadas con la depresión.

Asimismo, es conocido que en la fisiopatología de la depresión participan factores genéticos, responsables de la vulnerabilidad, sobre los que actúan factores adversos, como un entorno cultural y social hostil, así como el estrés y otros factores que condicionan una serie de cambios funcionales y estructurales que afectan también a la neuroplasticidad y neuroadaptación cerebral. Y, además, existe una gran evidencia científica de que los antidepresivos pueden corregir dichas alteraciones. En líneas generales, podemos considerar que, a nivel del funcionamiento del SNC, existe un equilibrio entre factores neurotróficos protectores, entre los que se encuentran la familia de las neurotrofinas, NGF (*nerve growth factor*) y BDNF, junto a otros factores, como el IGF (*insulin-like growth factor*), FGF (*fibroblast growth factor*) o VEGF, y la presencia de factores agresivos, muchos de ellos en íntima relación con el estrés, como son el cortisol, los aminoácidos excitatorios o los procesos inflamatorios, entre otros (Nandam et al., 2020; Patel et al., 2023). En caso de desequilibrio, los antidepresivos potenciarían los factores protectores, a través del CREB y las neurotrofinas, restaurando los daños ocasionados por los factores agresivos (Figura 11).

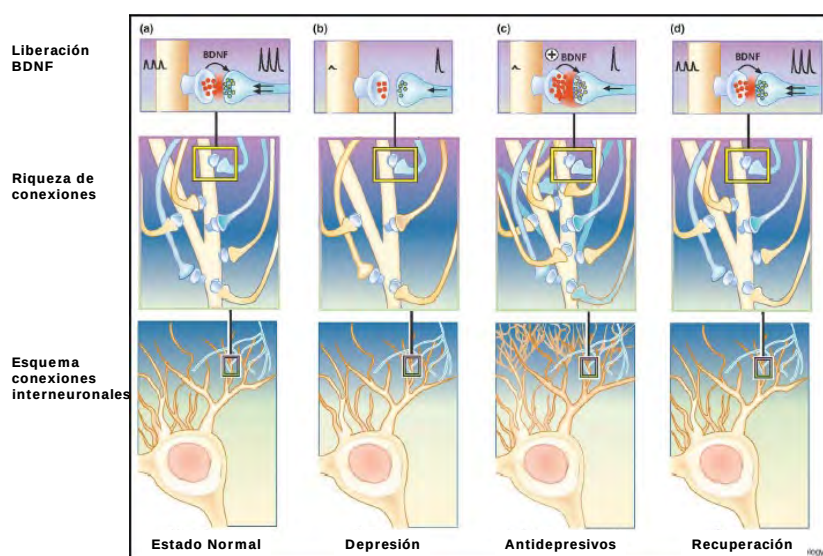


Figura 11: Modelo del efecto de la depresión y de la administración de antidepresivos sobre la liberación de BDNF y las conexiones neuronales responsables de la actividad interneuronal en el cerebro.

Como se ha comentado, la administración crónica de antidepresivos, así como la TEC, aumenta la expresión del BDNF y de sus receptores específicos TrkB (*tropomyosin receptor kinase B*) (Casarotto et al., 2021) en el hipocampo, corteza cerebral y en zonas ricas en neuronas colinérgicas, dopaminérgicas y serotoninérgicas, donde su papel es fundamental en la supervivencia, diferenciación, crecimiento y plasticidad sináptica. Este efecto es sincrónico con el efecto terapéutico. También se ha constatado un aumento de los niveles plasmáticos de BDNF en pacientes tratados con antidepresivos, lo que podría constituir un marcador biológico periférico de la respuesta antidepresiva (Matrisciano et al., 2009; Meshkat et al., 2022). En humanos, el tratamiento prolongado durante varias semanas con antidepresivos aminérgicos ocasiona una regulación al alza de la vía BDNF-TrkB en la corteza prefrontal y el hipocampo, que se acompaña de una respuesta antidepresiva y un aumento de la resiliencia al estrés (Zanos y Gould, 2018). Pero estos efectos se observan también con la agomelatina, un antidepresivo melatoninérgico (López-Muñoz et al., 2016), así como con la tianeptina, un antidepresivo glutamatérgico. Incluso la ketamina aumenta rápidamente, en menos de una hora, los niveles de BDNF, lo que se asocia con un aumento de la neurogénesis y con los efectos antidepresivos rápidos de este agente (Ma et al., 2017). Por tanto, parece existir una correlación temporal entre el aumento de BDNF y el efecto antidepresivo, que no es exclusivo de los antidepresivos de mecanismos monoaminérgicos. Recientemente se ha descrito que los antidepresivos se unen al receptor TrkB y aumentan la señalización del BDNF (Casarotto et al., 2021). Este hecho podría explicar que los antidepresivos puedan favorecer directamente la neuroplasticidad neuronal por su afinidad sobre los receptores TrkB, sin necesidad de la intervención de otros tipos de receptores.

La hiperactividad del eje hipotálamo-hipófiso-adrenal (HHA), una característica fundamental de las situaciones que cursan con estrés, puede desempeñar también un relevante papel en el desencadenamiento y curso de la depresión (Menke, 2019), al alterar la neurogénesis hipocampal. Este fenómeno tiene lugar por la desensibilización del receptor corticosteroide (RC), lo que impide la inhibición de la secreción de CRF (*corticotropin releasing factor*) que aumenta la liberación de la ACTH (hormona adrenocorticotropa) y del cortisol (Stalh y Wise, 2008), todos ellos responsables de una serie de síntomas y signos relacionados con la depresión (Nandam et al., 2020). En

pacientes con TDM, se ha constatado que el tratamiento crónico con antidepresivos de diferentes familias farmacológicas, así como la TEC, normaliza la sensibilidad de los RC, lo que restablece el mecanismo de retroalimentación, disminuye la hiperactividad del eje HHA y normaliza los niveles de cortisol (Anacker et al., 2011). Estos hechos se relacionan con el efecto antidepresivo.

Las vías glutamatérgicas también parecen jugar un destacado papel en la fisiopatología de los cuadros depresivos (Kugaya y Sanacora, 2005; Álamo et al., 2014b). El glutamato (GLU) es el principal neurotransmisor excitatorio en el SNC, donde tiene una distribución amplia y ubicua, conectando zonas corticales con regiones subcorticales, tales como el locus coeruleus o los núcleos del rafe, muy relacionadas con la afectividad. El GLU modula vías monoaminérgicas, por lo que participa en una amplia gama de funciones relacionadas con el estado de ánimo, cognición y memoria (Geddes et al., 2015). Cuando existe una hiperfunción glutamatérgica, como sucede en algunos tipos de depresión, el exceso de GLU estimula los receptores NMDA y es claramente neurotóxico (Kalkman, 2019) y cuando se antagonizan estos receptores se produce un incremento de la neurotrofina neuroprotectora BDNF (Gariboya et al., 2019). Algunos agentes moduladores de la función glutamatérgica muestran eficacia experimental y clínica antidepresiva y diversos antidepresivos, como los ADTs, IMAOs o ISRS, en administración prolongada, antagonizan el locus de glicina del receptor NMDA, por lo que lo desensibilizan, contrarrestando la hiperfunción glutamatérgica propuesta en la depresión. Estos datos, junto con la eficacia clínica antidepresiva del antagonista de estos receptores, la ketamina (Álamó et al., 2014c; Amidfar et al., 2019), y la presencia de alteraciones de los receptores NMDA en pacientes que han cometido suicidio (Gray y Hyde, 2015), apoyan la participación de los mecanismos glutamatérgicos en un posible mecanismo de acción común de los antidepresivos (Frizzo, 2019).

La esketamina, el S-enantiómero de la ketamina, posee una alta afinidad por los receptores NMDA (Wei et al., 2020), sobre los que actúa como un antagonista no competitivo. Este fármaco, administrado a dosis subanestésicas, bloquea selectivamente los receptores NMDA de las interneuronas inhibitorias gabaérgicas, frenando la liberación de ácido γ -aminobutírico (GABA) por lo que se disparan las neuronas glutamatérgicas piramidales que descargan intensamente en el hipocampo (Widman y

McMahon, 2018). Este exceso de GLU estimularía fundamentalmente a los receptores AMPA (ácido propiónico α -amino-3-hidroxi-5-metil-4-isoxazol), ya que los NMDA estarían bloqueados por la propia esketamina. El estímulo de los receptores AMPA aumenta la liberación de BDNF de forma rápida y activa la vía de transducción de la mTOR (*mammalian target of rapamycin*) (Henley y Wilkinson, 2026), que incrementa de forma rápida la síntesis nuevos receptores AMPA y su externalización a la superficie neuronal, amplificando el efecto. Además, la estimulación de estas vías eleva la síntesis de proteínas sinápticas, como el propio BDNF, la sinapsina I, la GluA1-2, la PSD95 (*postsynaptic density protein 95*) y la proteína Arc del citoesqueleto, que promueven la sinaptogénesis, mejorando la actividad sináptica (Strasburguer et al., 2017). Estos efectos se producen muy rápidamente, entre 1 y 2 horas, relacionándose temporalmente con su efecto antidepresivo (Figura 12). De hecho, la esketamina es, de momento, el único antidepresivo comercializado con un inicio rápido de la acción antidepresiva.

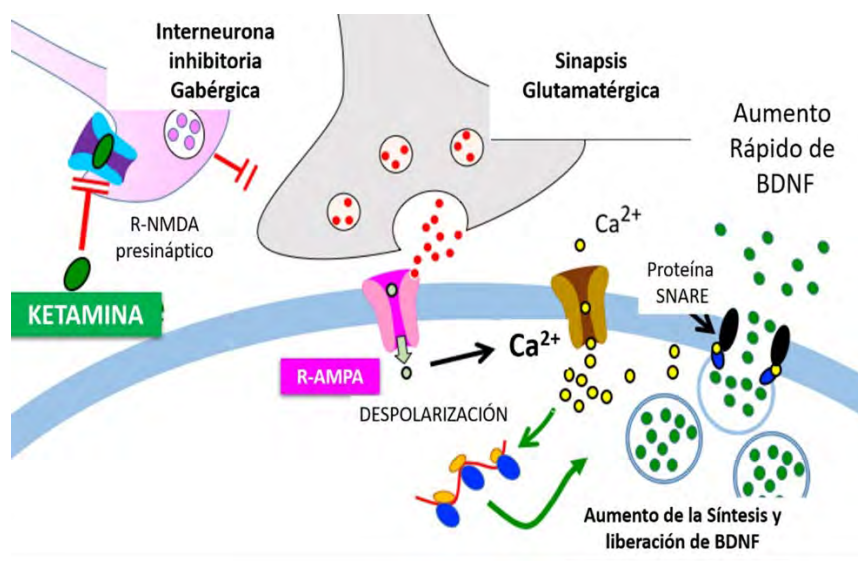


Figura 12: Representación esquemática del hipotético mecanismo de acción antidepresivo de la esketamina: la desinhibición de la interneurona gabaérgica por bloqueo de los receptores NMDA inhibe la liberación de GABA, por lo que se dispara la neurona piramidal glutamatergica. En consecuencia, se libera glutamato, que estimula los receptores AMPA y activa la producción de BDNF.

Finalmente, es preciso comentar que, más allá de las monoaminas y el GLU, existen componentes neurológicos, neuropeptídicos, endocrinológicos, metabólicos, opioidérgicos e inflamatorios y probablemente algunos aún no explorados, implicados en la fisiopatología de la depresión (Maletic et al., 2007; Belmaker y Agam, 2008). El

conocimiento de estos factores tiene gran interés, ya que podrían constituir futuras dianas terapéuticas antidepresivas (Álamo et al., 2020).

El sistema opioide ha sido implicado en la fisiopatología de la depresión y en el mecanismo de acción de los antidepresivos (Ragguett et al., 2019; Jelen et al., 2022). De hecho, se sabe que algunos opiáceos podrían tener cierto poder antidepresivo experimental y que la TEC y algunos antidepresivos incrementan los niveles de opioides endógenos (Peciña et al., 2019). Además, históricamente, los opioides han sido empleados en el manejo de los trastornos depresivos, incluso mucho antes de que se introdujeran en clínica los ADTs y los IMAOs, aunque su potencial adictivo siempre ha desaconsejado su empleo como antidepresivos.

Algunos ADTs, así como la mianserina y la mirtazapina, muestran afinidad por los receptores opioides kappa (κ) y los antagonistas de los opioides inhiben su efecto antidepresivo. La tianeptina, antidepresivo glutamatérgico, también es agonista del receptor opioide mu (μ), si bien su potencia es unas 500 veces inferior a la de la morfina. Puesto que con tianeptina no se presenta tolerancia ni síndrome de abstinencia, se postula que podría actuar como un agonista sesgado del receptor μ , poniendo en marcha vías de transducción diferentes a la de los opioides clásicos, pese a actuar sobre el mismo receptor (Nishio et al., 2024). Finalmente, comentar que la ketamina y la tianeptina también podrían utilizar mecanismos opioides en su efecto antidepresivo, merced a su interacción entre el receptor NMDA y el sistema opioide. En la actualidad, se está desarrollando una amplia investigación encaminada a obtener algún agente opioide con propiedades antidepresivas que no sea adictivo (Ragguett et al., 2019).

La neuroinflamación y la inmunidad parecen jugar algún papel en la fisiopatología de los trastornos depresivos. Los pacientes con depresión presentan a menudo una respuesta inmune elevada, junto a factores proinflamatorios, como el factor de necrosis tumoral TNF-alfa, proteína C reactiva, IL-6 y antagonista del receptor de interleucina-1, mientras que los pacientes con trastornos somáticos que cursan con inflamación presentan un mayor riesgo de desarrollar depresión (O'Brien et al., 2004; McNally et al., 2008). Se ha comprobado que tanto los ISRS como los antidepresivos duales o mixtos pueden reducir la expresión de citoquinas proinflamatorias, particularmente la IL-6 y TNF-alfa, a la vez

que aumentan los niveles de la interleucina antiinflamatoria IL-10. En definitiva, algunos antidepresivos parecen capaces de reducir la "tormenta de citoquinas" relacionada con la inflamación aguda (Mahli y Mann, 2018).

3.2. Trastorno bipolar y reguladores del humor

En relación con el trastorno bipolar, los mecanismos etiopatogénicos de esta patología son aún más desconocidos que en el caso de los trastornos depresivos y la aproximación "farmacocéntrica" a su fisiopatología es todavía más evidente. De hecho, gran parte de los procesos neuroquímicos subyacentes en esta patología se han conocido gracias a la introducción clínica del litio en 1949 (Cade, 1949; López-Muñoz et al., 1999) y el posterior uso de los fármacos antiepilépticos. Las publicaciones sobre el mecanismo de acción del litio y otros fármacos eutimizantes se han ido incrementando durante las últimas tres décadas y esto ha supuesto un gran avance en el conocimiento de la etiopatogenia del trastorno bipolar (López-Muñoz et al., 2006).

Sin embargo, a pesar de estos avances, existen diferentes problemas que limitan el conocimiento de las bases etiopatogénicas del trastorno bipolar y del mecanismo de acción de los fármacos eutimizantes. Entre ellos puede mencionarse la falta de modelos animales homologados de estos trastornos o la complejidad de la fisiopatología del trastorno bipolar, enfermedad en la que se estima la existencia de alteraciones en la regulación de un elevado número de vías de neurotransmisión interconectadas (Manji et al., 1995; Lenox et al., 1998; Álamo et al., 2008b).

Desde la perspectiva histórica, las primeras hipótesis sobre el mecanismo de acción de los agentes eutimizantes o reguladores del humor se fundamentaron en una posible modificación del transporte iónico, sobre todo de sodio, y en la facultad de alterar las propiedades electrofisiológicas de las membranas neuronales, dado que el único agente terapéutico eficaz disponible en esos momentos era el litio, esto es, un catión. Posteriormente, tras descubrirse el papel jugado por los antidepresivos en la modificación de los mecanismos de neurotransmisión en el SNC y su efecto positivo en la mejoría de la sintomatología de los cuadros depresivos, se incrementó la investigación en aspectos relativos a estos mecanismos, como las alteraciones de la neurotransmisión

monoaminérgica, colinérgica o gabaérgica o las modificaciones del transporte de la colina y los aminoácidos (Cuenca et al., 2000; Chen y Manji, 2006). Finalmente, hay que reseñar que las principales líneas de investigación durante los últimos años en este ámbito están enfocadas en dilucidar los mecanismos moleculares intraneuronales relacionados con la transducción de señales, que constituyen una complicada cascada bioquímica en la que vienen a converger diferentes sistemas de neurotransmisión, destacando las vías de los fosfoinositoles y de la AC. Y todo ello intermediado por las PG (Waldmeier, 1990), en vías que activan diferentes factores génicos de transcripción a nivel nuclear (Quiroz et al., 2004; Chen y Manji, 2006). Del mismo modo, se ha podido constatar el relevante papel neuroprotector de los factores de crecimiento neuronal, puesto de manifiesto ya, en 1994, en el caso de las sales de litio (D'Mello et al., 1994; Volonte et al., 1994).

Los canales iónicos presentes en las membranas neuronales, como los canales iónicos voltaje-dependientes de sodio, potasio y calcio, parecen jugar un gran papel en la etiopatogenia de numerosas patologías psiquiátricas, incluyendo el trastorno bipolar. El canal de sodio dependiente de voltaje es el responsable de generar los potenciales de acción en respuesta a la despolarización parcial de la membrana neuronal, y sobre este canal actúan la mayor parte de los fármacos antiepilépticos, tanto clásicos (carbamazepina y valproato), como algunos modernos (lamotrigina o topiramato) (Figura 13). Estos fármacos, al bloquear el canal del sodio, ocasionan una estabilización de la membrana, generando un freno en la liberación presináptica de neurotransmisores excitatorios, como el GLU y el aspartato (Wang et al., 1996). Este mecanismo de acción podría explicar parte de la eficacia de lamotrigina en el tratamiento del trastorno bipolar, aunque su mecanismo de acción eutimizante concreto continúa sin estar dilucidado (Álamo et al., 2008b).

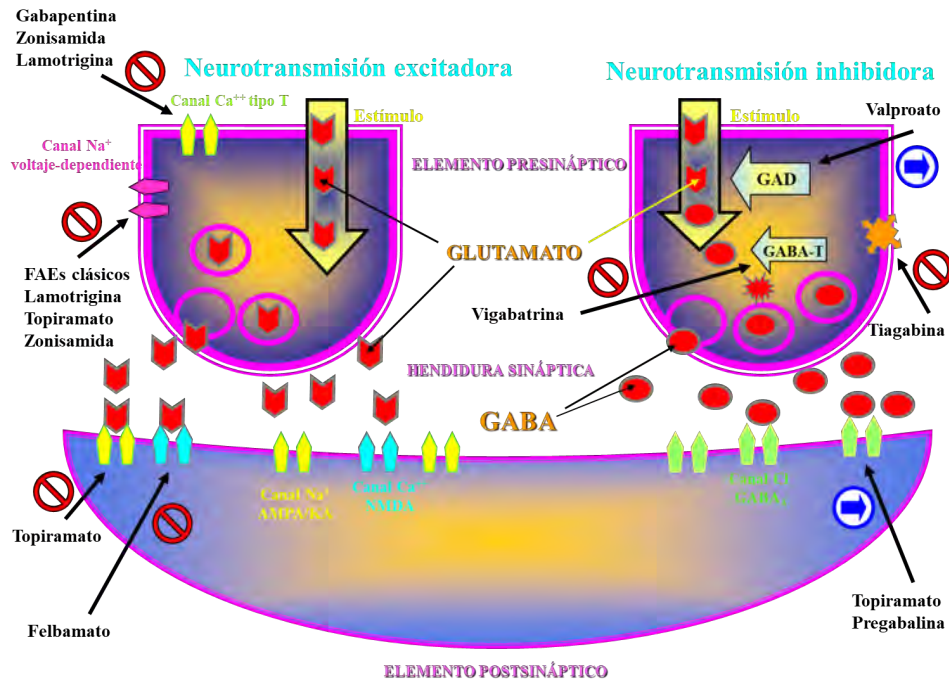


Figura 13: Representación esquemática del mecanismo de acción de los fármacos antiepilépticos.

El litio también es capaz de utilizar, aunque en pequeña proporción, la bomba sodio/potasio ATPasa dependiente, y en pacientes bipolares se ha constatado que existe una disminución de la actividad de esta bomba a nivel eritrocitario (Hokin-Neaverson y Jefferson, 1989a), que se normaliza tras el tratamiento crónico con litio (Hokin-Neaverson y Jefferson, 1989b; Dubovsky, 1995). Todo ello sugiere la implicación de la bomba sodio/potasio ATPasa dependiente en la fisiopatología del trastorno bipolar y en el mecanismo de acción de este fármaco. El déficit de esta bomba ocasionaría un aumento de la excitabilidad neuronal, responsable del proceso maníaco, y, además, una disminución de la liberación de neurotransmisores, evento asociado con la fase depresiva (El-Mallakh y Wyatt, 1995). Finalmente, comentar que las sales de litio, al igual que diferentes agentes anticonvulsivantes, como la lamotrigina, ocasionan, a través de diferentes mecanismos, una disminución de la entrada neuronal de calcio (Nonaka et al., 1998). En el caso de la carbamazepina se ha estimado que pueda ser debido a su acción directa sobre el receptor NMDA.

Además, es conocido el papel que desempeñan los sistemas de neurotransmisión monoaminérgicos en el funcionalismo cerebral, y actuando sobre ellos pueden controlarse los síntomas de numerosas patologías psiquiátricas, entre las que se pueden encontrar

todos los trastornos del humor, incluyendo el trastorno bipolar. A título de ejemplo, la administración de litio aumenta los niveles de 5-HT en la hendidura sináptica (Hotta y Yamawaki, 1988; Tamayo et al., 2004), gracias a la disminución de la sensibilidad de los receptores somatodendríticos 5-HT_{1A}, lo que podría explicar su eficacia en la fase depresiva del trastorno bipolar. En el caso de la lamotrigina sucede algo similar (Vinod y Subhash, 2002). Este antiepiléptico moderno es capaz de antagonizar los receptores postsinápticos serotoninérgicos tipo 3 (5-HT₃) (Ketter et al., 1997) y de regular la recaptación de ciertas monoaminas, básicamente la 5-HT, aunque sólo a concentraciones elevadas, lo que puede traducirse a nivel clínico en un incremento de la neurotransmisión serotoninérgica, que podría contribuir a explicar su utilidad en la estabilización de los episodios maníacos y/o mixtos (incluyendo cicladores rápidos), así como su eficacia en la prevención y tratamiento de los episodios depresivos del trastorno bipolar e, incluso, de la depresión unipolar (Southam et al., 1998). Otros autores han confirmado que la lamotrigina incrementa el funcionalismo dopaminérgico y ocasiona una regulación a la baja (*down regulation*) de la densidad de los receptores β -adrenérgicos, un efecto que es compartido con muchos agentes antidepresivos (Southam et al., 1998).

En relación a los antiepilépticos clásicos, la carbamazepina disminuye el recambio de DA y la liberación de NA, y aumenta los niveles sinápticos de 5-HT (Post et al., 1992), y el valproato aumenta la liberación sináptica de NA y ocasiona un incremento de la neurotransmisión serotoninérgica, mediante la hiposensibilización de los receptores 5-HT_{1A} (Shiah et al., 1997).

Aunque el mecanismo exacto por el que los fármacos antipsicóticos atípicos ejercen su actividad antimaníaca no está dilucidado claramente, podría relacionarse con las especiales propiedades neurobioquímicas de estos agentes y su acción sobre los sistemas de neurotransmisión monoaminérgicos, incluyendo sus característicos perfiles receptoriales (Tohen y Vieta, 2009). Además de bloquear los receptores dopaminérgicos D₂, los antipsicóticos atípicos también antagonizan los receptores serotoninérgicos 5-HT₂, básicamente los 5-HT_{2A} y 5-HT_{2C}, y algunos de ellos, como el aripiprazol, la ziprasidona y la asenapina, son agonistas parciales de los receptores 5-HT_{1A} (López-Muñoz y Álamo, 2011), lo que podría traducirse en una potenciación de la neurotransmisión noradrenérgica y dopaminérgica (Li et al., 2012).

Por su parte, el metabolito activo de la quetiapina, la norquetiapina, también se comporta como agonista parcial de los receptores 5-HT_{1A}, facilitando la transmisión serotoninérgica, además de inhibir intensamente el transportador de NA, lo que aumenta el funcionalismo noradrenérgico (López-Muñoz and Álamo, 2013; De Miranda et al., 2017). Del mismo modo, la lurasidona presenta un especial perfil farmacológico, también agonista parcial del receptor 5-HT_{1A} y antagonista del receptor 5-HT₇ (Ishibashi et al., 2010). Estos perfiles bioquímicos, junto a los ensayos clínicos específicos con resultados positivos que se han realizado, han posibilitado el uso de ambos antipsicóticos, en monoterapia, en el tratamiento de los episodios depresivos del trastorno bipolar. La estela de la lurasidona fue seguida por la lumateperona, un agente con una moderada capacidad para inhibir el transportador de la 5-HT y modular la liberación de DA y GLU (Greenwood et al., 2021), siendo también autorizado para el tratamiento de la fase depresiva del trastorno bipolar. Por tanto, se puede estimar que las propiedades antidepresivas de algunos antipsicóticos atípicos podrían deberse a su capacidad de modular los tres sistemas monoaminérgicos, noradrenérgico, serotoninérgico y dopaminérgico, implicados en la fisiopatología de la depresión (Álamó y López-Muñoz, 2012b).

Por otro lado, en la patogenia de algunas enfermedades neuropsiquiátricas, incluido el trastorno bipolar, jugaría su papel un desequilibrio en la función neurotransmisora de los aminoácidos, fundamentalmente los de naturaleza excitadora, como el GLU y el aspartato, y los de naturaleza inhibidora, como el GABA. El correcto equilibrio entre las actividades mediadas por el GLU, principal neurotransmisor excitador, y el GABA, principal neurotransmisor inhibidor, es básico para mantener una correcta función cerebral. El GLU ejerce su acción sobre dos tipos de receptores: unos receptores ionotrópicos ligados a canales, básicamente el receptor NMDA, asociado al calcio, y el receptor AMPA-kainato, asociado al sodio, y otros receptores metabotrópicos (mGlu), de los que existen al menos ocho subtipos. Por su parte el GABA ejerce su acción sobre el receptor ionotrópico GABA_A, asociado a un canal de cloro (Bormann, 2000).

La importancia de la estimulación del receptor NMDA en el espectro bipolar viene dada, entre otros factores, por su implicación en los fenómenos de atrofia y muerte neuronal

que se observan en el hipocampo en situaciones de estrés mantenido. De hecho, este constituye uno de los factores etiopatogénicos más relacionados con los trastornos del humor, en general. También es conocido que el estrés continuado ocasiona la atrofia de dendritas apicales de las neuronas piramidales CA3 (Duman, 2000; Manji et al., 2000). Alguno de estos efectos, subsiguientes al incremento de aminoácidos excitatorios en el hipocampo, es antagonizado por la fenitoína, un anticonvulsivante clásico que bloquea la liberación de glutamato y los canales T del calcio, que son estimulados por el GLU (McEwen y Magarinos, 1997). Aunque no se conoce el mecanismo por el que el estrés incrementa los niveles de GLU, parece factible que el bloqueo de los receptores NMDA no sólo prevenga la atrofia dendrítica ocasionada por el estrés, sino que este hecho esté relacionado con los efectos terapéuticos observados en los pacientes con trastorno bipolar.

Hay que destacar también las estrechas interrelaciones entre el receptor NMDA y el BDNF: mientras esta neurotrofina ejerce un efecto protector neuronal, el receptor NMDA, al incrementar el calcio intracelular, ejerce un efecto neurotóxico. En este sentido, se ha demostrado que el BDNF disminuye la entrada de calcio en las neuronas, de manera parecida al efecto ejercido por antagonistas del receptor NMDA (Brandoli et al., 1998).

Desde el punto de vista farmacológico, la carbamazepina y el valproato son capaces de disminuir el funcionalismo glutamatérgico, bien actuando directamente sobre los receptores NMDA y AMPA-kainato, o bien incrementando el metabolismo del GLU, activando la enzima glutamino-sintetasa a nivel de las células de glía (Li et al., 2002). Otros antiepilépticos modernos, como la lamotrigina o el topiramato, también son capaces de modular las vías de neurotransmisión de los aminoácidos excitatorios. La lamotrigina inhibe la liberación de glutamato al bloquear los canales voltaje-dependientes de sodio y calcio (Wang et al., 1996) en la neurona presináptica. Por su parte, el topiramato es un antagonista de los receptores AMPA-kainato (Rosenfeld, 1997), además de disminuir la liberación presináptica de GLU (Hanaya et al., 1998).

Actuando sobre el receptor el GABA también se puede modular la alteración del equilibrio entre los sistemas excitadores e inhibidores, en este caso potenciado la neurotransmisión inhibitoria gabaérgica. El valproato potencia las acciones agonistas del

receptor GABA_A (Olpe et al., 1988) y aumenta la densidad de receptores GABA_B en el hipocampo (Motohashi, 1992), mientras ciertos agentes antiepilépticos nuevos, como la gabapentina y la pregabalina, potencian los mecanismos gabaérgicos, incrementando la liberación presináptica de GABA (Sills, 2006). Todo ello avala la potencial eficacia de estos fármacos en el tratamiento de los pacientes con trastorno bipolar.

Aunque el mecanismo de acción del litio continua sin dilucidarse en la actualidad, la investigación se ha centrado durante las últimas décadas en los efectos intraneuronales de este ion a nivel de los mecanismos de transducción de las señales neuronales (Figura 14), lo que justificaría su efecto regulador del humor a largo plazo, sobre todo en la prevención de episodios maníacos y/o depresivos. En 1988 se comunicó la acción del litio sobre las PG, al observarse que este agente inhibía la función de los receptores β -adrenérgicos y muscarínicos acoplados a las PG, lo que situó a estas dianas biológicas como uno de los *loci* moleculares responsables de los efectos terapéuticos antimaníacos y antidepresivos de las sales de litio (Avissar et al., 1988). La familia de las PG heterotriméricas constituye un punto de convergencia esencial en la transmisión de señales a partir de varios primeros mensajeros. El litio estabilizaría las PG_s, lo que justificaría el efecto antimaníaco, y también las PG_i, lo que explicaría el efecto antidepresivo. Esta hipótesis tomó más cuerpo al comprobarse que otros tratamientos empleados en el trastorno bipolar, como la carbamazepina o la TEC, también modificaban la función de las PG (Schreiber y Avissar, 2003).

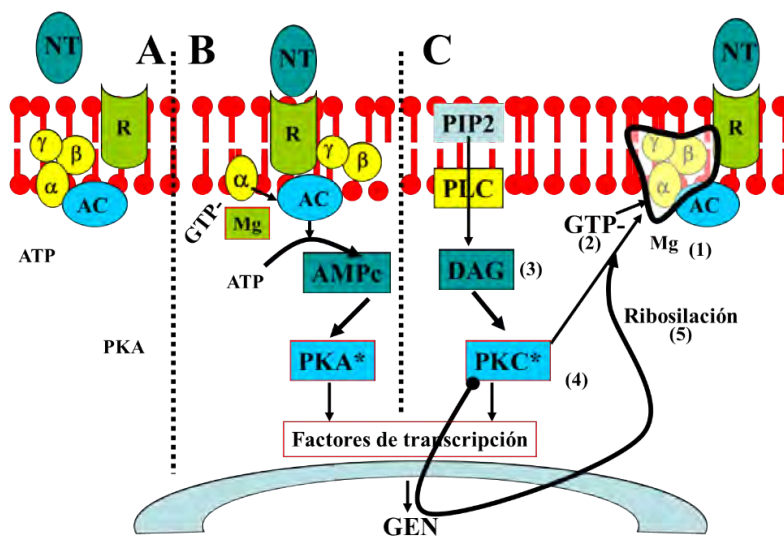


Figura 14: Representación esquemática del hipotético mecanismo de acción del litio a nivel intraneuronal.

Más allá de las PG, el litio también es capaz de actuar sobre los sistemas de transducción de la señal de segundos mensajeros, que incluyen a las vías mediadas por la AC y el fosfoinositol, donde se sitúan las proteincinasas A y C (PKA y PKC) (Williams y Harwod, 2000). Del mismo modo, el litio inhibe de forma directa a la glucógeno-sintetasa-cinasa-3 (GSK3), una cinasa que actúa como intermediaria en varias vías intracelulares y sobre la que también actúan otros eutimizantes, como el valproato (Quiroz et al., 2004; Gould et al., 2004; Gould, 2006).

Los datos aportados hasta el momento sobre el efecto de los eutimizantes sobre la vía de la AC son controvertidos, lo que pone de manifiesto la complejidad del mecanismo de acción de los reguladores del humor a este nivel. El tratamiento crónico con litio da lugar a un aumento de la expresión de los tipos I y II de la AC (tipos I y II), así como de sus correspondientes ARNm (Colin et al., 1991), lo que podría significar una sensibilización del sistema generador de AMPc y podría explicar el elevado riesgo de recaídas maníacas tras la suspensión del tratamiento con este fármaco (Manji et al., 1995). Por otro lado, la administración crónica de litio disminuye la actividad del AMPc, al reducir la actividad de la PG_s y aumentar la concentración de PG_i (Nestler et al., 1995; Belmaker, 2004). La carbamazepina también disminuye la actividad del AMPc (Lewin y Bleck, 1977), pero, aunque su administración crónica disminuye la actividad de la PG_i y la PG_s (Lesch et al., 1991; Post et al., 1992), se incrementan los niveles de AMPc sobre todo en la corteza frontal (Wiborg et al., 1997). Todos estos contradictorios datos no ayudan a establecer una hipótesis fehaciente sobre la implicación de estas vías bioquímicas en la patogenia del trastorno bipolar.

Otra hipótesis sobre el mecanismo de acción del litio implica a la vía del mioinositol, al comprobarse que este ion inhibe de forma directa y a dosis terapéuticas (Layden et al., 2000) algunas de las enzimas fosfomonoesterasas implicadas en el ciclo del fosfoinositol (Manji et al., 1999; Quiroz et al., 2004;), acción también descrita con el valproato (O'Donnell et al., 2000). El litio, a concentraciones terapéuticas, inhibe de forma directa y no competitiva la inositol-monofosfatasa (IMPasa) (Parthasarathy et al., 1993) y, secundariamente, la inositol-polifosfato-1-fosfatasa (IPPasa), provocando una depleción de mioinositol y un acúmulo de diacilglicerol en el SNC (Silva, 2001). Sin embargo, esta

hipótesis de la depleción del inositol no explica por sí misma los efectos reguladores del humor de las sales de litio, pudiéndose interpretar como el inicio de una cascada de señales que ocasionarían finalmente los efectos terapéuticos retardados del fármaco (Manji et al., 1996; Silva, 2001). Otros eutimizantes, como el valproato y la carbamazepina, también podrían regular esta cascada de señales del ciclo del fosfoinositol, pues disminuyen la expresión y la función del ARNm del transportador de alta afinidad del miosinositol (SMIT1), que se ha posicionado como una nueva diana biológica para el estudio de potenciales eutimizantes (Quiroz et al., 2004).

El otro segundo mensajero implicado en el ciclo de los fosfoinositoles es el diacilglicerol, cuya diana primaria es la PKC, sobre la que se han centrado numerosos estudios que la vinculan con el trastorno bipolar, pues su actividad se encuentra significativamente incrementada en los pacientes maníacos. Además, el litio y el valproato son capaces de reducir su actividad, lo que potencia la teoría de su intervención en la patogenia del trastorno bipolar (Sela, 2004). Mediante la modulación de la actividad enzimática de la PKC por parte de estos fármacos se puede regular la actividad de genes de respuesta temprana y de diversos factores de transcripción, como la proteína activadora 1 (AP-1) (Yuan et al., 1998).

En la fisiopatología del trastorno bipolar también se han involucrado diversos fenómenos de neurodegeneración consecuentes con procesos de daño neuronal (Li et al., 2002), en los que jugarían un destacado papel las vías de transducción intracelulares relacionadas con la neuroplasticidad, que podrían ser potenciadas por los reguladores del humor (Goodwin y Jamison, 2007). Entre ellas, cabe destacar el BDNF, el factor de crecimiento fibroblástico tipo 2 (FCF-2), el ERK (*extracellular signal-regulated kinase*) o el CREB, este último relacionado con los procesos de neurogénesis en el hipocampo en sujetos adultos (Manji et al., 2000). El BDNF y el ERK se están posicionando como dos vías de gran relevancia en los fenómenos de plasticidad sináptica y se han vinculado a la fisiopatología del trastorno bipolar (Chen y Manji, 2006; Shaltiel et al., 2007).

Aunque ya se conocía el efecto neuroprotector del litio, los clásicos antiepilépticos también parecen estar dotados de esta propiedad, al estimular la síntesis de diversos factores neurotróficos, minimizando el proceso de neurodegeneración asociado al

trastorno bipolar (Figura 15). El tratamiento crónico con litio y valproato aumenta la inmunorreactividad al BDNF en la corteza frontal (Einat et al., 2003) y el fenómeno de neurogénesis en el hipocampo, un efecto mediado, al menos en parte, por la activación de la vía ERK (Hao et al., 2004). Otros muchos datos apoyan esta teoría de la neuroprotección: la administración crónica de litio es capaz de proteger a células neuronales embrionarias sometidas a concentraciones apoptóticas de GLU (Nonaka et al., 1998); el litio y el valproato aumentan los niveles de factores de transcripción como el CREB y de bcl-2 (*B-cell lymphoma 2*), una proteína dotada de propiedades neuroprotectoras y antiapoptóticas (Chen et al., 1999); el litio inhibe directamente la GSK3 (Klein y Melton, 1996; Stambolic et al., 1996). Todas estas evidencias confirman la estrecha relación entre las alteraciones de la neuroplasticidad y el trastorno bipolar.

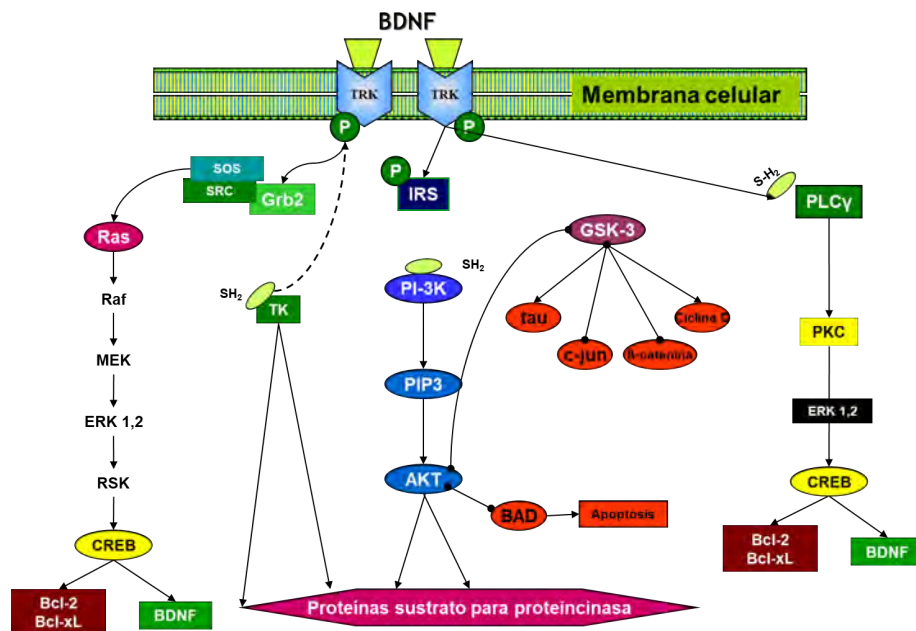


Figura 15: Vías de señalización intraneuronales relacionadas con la GSK3 y con diversos factores neurotróficos.

4. Tratamiento farmacológico de los trastornos del estado de ánimo

4.1. Fármacos antidepresivos

A principios del siglo XX se venían empleando en el manejo de los pacientes depresivos diferentes fármacos de acción inespecífica y dudosa eficacia, como el hidrato de cloral, los barbitúricos, las anfetaminas e, incluso, los derivados opiáceos en pacientes

melancólicos agitados (López-Muñoz y Álamo, 1998; López-Muñoz et al., 2014a). Durante la primera mitad de este siglo, y excluyendo a los tratamientos biológicos (los comas insulínicos, las terapias de choque, tanto químicas como eléctricas, o las famosas “curas de sueño” (López-Muñoz et al., 2010), cuyo uso fue muy amplio, sólo existían a disposición de los facultativos algunos preparados químicos inespecíficos, como el dinitrito succínico, el nitrito malónico o el ácido láctico, cuyos resultados antidepresivos eran igualmente insatisfactorios (Kalinowsky y Hoch, 1953).

Pero como se ha comentado, durante la década de 1950 tuvo lugar, en el ámbito de la psicofarmacología y de la psiquiatría, una auténtica “revolución”, con la introducción en clínica de los principales grupos de psicofármacos, empleados aún hoy en día. Baste destacar, en este sentido, y en el ámbito que nos incumbe, el descubrimiento de la acción antimaniaca del litio en 1949 (López-Muñoz et al., 1999) y el descubrimiento de la imipramina y del uso psiquiátrico de la iproniazida en 1957 (López-Muñoz et al., 2007a; 2008; Fangmann et al., 2008; López-Muñoz y Álamo, 2009b; López-Muñoz, 2023a; 2023b). Así pues, ésta puede considerarse como la auténtica “década de oro” de la psicofarmacología (López-Muñoz et al., 2000).

En la actualidad, los antidepresivos constituyen un amplio grupo de medicamentos empleados en el tratamiento de los trastornos depresivos (Álamó et al., 2012), pero su uso abarca otra serie de trastornos mentales, como los de ansiedad, el trastorno obsesivo compulsivo (TOC), el trastorno de estrés postraumático (TEPT), así como cuadros somáticos, entre los que destaca el tratamiento del dolor crónico o el síndrome disfórico premenstrual.

La clasificación más usada de los antidepresivos se fundamenta en conceptos surgidos durante las décadas de 1960 y 1970 que no permiten una rápida aproximación a las propiedades farmacodinámicas, de tolerabilidad o de seguridad de estos agentes. De hecho, en muchos casos, el primer efecto psicofarmacológico identificado (efecto primario) se convirtió en el término preferido. Prueba de ello es la habitual clasificación elaborada por la OMS en 1976 (Tabla 3), que establece los grupos terapéuticos y/o códigos ATC (*Anatomical, Therapeutic, Chemical Classification System*). Pero la terminología usada en esta clasificación está desactualizada y es inexacta, lo que favorece

la perpetuación del estigma asociado a estos trastornos mentales. Además, suscita una cierta confusión clínica al mezclarse las indicaciones terapéuticas y los efectos de los diferentes agentes antidepresivos; por ejemplo, un ISRS puede ser ansiolítico, mientras que otros antidepresivos, como el bupropion, pueden provocar ansiedad. Mucho más recientemente, a instancias del European College of Neuropsychopharmacology (ECNP), se creó una *taskforce* para establecer una nomenclatura en el ámbito de la psicofarmacología, que incluyó al Asian College of Neuropsychopharmacology (AsCNP), el American College of Neuropsychopharmacology (ACNP), el Collegium Internationale Neuro-Psychopharmacologicum (CINP), y la International Union of Basic and Clinical Pharmacology (IUPHAR), y promovieron, a partir de 2016, una nomenclatura basada en la neurociencia, que ya va por su segunda edición (NbN2), con un enfoque basado en el mecanismo de acción de estos fármacos, con el objetivo de reducir la confusión de la clasificación de la OMS (Tabla 3), aunque también ha generado algunas críticas. Así, algunos de los mecanismos de acción mencionados son incompletos, como en el caso de la desipramina y nortriptilina, agentes denominados “moduladores noradrenérgicos”, aunque también actúan como moduladores serotoninérgicos. Además, ciertos antidepresivos “multimodales” no están incluidos en esta clase. Por tanto, no parece existir la clasificación perfecta por lo que en la Tabla 3 se muestran las clasificaciones de la OMS y de la NbN2. Atendiendo a ambas, podríamos asumir las siguientes familias de fármacos antidepresivos:

Tabla 3. Clasificación de los fármacos antidepresivos, según las nomenclaturas ATC y NbN2.

Grupo ATC - OMS	Acrónimo	Clase NbN2 (mecanismo de acción)	Fármaco prototipo
Antidepresivos tricíclicos	ADT	AIVc (inhibidores de la recaptación de 5-HT y NA con actividad antagonista de diversos receptores)	Imipramina
Inhibidores de la monoamino-oxidasa	IMAO	AIa (inhibidores irreversibles de la MAO)	Fenelzina
Antidepresivos heterocíclicos o de “segunda generación”		AIVb (inhibidores de la recaptación de NA con actividad antagonista de diversos receptores)	Maprotilina
		AIVb (antagonistas de los autorreceptores α_2 adrenérgicos y de otros receptores)	Mianserina

		(inhibidores de la recaptación de DA y NA con actividad antagonista de diversos receptores)	Nomifensina
		AIVa (inhibidores de la recaptación de 5-HT y antagonistas de los receptores 5-HT ₂)	Trazodona
Inhibidores selectivos de la recaptación de serotonina	ISRS	AIIa1 (inhibidores de la recaptación de 5-HT, sin actividad antagonista de receptores)	Fluoxetina
Inhibidores reversibles de la monoamino-oxidasa	RIMA	AIC (inhibidores reversibles de la MAO-A)	Moclobemida
Inhibidores selectivos de la recaptación de noradrenalina y dopamina	IRND	AIIc (inhibidores de la recaptación de NA y DA, sin actividad antagonista de receptores)	Bupropion
Inhibidores selectivos de la recaptación de noradrenalina y serotonina	IRNS	AIIb (inhibidores de la recaptación de NA y 5-HT, sin actividad antagonista de receptores)	Venlafaxina
Inhibidores selectivos de la recaptación de noradrenalina	ISRN	(inhibidores de la recaptación de NA, sin actividad antagonista de receptores)	Reboxetina
Antidepresivos noradrenérgicos y serotoninérgicos específicos	NaSSA	AIII (antagonistas de los autorreceptores y heterorreceptores α_2 , y de los receptores 5-HT _{2A})	Mirtazapina
Agonistas melatoninérgicos	AM	B (agonistas de receptores melatoninérgicos MT ₁ y MT ₂ , y antagonistas de receptores 5-HT _{2C})	Agomelatina
Moduladores glutamatérgicos	MG	(antagonistas de receptores NMDA y estimulantes de receptores AMPA)	Esketamina
Moduladores y estimuladores serotoninérgicos	SMS	AIVa (inhibidores de la recaptación de 5-HT y agonistas / agonistas parciales / antagonistas de diferentes receptores 5-HT)	Vortioxetina

5-HT (serotonina); NA (noradrenalina); DA (dopamina).

ADT (antidepresivos tricíclicos); IMAO (inhibidores irreversibles de la monoamino-oxidasa); ISRS (inhibidores selectivos de la recaptación de serotonina); RIMA (inhibidores irreversibles de la monoamino oxidasa); IRND (inhibidores selectivos de la recaptación de noradrenalina y dopamina); INRS (inhibidores selectivos de la recaptación de noradrenalina y serotonina); ISRN (inhibidores selectivos de la recaptación de noradrenalina); NaSSA (antidepresivos noradrenérgicos y serotoninérgicos específicos); AM (agonistas melatoninérgicos); MG (moduladores glutamatérgicos); SMS (moduladores y estimuladores serotoninérgicos).

ATC (sistema de Clasificación Anatómica, Terapéutica, Química de la Organización Mundial de la Salud); NbN2 (segunda edición de la nomenclatura basada en la neurociencia, promovida, fundamentalmente, por The International Collegue of Neuropsychopharmacology –CINP– y European Collegue of Neuropsychopharmacology –ECNP–).

Inhibidores de la monoaminoxidasa (IMAO): estos agentes inhiben el catabolismo de la NA, 5-HT y DA, por parte de la enzima MAO, por lo que se produce una potenciación de la neurotransmisión aminérgica. Asimismo, los IMAO impiden la desaminación de la tiramina, un simpaticomimético indirecto presente en múltiples alimentos (quesos curados, carnes ahumadas, conservas, salsas de soja y otras, guisantes, habas, frutas secas, bebidas alcohólicas, etc.), pudiendo ocasionar crisis hipertensivas graves, conocidas como “reacción al queso” (Finberg y Gillman, 2011). Por este motivo, los IMAO irreversibles (clase A1a de la NbN2) no están contemplados como tratamiento de primera línea para la depresión. De hecho, en España no existe comercializado ningún IMAO irreversible.

Un grupo denominado RIMA (*reversible inhibitor monoaminoxidase*) está representado por la moclobemida (clase A1c de la NbN2). Este fármaco, debido a su corta vida media, puede metabolizar a la tiramina de los alimentos cuando los niveles son bajos y no ocasiona crisis hipertensivas. Sin embargo, su eficacia antidepresiva no se ha visto refrendada en la práctica clínica diaria, por lo que su uso, en la actualidad, es muy escaso (Bonnet, 2003).

Antidepresivos tricíclicos (ADTs): estos fármacos se encuadran en la clasificación NbN2 dentro de la clase de agentes multimodales categoría AIVc “noradrenérgicos y serotoninérgicos (con antagonismo muscarínico significativo)”. El prototipo de este grupo es la imipramina. Estos agentes son inhibidores de la recaptación de NA y 5-HT y además son antagonistas colinérgicos, histaminérgicos y adrenérgicos, con manifiestas diferencias interindividuales, por lo que se considera que poseen muy poca “limpieza bioquímica”, lo que se relaciona con su mala tolerabilidad general y baja seguridad en sobredosis (Richelson, 2001). El bloqueo de los receptores α -adrenérgicos, sobre todo en el caso de la amitriptilina, clomipramina y doxepina, puede provocar hipotensión ortostática y taquicardia refleja; el antagonismo de los receptores histaminérgicos H_1 sedación, destacando la amitriptilina, la clomipramina y la imipramina; el bloqueo de receptores muscarínicos ocasiona una pléyade de efectos anticolinérgicos periféricos (estreñimiento, sequedad de boca, retención urinaria, trastornos de la acomodación visual o crisis de glaucoma) y centrales (trastornos de la memoria, confusión y delirio), especialmente en los ancianos; y la afinidad sobre los receptores 5-HT₂, destacable en el

caso de la amoxapina, la amitriptilina, la clomipramina, la doxepina y la trimipramina, una propensión al aumento de peso, manifestándose por una excesiva apetencia por alimentos hidrocarbonados (Baldaçara et al., 2024).

Inhibidores selectivos de la recaptación de serotonina (ISRS): se incluyen en la clasificación Nbn2 dentro de la clase AIIa1. El representante de este grupo es la fluoxetina, aunque existen además otras moléculas muy utilizadas en clínica con esta propiedad (Álamo et al., 2000). Todos los ISRS comparten la acción específica de producir el bloqueo de la recaptación de 5-HT, aumentando la transmisión sináptica serotoninérgica. Además, presentan una afinidad por receptores de neurotransmisores prácticamente despreciable, en comparación con los ADTs, aunque existen excepciones (Richelson, 2001); la paroxetina ejerce un antagonismo de los receptores muscarínicos ligeramente inferior a la de algunos ADTs, pudiendo provocar estreñimiento, sequedad de boca, etc.; el citalopram muestra una elevada afinidad por receptores histaminérgicos, incluso superior a la de algunos ADTs, provocando somnolencia y fatiga. Sin embargo, su enantiómero S, el escitalopram, carece de afinidad por estos receptores y es el más selectivo de los ISRS. Los efectos adversos gastrointestinales, tan típicos de los ISRS, como las náuseas y los vómitos, se deben a una sobreestimulación serotoninérgica de los receptores 5-HT₃ del tracto gastrointestinal, por el aumento de la tasa sináptica de 5-HT, y las disfunciones sexuales, como la anorgasmia y la disminución de la libido, pueden estar mediadas por el estímulo de los receptores 5-HT_{2A}.

Con la administración continuada de ISRS aumentan los niveles de AMPc y se ponen en marcha mecanismos de transducción que aumentan la expresión de neurotrofinas como el BDNF (Yoshimura et al., 2023), lo que conlleva un incremento de la neurogénesis. Pero hay que resaltar que esta especificidad serotoninérgica no es absoluta en estos fármacos. Así, la sertralina es el antidepresivo con mayor capacidad para inhibir el transportador de DA, siendo casi tan potente como el metilfenidato y muy superior al bupropion. Asimismo, la paroxetina es el ISRS más potente, pero también se comporta como un inhibidor de la recaptación de NA y un potente agente anticolinérgico (Sánchez et al., 2014).

Inhibidores de la recaptación de noradrenalina y serotonina (IRNS): estos antidepresivos son denominados también “duales” y se encuadran dentro de la clasificación NbN2 en la categoría AIIb. En este grupo se incluyen la venlafaxina y la duloxetina. La venlafaxina inhibe la recaptación de 5-HT y se metaboliza en desvenlafaxina, responsable de la inhibición de la recaptación de NA (Aldosary et al., 2022). La duloxetina posee una actividad más equilibrada sobre ambos transportadores. Estos fármacos presentan una baja afinidad por otros receptores monoaminérgicos (Baldaçara, 2024).

Inhibidores selectivos de la recaptación de noradrenalina y dopamina (IRND): estos fármacos pertenecen al grupo AIIc de la clasificación NbN2, siendo el bupropion el único representante de este grupo (Foley et al., 2006).

Antagonistas de receptores α_2 -noradrenérgicos y serotoninérgicos específicos (NaSSA): la mirtazapina es el único representante de esta familia, encuadrada en la clasificación NbN2 en la categoría AIII. La mirtazapina actúa bloqueando los receptores adrenérgicos α_2 presinápticos, tanto autorreceptores (situados en neuronas noradrenérgicas y que facilitan la liberación de NA, como heterorreceptores (situados en neuronas serotoninérgicas y que incrementan la liberación de 5-HT). Además, la mirtazapina antagoniza el receptor 5-HT_{2A}, por lo que aumenta la NA y DA en la corteza cerebral. En definitiva, sin inhibir los transportadores de NA y 5-HT, aumenta la tasa de monoaminas de modo similar a los duales (Cuenca et al., 1998). Sin embargo, la mirtazapina muestra una elevada afinidad, incluso superior a la exhibida por los ADTs, por los receptores histaminérgicos H₁, lo que explica su efecto sedante y el incremento del apetito y peso.

Inhibidores selectivos de la recaptación de noradrenalina (ISRN): el único representante de este grupo comercializado en Europa es la reboxetina, un fármaco que no presenta afinidad por otros receptores del SNC (Cuenca et al., 1999; 2001).

Antidepresivos multimodales serotoninérgicos: entre estos fármacos, englobados en la categoría AIVa de la clasificación NbN2, se encuentran la vortioxetina, la vilazodona y la trazodona. La trazodona antagoniza los receptores postsinápticos 5-HT_{2A} y 5-HT_{2C} e

inhibe débilmente la recaptación de 5-HT, a la vez que bloquea los receptores α_1 -adrenérgicos y los histaminérgicos H_1 postsinápticos. La trazodona es muy utilizada como hipnótico por sus propiedades antihistamínicas (Alcántara-López et al., 2009). La vilazodona es un modulador serotoninérgico que inhibe la recaptación de 5-HT y es un agonista parcial de los receptores 5-HT_{1A} postsinápticos (Wang et al., 2016), aunque no está comercializada en Europa. Por último, la vortioxetina puede considerarse como el prototipo de antidepresivo multimodal, ya que actúa como inhibidor del transportador de 5-HT y es un agonista de los receptores serotoninérgicos 5-HT_{1A}, agonista parcial de los receptores 5-HT_{1B} y antagonista de los receptores 5-HT_{1D}, 5-HT₃, y 5-HT₇ (Salegre et al., 2018). La vortioxetina, a través de estos mecanismos, potencia las acciones de la 5-HT y facilita la liberación de cuatro neurotransmisores procognitivos (DA, NA; acetilcolina e histamina). En clínica, se ha podido demostrar que la vortioxetina incrementa los niveles de BDNF (Sagud et al., 2016), probablemente por estimular indirectamente los receptores AMPA, como sucede con la ketamina.

Moduladores multimodales noradrenérgicos: categorizados como AIVb en la clasificación NbN2, incluyen a la mianserina y la maprotilina. Estos antidepresivos se conocían clásicamente como atípicos o de segunda generación. La mianserina bloquea los receptores 5-HT₂, los receptores H_1 y los auto- y heterorreceptores α_2 presinápticos, por lo que aumenta la neurotransmisión NA y 5-HT (Danilov, 2020). La maprotilina es un antidepresivo tetracíclico que inhibe la recaptación de NA de forma selectiva y tiene propiedades como antagonista de los receptores α -adrenérgicos (Baumann y Maître, 1979).

Agonistas de los receptores melatoninérgicos (MT₁ y MT₂): se trata de moduladores no monoaminérgicos encuadrados en la clase B de la clasificación NbN2. El único representante de este grupo es la agomelatina (Álamo et al., 2008a; 2014a). Este fármaco es un agonista de receptores melatoninérgicos MT₁ y MT₂, pero además es un antagonista de los receptores 5-HT_{2C}, por lo que aumenta la tasa de NA y DA en la corteza prefrontal. Además, la agomelatina carece de afinidad por otros receptores, responsables en parte de los efectos adversos de otros antidepresivos (Srinivasan et al., 2016).

Antidepresivos glutamatérgicos: la tianeptina es un antidepresivo glutamatérgico que además presenta una débil acción agonista sobre los receptores opioides tipo μ , lo que podría explicar la liberación de DA en el sistema límbico y su participación en la modulación de mecanismos glutamatérgicos (Álamo et al., 2019). Por su parte, la esketamina es un antagonista de los receptores NMDA que inhibe las interneuronas inhibitorias gabaérgicas, por lo que se produce una descarga de GLU por las neuronas piramidales sobre el hipocampo que estimularía a los receptores AMPA, ya que los receptores NMDA estarían bloqueados por esketamina (Widman y McMahon, 2018). El estímulo de los receptores AMPA aumentaría la liberación de BDNF y la activación de otras vías de transducción que facilitarían la sinaptogénesis (Strasburguer et al., 2017).

4.2. Agentes eutimizantes o reguladores del humor

El recorrido histórico de los agentes reguladores del humor es relativamente corto (López-Muñoz et al., 2018; 2023b). De hecho, el inicio de la denominada “era de la psicofarmacología moderna”, en la década de 1950 (López-Muñoz et al., 2000; 2014a), comenzó con el descubrimiento de la eficacia antimaniaca de las sales de litio (Cade, 1949). No obstante, la siguiente herramienta aprobada para estos pacientes no llegaría hasta la mitad de la década de 1990, cuando se confirmó la eficacia antimaniaca del valproato.

Hasta el descubrimiento del efecto antimaniaco del litio, los agentes terapéuticos que se venían empleando en clínica mostraban una eficacia muy reducida (López-Muñoz et al., 2014a), siendo los sedantes los fármacos más empleados en el manejo de los pacientes maníacos. Entre ellos cabe mencionar el opio y la morfina, así como los alcaloides obtenidos de las plantas de la familia *Solanaceae*, como la hiosciamina y la hioscina o escopolamina (Álamo et al., 1998; López-Muñoz et al., 2010; López-Muñoz et al., 2018), durante el siglo XIX, y posteriormente en la primera mitad del siglo XX, se recurrió al hidrato de cloral (Shorter, 1997), los bromuros (Sourkes, 2014) y sobre todo los barbitúricos (López-Muñoz et al., 2004a; 2004b; López-Muñoz et al., 2005a; Ucha-Udabe et al., 2014).

Exceptuando las sales de litio, el resto de reguladores del humor han sido aprobados e incorporados al arsenal terapéutico del trastorno bipolar durante los últimos 30 años: el ácido valproico en 1995 y la carbamazepina en 2004, posicionándose los clásicos anticonvulsivantes como agentes antimaníacos consolidados (Álamo et al., 2008b; Wu-Chou et al., 2014), y finalmente, a partir del año 2000, fueron autorizados los antipsicóticos atípicos, fundamentalmente, aunque no exclusivamente, para la indicación antimaníaca, y la lamotrigina, un agente antiepiléptico moderno, para la prevención de los episodios depresivos del trastorno bipolar (Figura 16) (Álamo et al., 2003; López-Muñoz et al., 2018).

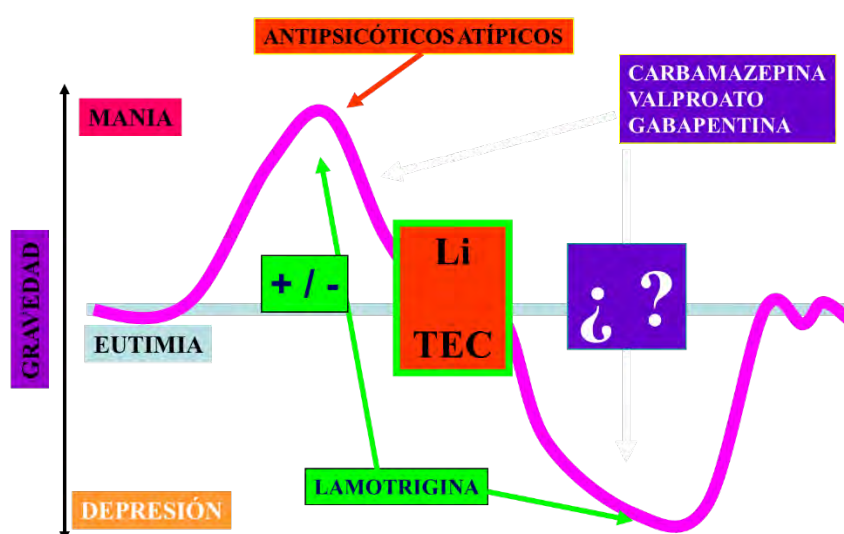


Figura 16: Esquema de la evolución del trastorno bipolar y de las indicaciones de los agentes eutimizantes en los distintos episodios de esta patología.

La Tabla 14 muestra todos los agentes eutimizantes aprobados por las agencias reguladoras, aunque hay que tener presente que la polifarmacia con fármacos de grupos terapéuticos distintos es una práctica muy habitual en los pacientes con trastorno bipolar.

Tabla 4. Fármacos aprobados por alguna administración reguladora para el tratamiento de los pacientes con trastorno bipolar

Grupo / Familia	Fármaco
Sales	Litio
Antiepilépticos clásicos	Carbamazepina Valproato / Divalproex sódico
Nuevos anticonvulsivantes	Lamotrigina
Antipsicóticos clásicos	Clorpromazina
Antipsicóticos atípicos	Aripiprazol Asenapina Cariprazina Lumateperona Lurasidona Olanzapina Quetiapina Risperidona Ziprasidona

Sales de litio: desde el punto de vista químico, el litio es el fármaco más sencillo de todos los utilizados en el tratamiento de los trastornos mentales, ya que se trata del metal más ligero existente en la naturaleza. Tras el descubrimiento de su efecto antimaniaco en 1949 (Cade, 1949), en las décadas siguientes se confirmaron sus efectos profilácticos en la prevención de recurrencias de los episodios maníacos, al disminuir el número de episodios y la duración de los mismos y aumentar el tiempo comprendido entre los episodios (Schou, 1997). En la actualidad, las sales de litio siguen siendo consideradas como tratamiento de primera elección de las fases maníacas de los trastornos bipolares, así como herramientas profilácticas indispensables en la prevención de episodios del trastorno bipolar, y todo ello a pesar de los inconvenientes del tratamiento, con la periódica determinación de la litemia, y sus frecuentes y graves efectos adversos, desde temblor de manos hasta toxicidad renal.

El mecanismo de acción del litio sigue sin ser completamente conocido en la actualidad, aunque se ha constatado que es capaz de influir sobre una serie de procesos fisiológicos, relacionados con su acción terapéutica y/o tóxica, entre los que cabe mencionar el transporte de colina y aminoácidos, la neurotransmisión monoaminérgica, colinérgica o gabaérgica o los sistemas de transducción intraneuronales, destacando su efecto sobre las distintas fracciones de las PG, el metabolismo de los fosfoinositoles o la vía de la AC (Waldmeier, 1990; Cuenca et al., 2000).

Antiepilépticos clásicos: el valproato y la carbamazepina se integran, junto a la fenitoína, en un grupo terapéutico al que se ha denominado como antiepilépticos clásicos. El valproato fue introducido como antiepiléptico en 1967 y no se aprobó como agente antimaníaco hasta 1995 (Wu-Chou et al., 2014), cuando diferentes ensayos clínicos confirmaron su eficacia en el tratamiento de la fase maníaca del trastorno bipolar (Freeman et al., 1994). Sin embargo, su perfil de seguridad, aunque mejor que el del litio, puede también limitar su uso, siendo habituales los efectos adversos gastrointestinales, además de temblor, sedación, pancreatitis, toxicidad hepática, aumento de peso y síndrome de ovario poliquístico.

El descubrimiento de las propiedades antiepilépticas de la carbamazepina tuvo lugar en 1963, pero no fue hasta 2004 cuando se autorizó su uso como agente antimaníaco (Wu-Chou et al., 2014). Su empleo también está limitado por su mala tolerabilidad y los frecuentes y a veces graves efectos adversos, entre los que cabe mencionar una pronunciada somnolencia, ataxia, diplopía, disfunción cognitiva, rash cutáneo (5-10% de los pacientes) o discrasias sanguíneas, poco frecuentes, pero fatales.

El principal mecanismo de acción de estos dos fármacos anticonvulsivantes clásicos es la inhibición de los canales voltaje-dependientes de sodio. Sin embargo, el valproato también es capaz de inhibir los canales de calcio, aumentar los niveles endógenos de GABA por estímulo de la enzima descarboxilasa del ácido glutámico, y potenciar la actividad dopaminérgica. Por su parte la carbamazepina, también presenta un efecto inhibidor de la liberación de aminoácidos excitatorios (GLU y aspartato) y potenciador de los mecanismos serotoninérgicos presinápticos. Además de todo ello, estos fármacos comparten algunos de los efectos del litio sobre las cascadas bioquímicas intraneuronales (Cook y Bensalem-Owen, 2011).

Lamotrigina: este es uno de los nuevos fármacos antiepilépticos, aprobado en esta indicación en 1990. En los primeros estudios como agente antiepiléptico se observó que la lamotrigina también ocasionaba una mejoría del humor y de la capacidad de comunicación en estos pacientes (Smith et al., 1993). Los ensayos clínicos posteriores confirmaron su especial eficacia en la profilaxis de recaídas en pacientes con trastorno bipolar, básicamente de las fases depresivas, aunque también una cierta eficacia en la

prevención de la manía, aunque los resultados no fueron tan robustos como con el litio (Goodwin et al., 2004). Estos resultados pusieron de manifiesto el perfil característicamente antidepresivo de la lamotrigina como eutimizante, a diferencia de los fármacos disponibles hasta ese momento, lo que permitió su aprobación para el tratamiento del trastorno bipolar en 2003. El mecanismo eutimizante de la lamotrigina (Cook y Bensalem-Owen, 2011) podría estar relacionado con su potente efecto anti-kindling, su capacidad para bloquear los canales de sodio dependientes de voltaje, así como de los canales de calcio en el tálamo, su actividad anti-glutamatérgica, la hiporregulación de los receptores β -adrenérgicos, la potenciación del funcionalismo serotoninérgico y dopaminérgico y algún efecto intraneuronal a nivel del sistema del inositol-trifosfato.

Clorpromazina: este fármaco fue el primer agente neuroléptico introducido en clínica, en 1952 (López-Muñoz et al., 2002; 2004c; 2005b) y no fue autorizado en el tratamiento de los pacientes maníacos hasta 1973. En la actualidad su uso en esta indicación es prácticamente anecdótico, debido a la introducción de los nuevos agentes antipsicóticos atípicos, mucho mejor tolerados que la clorpromazina, tanto a corto como a largo plazo. Como todos los antipsicóticos clásicos, la clorpromazina presenta un perfil receptorial muy poco selectivo, ya que antagoniza de forma potente los receptores dopaminérgicos D_2 , lo que ocasiona numerosos efectos neurológicos, incluyendo los síntomas extrapiramidales, los receptores $5-HT_2$, los receptores α_1 y α_2 -adrenérgicos, responsables de sus efectos cardiotóxicos, los receptores H_1 (aumento de peso) y los receptores muscarínicos, que también dan lugar a una pléyade de efectos anticolinérgicos, como estreñimiento, sequedad de boca, visión borrosa, retención urinaria, alteración memoria, somnolencia, deterioro cognitivo, etc. (Peroutka y Synder, 1980).

Antipsicóticos atípicos: durante los últimos 25 años han ido siendo autorizados de forma paulatina diferentes fármacos antipsicóticos atípicos en el tratamiento del trastorno bipolar, desde la autorización en el año 2000 de la olanzapina. En la actualidad, poseen la indicación antimaníaca la olanzapina, risperidona, quetiapina, ziprasidona, aripiprazol, asenapina y cariprazina, y la indicación antidepresiva la quetiapina, olanzapina, lurasidona, lumateperona y cariprazina. Aunque en gran medida desconocido, el mecanismo de acción eutimizante de estos fármacos estaría relacionado con su perfil

receptorial, al bloquear receptores dopaminérgicos D₂ y los receptores serotoninérgicos 5-HT₂, básicamente los 5-HT_{2A} y 5-HT_{2C}. Algunos de estos fármacos, como el aripiprazol, la ziprasidona y la asenapina también poseen una actividad agonista parcial de los receptores 5-HT_{1A} (López-Muñoz y Álamo, 2011). Todo ello podría traducirse en una modulación de la neurotransmisión serotoninérgica y dopaminérgica (Li et al., 2012), responsable del efecto normalizador del humor.

DOCUMENTO 1

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Monoaminergic Neurotransmission: The History of the Discovery of Antidepressants from 1950s Until Today

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Abstract: The 1950s saw the clinical introduction of the first two specifically antidepressant drugs: iproniazid, a monoamine-oxidase inhibitor that had been used in the treatment of tuberculosis, and imipramine, the first drug in the tricyclic antidepressant family. Iproniazid and imipramine made two fundamental contributions to the development of psychiatry: one of a social-health nature, consisting in an authentic change in the psychiatric care of depressive patients; and the other of a purely pharmacological nature, since these agents have constituted an indispensable research tool for neurobiology and psychopharmacology, permitting, among other things, the postulation of the first aetiopathogenic hypotheses of depressive disorders. The clinical introduction of fluoxetine, a selective serotonin reuptake inhibitor, in the late 1980s, once again revolutionized therapy for depression, opening the way for new families of antidepressants. The present work reviews, from a historical perspective, the entire process that led to the discovery of these drugs, as well as their contribution to the development of the neuroscientific disciplines. However, all of these antidepressants, like the rest of those currently available for clinical practice, share the same action mechanism, which involves the modulation of monoaminergic neurotransmission at a synaptic level, so that the future of antidepressant therapy would seem to revolve around the search for extraneuronal non-aminergic mechanisms or mechanisms that modulate the intraneuronal biochemical pathways.

Key Words: Depression, antidepressants, iproniazid, imipramine, fluoxetine, monoaminergic neurotransmission, history.

1. INTRODUCTION

Therapeutic approaches to affective disorders, from the perspective of current scientific pharmacology, date from the 1950s, with the introduction of imipramine and iproniazid. Prior to the clinical introduction of these first antidepressants, the therapeutic tools employed in dealing with mood disorders were extremely scarce [1]. In the early 20th century the agents used were chloral hydrate, barbiturates, amphetamines, and even opiate derivatives in agitated melancholic patients. During the first half of that century, and excluding biological treatments (insulin comas, chemical and electrical shock therapy, or the famous "sleep cures"), whose use was widespread, the only chemical preparations available to physicians were some non-specific ones, such as succinic dinitrite, malonic nitrite or lactic acid, whose antidepressant results were rather unsatisfactory.

It was in the 1950s that a veritable revolution took place in the fields of psychopharmacology and psychiatry, with the clinical introduction of the main groups of psychoactive drugs still used today. Although it is clear that in these early phases of psychopharmacology serendipity played an important role in the discovery of the majority of psychotropic drugs [2,3] –in addition, naturally, to large doses of wisdom and astute clinical observation [4]– what was truly important were the final results of these research processes. It suffices to highlight, apart from the discovery of imipramine and the

psychiatric use of iproniazid, the discovery of the antimanic action of lithium in 1949, the clinical introduction of chlorpromazine in 1952 and meprobamate in 1954, and the introduction, finally, of chlordiazepoxide in 1960. This is indeed why the 1950s is often considered the "golden decade" of psychopharmacology [5].

Thus, when we speak of a "revolution" in the area of psychoactive drugs during the 1950s, our intention is to highlight the crucial importance of the introduction of truly effective therapeutic tools for treating the different psychiatric disorders. And this is the case of iproniazid, and above all of imipramine, two drugs which not only marked a new era in the treatment of depression, but also relegated Ugo Cerletti's electroconvulsive therapy, previously the only antidepressive treatment with significant rates of effectiveness, to use only in highly specific cases [1]. Even so, the clinical introduction of these drugs had many critics, since psychoanalytic currents, doctrinally dominant in the psychiatry of the time, considered depression as a symptomatological manifestation of certain internal personality conflicts. According to this view, such conditions were even deemed to have positive characteristics, in that they were a form of externalizing a whole series of subconscious and traumatic internal conflicts, supposedly processed by the patients themselves. In this framework, the pharmacological treatment of depressive symptoms (as would occur some years later in the case of anxiety disorders) was viewed by a large part of the psychiatric community as a real error, since it would prevent patients from discovering the "true" roots of their internal conflicts. In our opinion, iproniazid and imipramine made two fundamental contributions to the devel-

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Monoaminergic Neurotransmission: The History of the Discovery of Antidepressants from 1950s until Today

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ABSTRACT

The 1950s saw the clinical introduction of the first two specifically antidepressant drugs: iproniazid, a monoamine-oxidase inhibitor that had been used in the treatment of tuberculosis, and imipramine, the first drug in the tricyclic antidepressant family. Iproniazid and imipramine made two fundamental contributions to the development of psychiatry: one of a social-health nature, consisting in an authentic change in the psychiatric care of depressive patients; and the other of a purely pharmacological nature, since these agents have constituted an indispensable research tool for neurobiology and psychopharmacology, permitting, among other things, the postulation of the first aetiopathogenic hypotheses of depressive disorders. The clinical introduction of fluoxetine, a selective serotonin reuptake inhibitor, in the late 1980s, once again revolutionized therapy for depression, opening the way for new families of antidepressants. The present work reviews, from a historical perspective, the entire process that led to the discovery of these drugs, as well as their contribution to the development of the neuroscientific disciplines. However, all of these antidepressants, like the rest of those currently available for clinical practice, share the same action mechanism, which involves the modulation of monoaminergic neurotransmission at a synaptic level, so that the future of antidepressant therapy would seem to revolve around the search for extraneuronal non-aminergic mechanisms or mechanisms that modulate the intraneuronal biochemical pathways.

Key Words: Depression, antidepressants, iproniazid, imipramine, fluoxetine, monoaminergic neurotransmission, history.

INTRODUCTION

Therapeutic approaches to affective disorders, from the perspective of current scientific pharmacology, date from the 1950s, with the introduction of imipramine and iproniazid. Prior to the clinical introduction of these first antidepressants, the therapeutic tools employed in dealing with mood disorders were extremely scarce [1]. In the early 20th century the agents used were chloral hydrate, barbiturates, amphetamines, and even opiate derivatives in agitated melancholic patients. During the first half of that century, and excluding biological treatments (insulin comas, chemical and electrical shock therapy, or the famous “sleep cures”), whose use was widespread, the only chemical preparations available to physicians were some non-specific ones, such as succinic dinitrite, malonic nitrite or lactic acid, whose antidepressant results were rather unsatisfactory.

It was in the 1950s that a veritable revolution took place in the fields of psychopharmacology and psychiatry, with the clinical introduction of the main groups of psychoactive drugs still used today. Although it is clear that in these early phases of psychopharmacology serendipity played an important role in the discovery of the majority of psychotropic drugs [2,3] –in addition, naturally, to large doses of wisdom and astute clinical observation [4]– what was truly important were the final results of these research processes. It suffices to highlight, apart from the discovery of imipramine and the psychiatric use of iproniazid, the discovery of the antimanic action of lithium in 1949, the clinical introduction of chlorpromazine in 1952 and meprobamate in 1954, and the introduction, finally, of chlordiazepoxide in 1960. This is indeed why the 1950s is often considered the “golden decade” of psychopharmacology [5].

Thus, when we speak of a “revolution” in the area of psychoactive drugs during the 1950s, our intention is to highlight the crucial importance of the introduction of truly effective therapeutic tools for treating the different psychiatric disorders. And this is the case of iproniazid, and above all of imipramine, two drugs which not only marked a new era in the treatment of depression, but also relegated Ugo Cerletti’s electroconvulsive therapy, previously the only antidepressive treatment with significant rates of effectiveness, to use only in highly specific cases [1]. Even so, the clinical introduction of these drugs had many critics, since psychoanalytic currents, doctrinally dominant in the psychiatry of the

time, considered depression as a symptomatological manifestation of certain internal personality conflicts. According to this view, such conditions were even deemed to have positive characteristics, in that they were a form of externalizing a whole series of subconscious and traumatic internal conflicts, supposedly processed by the patients themselves. In this framework, the pharmacological treatment of depressive symptoms (as would occur some years later in the case of anxiety disorders) was viewed by a large part of the psychiatric community as a real error, since it would prevent patients from discovering the “true” roots of their internal conflicts. In our opinion, iproniazid and imipramine made two fundamental contributions to the development of psychiatry: one of a social-health nature, consisting in an authentic change in the psychiatric care of depressive patients; and the other of a purely pharmacological nature, since these agents have constituted an indispensable research tool for neurobiology and psychopharmacology, permitting, among other things, the postulation of the first aetiopathogenic hypotheses of depressive disorders.

Table 1. Classification of monoaminergic antidepressants according to action mechanism and historical perspective on their clinical introduction.

FAMILY	Acronym	Prototype substance	Period
5-HT and NA reuptake inhibitors with blocking action of diverse receptors	TCA	Imipramine	1957-1980
Irreversible MAO inhibitors	MAOI	Phenelzine	1960-1965
NA reuptake inhibitors with blocking action of diverse receptors		Maprotiline	1970-1980
Antagonists of α_2 auto-receptors		Mianserine	1970-1980
Selective DA reuptake inhibitors	SDRI	Bupropion	1980-1990
Selective 5-HT reuptake inhibitors	SSRI	Fluoxetine	1980-1990
Reversible MAO inhibitors	RIMA	Moclobemide	1980-1995
5-HT reuptake inhibitors and blockers of 5-HT ₂ receptors		Nefazodone	1985-1995
Antagonists of α_2 auto- and hetero-receptors and 5-HT ₂ and 5-HT ₃ receptors	NaSSA	Mirtazapine	1975-2000
NA and 5-HT reuptake inhibitors	NSRI	Venlafaxine	1975-2000
Selective NA reuptake inhibitors	SNRI	Reboxetine	1980-2000

Modified by López-Muñoz et al. [1].

The introduction of the so-called atypical, heterocyclic or “second generation” antidepressants (maprotiline, nomifensine, trazodone, mianserine, among others) in the 1970s did not bring the heralded momentous progress, from either the therapeutic or safety perspective, except in individual cases, with respect to the classical antidepressants. On the other hand, the clinical introduction of selective serotonin reuptake inhibitors (SSRIs), in the late 1980s, once again revolutionized therapy for depression [1], opening the way for new families of antidepressants (see Table 1). Nevertheless, they all continue to employ the same action mechanism as the classical drugs, that is, the modulation of monoaminergic neurotransmission at a synaptic level.

IPRONIAZID AND MONOAMINE-OXIDASE INHIBITORS

The discovery of hydrazide compounds and of their pharmacological properties

Hydrazines have their origins in the research carried out by Emil Fischer in the 1870s. This father of organic chemistry discovered phenylhydrazine in 1874, accidentally, while he was working in the laboratory of Adolf von Baeyer in Strasbourg [6]. From hydrazine hydrate, a powerful reducing agent, Hans Meyer and Josef Malley, of the German Charles-Ferdinand University (Prague), synthesized isonicotinyl-hydrazine in 1912, as part of the work for their doctoral thesis [7]. However, forgotten for almost 40 years, it would not be until the early 1950s that it was resynthesized and that it was discovered, by chance, that the compound had, at any experimental level, powerful antitubercular properties [8]. A decisive influence on this discovery were the large stocks of hydrazine discovered after World War II, having been used by the German army as fuel for their V2 rockets, and which were distributed to the chemical and pharmaceuticals industry at low cost [9].

The discovery of the antitubercular effects of this hydrazine derivative, which took place in 1951, is due to the research work carried out, independently, by two scientific teams, led by Herbert Hyman Fox of Hoffmann-La Roche Laboratories (Nutley, New Jersey) and Harry L. Yale of the Squibb Institute for Medical Research (Princeton, New Jersey), respectively [10]. In the framework of a research programme on anti-infectious drugs at the Squibb Institute in the 1940s, under the direction of Frederick Wiseloge, hundreds of

compounds were synthesized and studied in mice previously infected with *Mycobacterium tuberculosis*. In 1951, one of the chemists in the group, Harry Yale, synthesized from a hydrazide intermediary (isonicotinyl-hydrazine), isonicotinyl-aldehyde-thiosemicarbazone, since researchers at the University of Indiana had already shown the tuberculostatic efficacy of thiosemicarbazones. However, there was enormous surprise when the synthetic intermediate employed was found to be much more active in the animal model than the final product. Almost at the same time, two weeks after the publication of the first Squibb report (10 January, 1952), Fox's team at Hoffmann-La Roche also announced the antitubercular properties of isonicotinyl-hydrazine [11]. Their research line started out from knowledge of the tuberculostatic effects of nicotinamide, a group B vitamin, so that their idea was to combine a pyridine derivative of this group with a thiosemicarbazone. As occurred with Yale, Fox's group found that the synthetic intermediary used, isonicotinyl-hydrazine, showed greater antitubercular power than the final product, isonicotinyl-aldehyde-thiosemicarbazone [10]. Clinical trials were carried out with this compound almost immediately in different hospitals in New York State; its antitubercular effectiveness was demonstrated, and it became known as isoniazid. Subsequently, this line of research was continued by Herbert H. Fox himself and John T. Gibas, at the Hoffmann-La Roche Laboratories, and among different derivatives of isoniazid, these two scientists synthesized an isopropyl derivative called iproniazid (1-isonicotinyl-2-isopropyl-hydrazine), whose tuberculostatic activity was similar to that of isoniazid in lab animals, but superior in humans [12].

The enormous significance of the introduction of these drugs for the treatment of tuberculosis is reflected in the mortality data for this illness in the United States, which fell from 188 deaths per 100,000 inhabitants in 1904 to just 4 in 1952, one year after the introduction into the field of isonicotinyl-hydrazine or isoniazid [13].

The pharmacological contributions of iproniazid

Prior to the discovery of the antitubercular properties of hydrazines, Mary L. Hare (Mary Bernheim), a researcher at the University of Cambridge, described for the first time in 1928 how an enzyme (which she called tyramine-oxidase) was capable of bringing about oxidative disamination of the biogenic amines [14]. This enzyme was identified in 1937

by the groups led by Herman Blaschko and Derek Richter, at the Physiology Department of Cambridge University [15], and by those of Caecilia E. Pugh and Juda H. Quastel, at the Biochemical Laboratory of Cardiff City Mental Hospital [16], being given the name monoamine-oxidase (MAO). Blaschko's group showed that MAO, isolated from cells of the liver, kidney and small intestine, was capable of metabolizing adrenaline through oxidation, a process that could be inhibited by ephedrine [15]. These authors concluded that the MAO inhibitors would act in a very similar way to ephedrine, activating the adrenergic system. However, this theory was rapidly discarded in 1939 by Richter himself and Tigney, as described by Amat and Cuenca [17]. For their part, Quastel and Pugh also identified this enzyme in the brain, though its significance remained unclear [16]. It would later be definitively demonstrated that MAO constitutes a flavoprotein enzymatic system located at the level of the mitochondrial membrane, and whose function is to produce oxidative disamination not only of the biogenic amines (serotonin and catecholamines), but of other, sympathomimetic amines (tyramine, benzylamine, β -phenylethylamine, etc.).

In 1952, the team led by Ernst Albert Zeller (Fig. (1)) at Northwestern University Medical School (Chicago, Illinois) observed for the first time that iproniazid (and not isoniazid) was capable of inhibiting MAO [18]. Subsequent studies found that serotonin in the brain was converted into hydroxyindoleacetic acid by MAO; for a long period, indeed, this process was thought to be the only path for the metabolism of serotonin. In 1957, Sidney Udenfriend and colleagues, at the National Institutes of Health (NIH) (Bethesda, Maryland), observed that administration of iproniazid to experimental animals produced a rapid increase in brain levels of serotonin, similar to those resulting from the administration of 5-hydroxytryptophan, a substance capable of crossing the blood-brain barrier and producing serotonin through decarboxylation [19]. Simultaneously, Bernard B. Brodie (Fig. (2A)) and his colleagues at the Laboratory of Chemical Pharmacology of the National Heart Institute (a division of the NIH), Parkhurst Shore and Alfred Pletscher (the latter being Director of Research at Hoffmann-La Roche in Switzerland) (Fig. (2B)), confirmed that reserpine and other compounds produced a release of serotonin in brain, platelets and intestine [20,21].

Fig. (1). Ernst Albert Zeller (1907-1987), biochemist at Northwestern University Medical School (Chicago, Illinois). His team demonstrated for the first time, in 1952, that iproniazid was an agent capable of inhibiting MAO.



Fig. (2). Bernard B. Brodie (1901-1989) (A) and Alfred Pletscher (1917-2006) (B). The research work of Brodie (Director of the Laboratory of Chemical Pharmacology at the National Institutes of Health, Bethesda, United States) on serotonin and catecholamines in the 1950s contributed highly valuable data for the subsequent postulation of the neurobiological hypotheses of depression. In 1967, Brodie was awarded the Lasker Prize for Basic Medical Research “for his extraordinary contribution to biochemical pharmacology”. The works of Pletscher (Director of Research at F. Hoffmann-LaRoche, S.A. in its headquarters in Basle and Professor of Pharmacology at the city’s University) with serotonin-reserpine-iproniazid, initially in collaboration with Brodie, opened the way to an understanding of the biochemical bases of affective disorders.



All such work opened up an interesting research line on brain functions, in the framework of which are the contributions of Charles Scott at Warner-Lambert Research Laboratories

(Morris Plains, New Jersey), who carried out certain animal experimentation studies that would be of great interest for the future characterization of these hydrazide drugs as antidepressants [22,23]. Scott believed that the tranquillizing effects observed in animals given reserpine, an alkaloid of *Rauwolfia serpentina*, were due to the release of serotonin caused by the reserpine. With this hypothesis, and knowing the results of Zeller's work, Scott administered iproniazid with the aim of limiting the enzymatic destruction of serotonin. However, the pre-treatment with iproniazid carried out by Scott before administering the reserpine had the opposite result to that expected by the researcher: a stimulant effect, rather than the predicted tranquillizing effect [24]. Similar results were obtained by Brodie's team at the NIH. In 1956, Scott's group described this effect of experimental alertization with iproniazid, which he called "marsilization", in reference to the trade name of this agent [24].

Discovery of the antidepressant effects of iproniazid: an example of serendipity

The origin of the first specifically antidepressant drugs, the MAO inhibitors (MAOIs), lies in the antitubercular hydrazide agents that had been used since the early 1950s [1,22,23]. It was precisely in 1952 that studies began, at the Sea View Hospital on Staten Island (New York), on the clinical effects of iproniazid, carried out by Irving J. Selikoff and Edward Robitzek, who observed that this drug possessed, compared to isoniazid, greater power to stimulate the Central Nervous System (CNS), an effect initially interpreted as a side effect [25]. The psychological changes observed in tuberculosis patients treated with iproniazid were especially striking [1,9,23,26]: these patients showed greater vitality, to the point in some cases of wanting to leave hospital, and a gradual increase in their social activity. A photograph by *Associated Press* from 1953 immortalized the effects of iproniazid. It shows several patients at the Sea View Hospital in party mood, even dancing. Under the picture it says: "A few months ago, the only sound here was the sound of victims of tuberculosis, coughing up their lives". Other authors reported that patients were "dancing in the halls tho' there were holes in their lungs" [9]. Similar psychostimulant effects were also observed in patients with other chronic illnesses, such as rheumatoid arthritis or cancer, treated with iproniazid [27].

However, the results of the first clinical trials with iproniazid indicated a safety profile, in the treatment of tuberculosis, inferior to that of isoniazid, so that it was practically abandoned, except in particular cases. For example, David M. Bosworth, Director of Orthopedics at St. Luke's and Polyclinic Hospital in New York insisted on the superiority of iproniazid for treating bone tuberculosis [28]. But at this point in the story serendipity came into play [4], when a few very wise clinicians saw in the psychostimulant "side effect" –which had emerged by chance– a potential "primary effect" that could be useful in other types of patient, basically those of a psychiatric nature. These inspired individuals included Jackson A. Smith, of Baylor University, (Waco, Texas), who in his analysis of iproniazid as a "tranquillizer" observed some improvement in two depressed patients from a group of 11 treated over a period of two weeks (increased appetite, weight gain, increased vitality and improved sleep) [29]; Gordon R. Kamman, of the University of Minnesota (Twin Cities) [30]; and Carlos Castilla del Pino, of the University of Córdoba (Spain), who described the euphoric and mood-raising effects of hydrazide therapy in tuberculosis patients [31]. Some studies were even published that assessed the mood-raising effect of isoniazid in psychiatric patients [32-34]. Indeed, it may even have been one of these authors, Max Lurie (a psychiatrist with a private practice in Cincinnati), who coined the term "antidepressant" to refer to the effect of isoniazid in depressed patients [35].

Finally, the year 1957 would be a key one for the future of hydrazide drugs as antidepressant agents, since it was at a meeting of the American Psychiatric Association (APA) in April of that year, in Syracuse, that the first data on the effects of iproniazid on depression were presented. Although it was much less widely used than isoniazid, George Crane, of New York's Montefiore Hospital, reported improved mood in 11 out of 20 tuberculosis patients with concomitant depression [36] treated with iproniazid, while Frank Ayd, an assistant at the Taylor Manor Hospital in Baltimore [37], reported similar results. Nevertheless, these researchers never referred to iproniazid as an "antidepressant". On the other hand, Nathan S. Kline (Fig. (3)) and colleagues (Harry P. Loomer and John C. Saunders), of Rockland State Hospital (Orangeburg, New York), who knew about Scott's research, especially the capacity of iproniazid for preventing the immobility in mice induced by reserpine [24], were the first psychiatrists to assess the efficacy of iproniazid in non-tuberculosis depressed patients (chronic psychotic

depression), carrying out the same procedures with humans as Scott did with animals. For their study they recruited 17 highly inhibited subjects with severe schizophrenia and 7 with depression, all patients at Kline's private surgery; participants were given a 50 mg dose of iproniazid 3 times a day. Their results, also reported at the Syracuse Meeting but not published until the following year, indicated that iproniazid had a stimulant effect on depressed patients, and that 70% of the patients who received iproniazid had undergone a substantial improvement (raised mood, weight gain, better interpersonal capacity, increased interest in their surroundings and themselves, etc.) [38]. Such was the impact of the new drug that, in November of that same year, the Hoffmann-La Roche company sponsored the *Symposium on the Biochemical and Clinical Aspects of Marsilid and Other Monoamine Oxidase Inhibitors*, which discussed its effectiveness not only for depression, but also for other pathologies, such as hypertension or angina. Within the framework of this symposium eight studies were presented, covering a total of some 300 patients affected by different mental disorders, mainly depression.

Fig. (3). Nathan S. Kline (1916-1983), one of the great pioneers of psychopharmacology. In 1952 he set up the Research Unit at Rockland Psychiatric Center (later called Rockland State Hospital) in Orangeburg (New York). Kline was the man responsible for the clinical introduction in psychiatry of iproniazid and reserpine, and was twice awarded the prestigious Lasker Prize; first, in 1957, for his studies of the antipsychotic effect of reserpine, and again in 1964, for his contribution to the development of MAOIs.



In 1957, Kline, who combined his work in clinical research with the post of Assistant Professor of Psychiatry at the University of Columbia, published a report on the first neuropsychiatric experiences with iproniazid (previously presented at the annual meeting

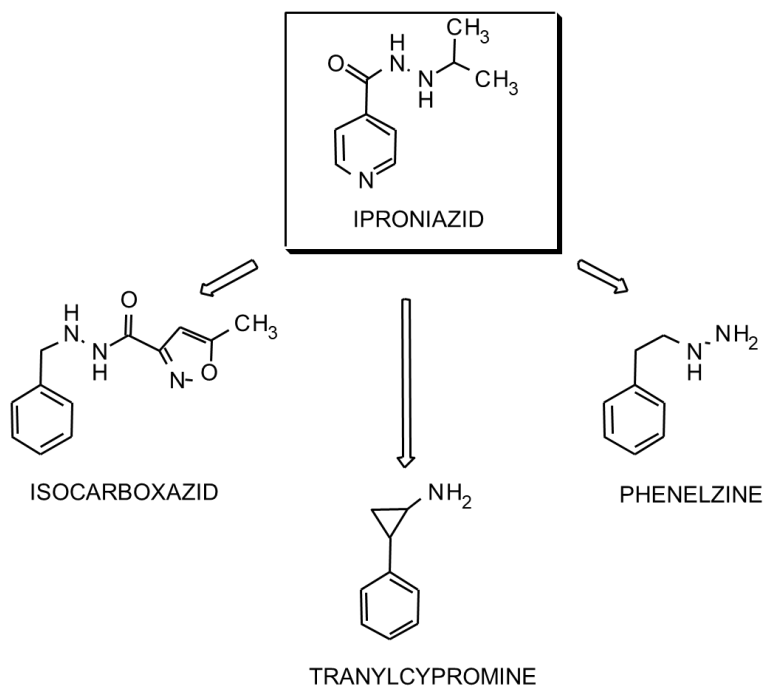
of the APA in Syracuse), during a Congress of the Committee on Appropriations of the United States Senate, held in May [39], proposing the term “psychic energizer” to refer to the drug’s action [40]. Even two years later, at a symposium held in Montreal, Werner Janzarik proposed using the term “thymmeretics”, that is, substances that act through an increase in the stimulative action of the impulse, to cover all the drugs that presented a spectrum of action similar to that of the incipient MAOIs. However, Kline’s group ran into considerable difficulties for pushing further with the study of the antidepressant effect of iproniazid: in early 1957, when their clinical research project was already under way, they lost the explicit support of the doctors in charge at Hoffmann-La Roche, who judged the indication of their drug as an antidepressant to be subject to an uncertain and inadequate market [26]. Without losing hope, they managed, according to Kline [39] himself, to arrange a secret meeting with L. David Barney, President of the pharmaceutical company, at Theodore’s Restaurant in New York. During the course of this meal, the researchers from Rockland State Hospital managed to interest Barney in their project, which was thus able to continue. Incidentally, the problems continued just after the APA meeting of April 1957, as the three members of the research group became involved in a serious conflict among themselves, carried on first through the pages of medical journals (*Journal of the American Medical Association*, 1965), and later even in the courts (Appellate Division of the Supreme Court, First Judicial County of New York, Index No. 7770, April 15, 1980; New York Court of Appeals, Decision of the Appellate Division of the Supreme Court, Upheld in *Saunders vs. Kline*, No. 141, March 26, 1981), over the attribution of the discovery of the antidepressant effect of iproniazid [9].

One year after the Syracuse meeting, and despite the fact that iproniazid was only marketed as an antitubercular agent, under the trade name Marsilid®, more than 400,000 patients affected by depression had been treated with the drug [10], which opened the way for the first group of specifically antidepressant drugs, later known as MAOIs. This great initial success of iproniazid was due, in part, to two important factors [1,23]: the good previous results obtained in the treatment of tuberculosis patients, and the lack at the time of truly useful therapeutic tools in the treatment of depression, so that the demand was enormous.

The saga moves on

Iproniazid soon gave way to other agents with much greater power to inhibit MAO [41], such as isocarboxazid (Hoffman-LaRoche), tranylcypromine (Smith, Kline & French) [42,43] and phenelzine (Warner-Lambert) [44] (Fig. (4)), as well as other hydrazine derivatives (nylamide, mebanazine and pheniprazine) or indole derivatives (etryptamine) [45]. Standing out among all these MAOIs was tranylcypromine, a cyclopropylamine structurally unrelated to the hydrazines. This molecule had been synthesized in 1948 by Alfred Burger and William L. Yost, as an analogue of amphetamines (trans-dl-2-phenyl-cyclopropylamine sulphate) [46], but its MAOI action was not discovered until 1959, in Smith, Kline & French Laboratories [42,47]. Precisely because tranylcypromine was not, like isoniazid and iproniazid, a hydrazine derivative, its clinical interest increased enormously, as it was thought it might have a more acceptable safety profile than that of the previous MAOIs [48]. By the mid-1980s, tranylcypromine and phenelzine together accounted for over 90% of the market in MAOIs [49].

Fig. (4). Chemical structure of antidepressant drugs of the MAOI family.



The safety problems of MAOIs gave rise to a new research line on antidepressants in the 1970s. The existence of two functional forms of MAO (MAO-A, located preferentially in the intestinal lining and associated with depressive disorders, and MAO-B) was revealed in 1968 by J.P. Johnston, at the Research Laboratory of May & Baker Ltd. (Dagenham, United Kingdom), in rat brain [50]. Subsequent studies confirmed that MAO-A preferentially disaminated adrenaline, noradrenaline and serotonin, whilst MAO-B metabolized benzylamine and β -phenylethylamine. Moreover, both isoenzymes had dopamine and tyramine as substrates. The classic MAOIs (iproniazid, phenelzine and tranylcypromine) irreversibly inhibited both isoenzymes, even though it was demonstrated that the functional form involved in antidepressant action was MAO-A [51]. These facts encouraged the development of new molecules with two important characteristics: a) the selective inhibition of MAO-A, permitting MAO-B to remain active and exercise its metabolizing action on certain substances, such as the tyramine ingested with food, and whose failure to disaminate could lead to hypertensive crises; and b) reversible and competitive inhibition of the isoenzyme, so that other substrates, such as tyramine, could move it from its enzymatic union. There thus appeared the reversible and selective inhibitors of MAO (RIMA). The first molecule of this family to be registered was moclobemide, developed at Hoffmann-La Roche by W. Wurkard and Moussa Youdim, though it always had to bear the reputation of limited clinical antidepressant effectiveness [52,53]. Later, brofaromine was registered, though for the same reason it did not come onto the market [54,55]. Also marketed, within the group of classic or irreversible MAOIs, was a selective inhibitor of MAO-B, deprenyl, prescribed for the treatment of Parkinson's disease, together with levodopa and peripheral inhibitors of dopa-decarboxylase.

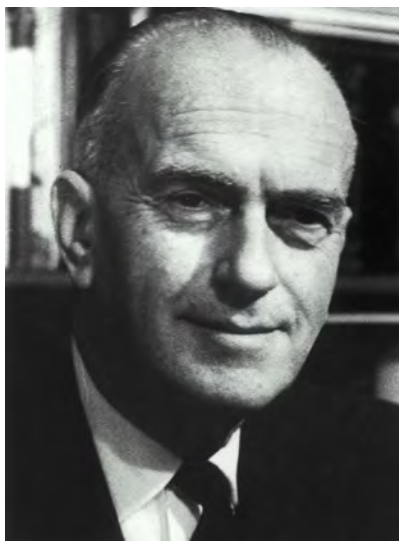
IMIPRAMINE AND TRICYCLIC ANTIDEPRESSANTS

Synthesis of iminodibenzyl derivatives

The history of tricyclic (TCAs) and tetracyclic antidepressants began in 1883, with the synthesis of the first phenothiazine by Prof. Heinrich August Bernthsen, a 28-year-old laboratory chief at the Badische Anilin und Soda Fabrik (BASF) in the German city of Mannheim [56], who was commissioned to experiment with chemical dyes, particularly

methylen blue [26,57]. In 1883 Bernthsen synthesized for the first time a phenothiazine that would serve as the basis for the subsequent synthesis, in 1899, of iminodibenzyl, by J. Thiele and O. Holzinger [58]. However, at the time, no use was found for this agent as a dye for the textile industry, so that it ended up gathering dust, so to speak, in a Basle warehouse, though remaining on the files of Swiss chemical company J.R. Geigy AG, which had used it at the end of the 19th century in the preparation of the Sky Blue dye [26].

Fig. (5). Robert Domenjoz (1908-2000). During his time as Director of the Pharmacology Section of the Swiss company J.R. Geigy AG, in the early 1950s, he carried out intensive psychopharmacological research, which would culminate in the clinical introduction of the first tricyclic antidepressant, imipramine.



Half a century later, the director of Geigy's Pharmacology Section, Robert Domenjoz (Fig. (5)), later to become director of the Pharmacology Institute at the University of Bonn, was impressed by data from the Paris company Rhône-Poulenc, which had developed, in close collaboration with the Institut Pasteur, some antihistamines that promised to be commercially successful as hypnotics or sedatives. Prof. Domenjoz encouraged his team to look into the effects of the phenothiazines, for which no important application had been found at that time, in the hope of their being useful as sedatives. In 1948, chemists Geigy F. Häflinger and W. Schindler used iminodibenzyl as the basis for synthesizing 42 derivatives [26,59]. The pharmacological tests carried out on these compounds revealed that the majority of them had, to a greater or lesser extent, antihistaminic effects, in addition to their sedative, analgesic and antispasmodic

properties, and that the differences between them were related to the chemical structure of their lateral chain. Moreover, the basic toxicological and lethal dose 50 (DL₅₀) studies carried out in mice revealed no significant adverse effects [60].

After these experiments in laboratory animals, and even some involving self-administration, these chemists contacted hospitals who might be interested in clinical research on these products, at a time when there were practically no bureaucratic restrictions on the implementation of these types of study. One of these substances – known internally as G-22150– was sent to Roland Kuhn (Fig. (6A)), assistant medical director at the Thurgausiche Heil- und Pflegeanstalt in Münsterlingen (close to Lake Constance) and pupil of Jakob Klaesi (who introduced the famous sleep cures), to see whether it could serve as a hypnotic. Kuhn discarded the possibility of using the substance in “pills for sleeping”, due to its irregular and rather unreliable results, but observed “a rather peculiar positive effect” [61]. However, interest in continuing the clinical development of this substance fell away.

Fig. (6). Roland Kuhn (1912-2005) (A), Medical Director at the Psychiatric Clinic of Thurgau Canton (B), in Münsterlingen, near Basle (Switzerland). Kuhn was one of the great pioneers of psychopharmacological research, and the discoverer of the antidepressant properties of imipramine.



Subsequently, in 1952, came the news that Pierre Deniker and Jean Delay had made an important discovery while testing a phenothiazine called chlorpromazine at the Saint-

Anne university hospital in Paris [56,62], with thirty-eight psychotic patients showing spectacular improvements. These findings spurred an intensification of the search for substances with similar properties by the pharmaceutical companies, concerned that Rhône-Poulenc might corner the new market that was opening up. The result was that some long-forgotten antihistamines filed away by the Geigy company were dusted off, in the hope that they might prove useful to psychiatry [26,61,63,64].

At this time, the prevailing doctrine on the aetiology of depression was that it was the result of psychodynamic processes, despite the fact that the therapeutic effects of electroconvulsive therapy were obvious. Consequently, the thesis that drugs could have some effects on the symptoms of mood states but would not modify the course of the illness itself enjoyed the support of a majority of specialists. Even Roland Kuhn himself was scientifically committed in this philosophical field of psychoanalysis, despite being considered as one of the pioneers of the new generation of “biologist psychiatrists” by virtue of his extensive knowledge of organic chemistry and biochemistry [63], especially after February 1954, when he contacted Geigy (or *vice versa*, according to some authors) to study the possible antipsychotic effects of G-22150, which he had tested years before. Kuhn had to interrupt some treatments with this substance due to problems of tolerance [59,61], but asked Geigy to send him another phenothiazine, in the hope of finding another potent antipsychotic agent for his patients and avoiding a shortage of drugs at the Münsterlingen clinic. In early 1956, Kuhn received a compound called G-22355, a substance with the same lateral chain as chlorpromazine, which had been synthesized by Häflinger and Schindler, in 1948, from promethazine, replacing the sulphate bridge of phenothiazine with an ethylene bridge [13,64]. This substance had been registered in 1951 with US licence number 2554736 [65].

Development and clinical introduction of imipramine as an antidepressant

The extensive clinical research that took place in 1956 at the Kantonsspital Münsterlingen (Fig. (6B)), near Basle, soon made it clear that agent G-22355 lacked any appreciable neuroleptic effect. Indeed, in some patients who had previously been treated with chlorpromazine their schizophrenic condition worsened, giving way to a state of agitation that gave cause for clinical concern. As a result, the clinic’s image was tarnished and

relations between its directors and the pharmaceutical company became strained [60]. However, Kuhn observed that three patients diagnosed with depressive psychosis showed a marked improvement in their general state within just a few weeks. Consequently, in a letter to Geigy dated 4 February 1956 [3], Kuhn raised for the first time the possibility that this substance might have an antidepressant therapeutic effect. Subsequently, another 37 depressive patients were given this drug, thus demonstrating its special efficacy in the treatment of depressive disorders [61,66,67]. The antidepressant effect of imipramine was, therefore, totally unexpected, and its discovery completely accidental.

Kuhn's impressions of the initial results, in a total of 40 depressive patients, were presented on 6 September 1957, at the II World Congress of Psychiatry in Zurich, to an audience of scarcely more than a dozen [66]: "The patients appear, in general, more animated; their voices, previously weak and depressed, now sound louder; they are more communicative, the lamentations and sobbing have disappeared. The depression, which had manifested itself through sadness, irritation and a sensation of dissatisfaction, now gave way to friendly, joyous and accessible feelings". These results were published for the first time on 31 August 1957, in German, in the journal *Schweizerische Medizinische Wochenschrift* ("Über die Behandlung depressiver Zustände mit einem Iminodibenzyl derivat (G 22355)") [66]. Moreover, during the Zurich Congress, Paul Schmidlin introduced the term "timoleptic" to describe the new substances whose action was similar to that of Geigy's compound [13].

Kuhn's reports of the efficacy of this compound, now formally called imipramine, were received, as the author would later confess [68], with some scepticism by the medical community, since the view emerging from the numerous conferences on pharmaceutical and pharmacological disciplines held between 1953 and 1958 was based on the assumption that there could never exist a truly effective antidepressant substance, which went beyond reducing the symptoms of depression. The most widespread hypothesis at this time, as referred to above, was that depression as such emerged from intrapsychic conditions and conflicts [69], leading to the conviction that chemical tools merely masked the true symptoms of depressive conditions. Despite this clear opinion among experts, the antidepressant effects of imipramine were confirmed by such prestigious specialists as Paul Kielholz and Raymond Battegay, and imipramine was put onto the Swiss market by

Geigy at the end of 1957, under the trade name Tofranil®. The drug came onto the market in the rest of Europe in the spring of 1958 [26,65], and represented a giant step in the treatment of depression, as the first example of a new family of drugs, known as imipraminic or tricyclic antidepressants (TCAs). As Kuhn [68] put it: “We have achieved a specific treatment of depressive states, not the ideal already going far in this direction. I emphasize ‘specific’, because the drug largely or completely restores what the illness has impaired –namely, the mental functions and capacity and what is of prime importance, the power to experience.”

In September 1958, at the I Congress of the recently founded Collegium Internationale Neuro-Psychopharmacologicum (CINP), held in Rome, an audience made up primarily of psychiatrists began to become aware of the positive effects of the new drug, though more than through the work of Kuhn, through that of other research teams. In fact, the year 1958 saw the publication of two new studies on imipramine in the *American Journal of Psychiatry*. One of these reproduced the lecture given by Roland Kuhn at Galesburg State Hospital in May of that year, and was published in the November issue. Although the article added nothing new with respect what had appeared previously in the *Schweizerische Medizinische Wochenschrift*, it did have greater international repercussions. In it, Kuhn described at length the pharmacological effects of imipramine, reported its efficacy data and adverse effects, and offered recommendations for its clinical use and dosage and the duration of treatment. He recounted how “the patients got up in the morning voluntarily, they spoke in louder voices, with greater fluency, and their facial expression became more lively. They began to do some individual activities, they once more sought to make contact with other people, they began to train on their own, to participate in games, to become happier and to recover their ability to laugh” [67]. His observations were confirmed later through studies with larger samples [68]. The following year, 1959, saw the publication of more than 60 studies assessing the therapeutic effects and adverse reactions of imipramine in different groups of patients. The countries in which there was most expectation in relation to the new drug were Italy, France and Canada, though positive results were also reported in Russia, Poland, Sweden and South Africa.

The introduction of imipramine in North America was due largely to the work of one of the great pioneers of psychopharmacology and the man who had previously introduced chlorpromazine there [62,70], Heinz E. Lehmann, a psychiatrist from Berlin who had fled Nazi Germany and was working at the Verdun Protestant Hospital in Montreal (now the Douglas Hospital). At the II World Congress of Psychiatry in Zurich, Lehmann heard Kuhn's lecture and immediately began treating groups of Canadian patients [26]. Lehmann designed and implemented a study on the efficacy of imipramine in a sample of 48 depressive patients, thus permitting the drug to be marketed in the United States [71]. The fact that Lehmann, an expert of great international prestige, put his faith in imipramine was of enormous importance for its acceptance worldwide.

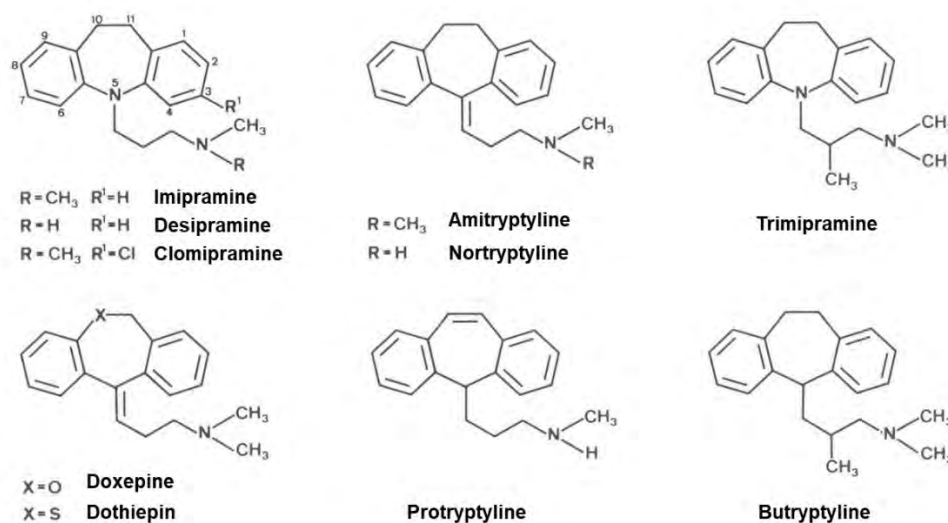
The first imipramine-placebo controlled clinical trial was performed in 1959 by Ball and Kiloh [72], demonstrating the efficacy of this substance, especially in so-called endogenous depressions and in psychotic depressions. In March of that same year, at the *McGill Conference on Depression and Allied States*, an international event held in Montreal, all the data on imipramine accumulated up to that time from North American and European studies were presented. However, it would be another six years before Gerald L. Klerman and Jonathan O. Cole demonstrated that imipramine was significantly superior to placebo in the treatment of depression, thanks to an analysis with data from 23 published studies and a total of 1000 patients treated with imipramine (550 patients) or with placebo (459 patients). The results of this analysis confirmed the rate of improvement at 65% in the imipramine group, as against 31% in the placebo group [73]. Indeed, imipramine has maintained its status as one of the most effective antidepressants up to the present day.

The development of new tricyclic antidepressants

Despite the great success of imipramine, it was not until 1961 that a second TCA came onto the market. Three years earlier, the research team at the Merck and Co. Pharmaceutical had developed amitriptyline, initially intended as an antipsychotic, after modifications to the central ring of the thioxanthene family, constituting the first compound in the dibenzocycloheptadien group [74]. Merck appointed Frank J. Ayd Jr. to lead the clinical research on this new compound. Ayd, one of the most prolific biologist

psychiatrists of his time [75], had gained prestige years earlier as one of the pioneers in the US of the study of chlorpromazine (1952) and would later (1962-1965) be a regular guest on the *Religion and Science* series broadcast by Radio Vatican. At the Baltimore Square Hospital, Ayd treated 130 patients with amitriptyline, finding the antidepressant effect to be similar to that of imipramine. On 7 April 1961, amitriptyline was approved as an antidepressant by the Food and Drugs Administration (FDA), under the trade name Elavil®. This substance would maintain some of the tranquillizing effects of the thioxanthenes, so that it supplanted imipramine in the treatment of patients with agitated or anxious depression. Simultaneously, European pharmaceutical firms Hoffmann-La Roche and, a little later, H. Lundbeck and Co. had succeeded in synthesizing amitriptyline, through the corresponding modification of the chemical structure of imipramine, though given the priority of its request, Roche received the European marketing rights under the name Saroten® [76].

During the 1960s a whole series of TCAs were developed (Fig. (7)) [64]. In 1963, nortriptyline was approved in the UK, as Allegron®, whilst in the USA it was approved by the FDA in November 1964, the year that also saw the approval of desipramine (J.R. Geigy), previously identified as the principal urinary metabolite of imipramine; trimipramine arrived in the UK and other European countries in 1966, under the trade name Surmontil®. Other TCAs soon followed: protriptyline (known as Concordin® in Europe and Vivactil® in the USA) in 1966, iprindol (Prondol®) in 1967, dothiepin (Prothiaden®) –not approved in the USA– and doxepine [77] –marketed in Europe by Boehringer subsidiary Galenus (Aponal®) and in the USA by Pfizer (Sinequan®) [78]– in 1969, and finally, clomipramine (Anafranil®), which was marketed in Europe from 1975 but was not approved in the USA. Moreover, the 1960s saw the dibenzazepine structure of imipramine undergo many modifications in order to obtain new antidepressants. Among the results of these were the so-called heterocyclic, tetracyclic or “second-generation” antidepressants [74], such as maprotiline, first sold by Ciba-Geigy in Europe and Japan in 1972 [26], or mianserine (Tolvin®).

Fig. (7). Chemical structure of tricyclic antidepressants (6-7-6), with a “classic” lateral chain.

The pharmacological contributions of imipramine

The efficacy of TCAs in the treatment of depression was indisputable by the end of the 1950s [79]. However, their action mechanism was not well understood. The year 1952 saw the introduction in German-speaking countries of reserpine for the treatment of schizophrenia, but it soon became clear that this substance had pro-depressive properties. In 1959, Robert Domenjoz, director of the Pharmacology Section at J.R. Geigy AG, and W. Theobald confirmed that imipramine produced an antagonism of the effects of reserpine [80]. Two years later, Bernard Brodie's team at the NIH demonstrated the physiopathological role of biogenic amines in depression, on finding, in studies with laboratory animals, that imipramine inhibited the absorption of noradrenaline. Another NIH team, led by Julius Axelrod –who maintained a great rivalry with Brodie, despite having been his pupil– demonstrated a reduction in the uptake of noradrenaline in the synaptic nerve endings during treatment with TCAs [81]. But the fruits of this between Brodie and Axelrod finally served at least as the basis for the subsequent work of William Bunney Jr. and Joseph Schildkraut, who in 1965 proposed the catecholamine-deficit hypothesis of the aetiology of depression [82].

BETWEEN THE DECLINE OF MAOIs AND THE RISE OF TCAs

Towards the end of the 1950s, the prevailing idea that depressive syndromes should not be treated solely and optionally with antidepressants began to change, with the pharmacological treatment option gaining more and more ground. First of all, and contrary to the postulates of Freudian doctrines, the new basic opinion of most psychiatrists was that depressive syndromes had not only psychodynamic but also biological causes, which could benefit from treatment with drugs [26,63]. Secondly, numerous clinical studies had demonstrated the superior efficacy and good tolerability of tricyclic agents. And finally, the pharmaceutical industry had discovered the enormous economic potential implied by the high prevalence of depression worldwide. The clinical introduction of diverse pharmacological agents with different action mechanisms (TCAs and MAOIs) intensified, in synergic fashion, competition and marketing strategies. As a consequence of such developments, depression ceased to be solely in the hands of “specialists”, that is, hospital psychiatrists. However, in spite of the enormous commercial opportunities opening up for antidepressant drugs, the two great families of pharmacotherapeutic agents evolved in markedly different ways: while TCAs achieved a success unprecedented in the history of psychiatry, MAOIs began a rapid decline, leading to their virtual disappearance from the therapeutic arsenal [13].

The rise of TCAs was due in large part to Merck and Co., since 1919 a legally independent US firm with the same name as its German mother company, which, after the II World War, continued its activities in the field of psychiatry. Merck’s introduction of amitriptyline, the second tricyclic agent, increased the confidence of general practitioners and specialists in these drugs. It was in this context that, in 1961, Frank Ayd –an arch example of the biologicist psychiatrist who advocated “treating not only the spirit but also the body” [75]– produced a book explaining depression and its treatment that made them easier to understand. For its part, Merck and Co., as a “typical” US company, had realized that what was most important was not selling drugs, but rather, selling an idea. In this case, the central message was the ability to treat with antidepressants not only the rare disorder known as “vital depression”, but all types of depressed mood [26]. Thanks to the commercial power of these two chemical multinationals and a marketing agreement between them (as Elavil® by Merck and as Tryptizol® by Roche) throughout the world,

except in the USA, covered exclusively by Merck, amitriptyline soon became the most widely prescribed antidepressant of its time.

As this process of acceptance became consolidated, many highly prestigious scientists became involved in it, and antidepressant therapy with TCAs continued to grow. But the story for MAOIs was totally different. Towards the end of the 1950s, MAOIs constituted possibly the family of therapeutic agents most widely used in the treatment of depression [83]. However, the situation changed suddenly, and the decline in the use of these drugs was as rapid as was their clinical introduction. Indeed, the commercial life of iproniazid was really quite short, since it was withdrawn from the US market in 1961 after accusations of its having induced a series of cases of jaundice and nephrotoxicity. The imputability of these adverse effects was fiercely challenged, since no specific immunological studies were carried out to determine whether the small number of jaundice cases observed were induced by the drug or were simply cases of viral hepatitis [39]. These hepatotoxic adverse effects of iproniazid were also described for the rest of the MAOI drugs from the hydrazine group, such as nylamide, isocarboxazid and phenelzine. As regards the last of these, more than 50% of deaths during treatment were attributed to hepatic cell damage, and this led to the withdrawal from the market of the majority of MAOIs at an international level [13,23].

As occurred with iproniazid, tranylcypromine was withdrawn from the US market, though for different safety reasons, in 1964, after reports of an increase in the number of hypertensive crises related to the drug. These hypertensive crises, associated with intense headaches and in some cases with subarachnoid intracranial haemorrhages, were described from the very moment the drug was approved, in 1961, and according to Barry Blackwell, at Maudsley Hospital in London, it was traced to the ingestion of certain cheeses, so that these crises became referred to as the “cheese effect” [84]. A.M. Asatoor and colleagues [85], at the Westminster Medical School in London, showed that after the ingestion of cheese there was a considerable increase in the excretion of metabolites of tyramine. Later, it was confirmed that many other foods (products made with yeast, chicken liver, snails, pickled herrings, red wines, some types of beer, tinned figs, broad beans, chocolate, products including cream, and so on) contained amines with indirect

action (chiefly tyramine), which could also provoke hypertensive episodes in patients treated with MAOIs.

Despite the dramatic nature of these reactions, their incidence was actually extremely low, and did not justify withdrawal of the product. However, these problems attributed to MAOIs, together with the results of some clinical trials, as the sponsored by the British Medical Research Council [86] (strongly questioned later on), that confirmed their lower efficacy for major depression *versus* TCAs, considerably limited their therapeutic use, especially in European countries [87], and favoured a generalized loss of prestige. In fact, today, MAOIs are always considered a second-choice drug, potentially of great help in cases of intolerance or lack of response to other antidepressants (refractory depression) [45,88].

THE GREAT CONTRIBUTION OF IPRONIAZID AND IMIPRAMINE TO THE HISTORY OF PSYCHIATRY: POSTULATE OF THE FIRST AETIOPATHOGENIC HYPOTHESES ON DEPRESSION

The clinical introduction of iproniazid and imipramine contributed, as we have seen, to revolutionizing therapy in the field of psychiatry. However, despite the importance of this contribution, it is not the only one of historical relevance for the progress of biological psychiatry. From the strictly scientific point of view, TCAs and MAOIs played a decisive role in the development of the first aetiopathogenic theories of affective disorders in the 1960s [82,89]. Thus, it could finally be demonstrated that psychotropic agents had the capacity to modify altered mental states, and that psychiatric disorders should no longer be filed under “Philosophy: alterations of the soul”. Moreover, with specific regard to the area of psychopharmacology, the development of these drugs made it possible to introduce new methods for assessing the antidepressant activity of different substances [90]. This permitted, in turn, enlargement of the arsenal of antidepressant therapy over the following decades, always in search –in line with the postulates set down half a century before by Paul Ehrlich– of a kind of “magic bullet” that would eradicate the illness without harming the patient.

The clinical incorporation of the new psychoactive drugs in the 1950s gave rise to a Copernican shift in the way the origin of mental illness was understood. Although they had only a very slight effect on people with normal mood state, in depressed patients these drugs brought about a marked reduction of symptoms, especially after a period of two or three weeks. Thus, support began to grow among the scientific community for the notion that these drugs might be correcting a kind of specific “chemical imbalance”, the underlying cause of the illness. Furthermore, this concept would be highly convenient and liberating for society in general, and for the mentally ill and their families in particular, since it would relieve patients of a heavy moral burden and allow the symptoms of the illness to be removed through administration of a series of chemical substances [91]. This concept of “chemical imbalance”, then, revolutionized the view held by the most traditional sectors of society about mental illness, entrenched in pseudo-medieval conceptions such as states of possession, and even by psychiatrist themselves, some of whom continued to see psychiatric patients as deranged individuals with moral defects, needful of moral therapy.

Thus, one of the main consequences of the discovery of the new psychoactive drugs in the 1950s, together with the simultaneous advances in knowledge of the neurochemical aspects of brain functioning –as in the case of neurotransmitters–, was the possibility of postulating the first biological hypotheses on the genesis of mental illnesses, and laying the bases of so-called “biological psychiatry” [92]. In this way, psychoactive drugs have helped to define the neurochemical process underlying mental illness and generate a physiopathological theory of it, in an eminently “pharmacocentric” approach, as some authors put it [93].

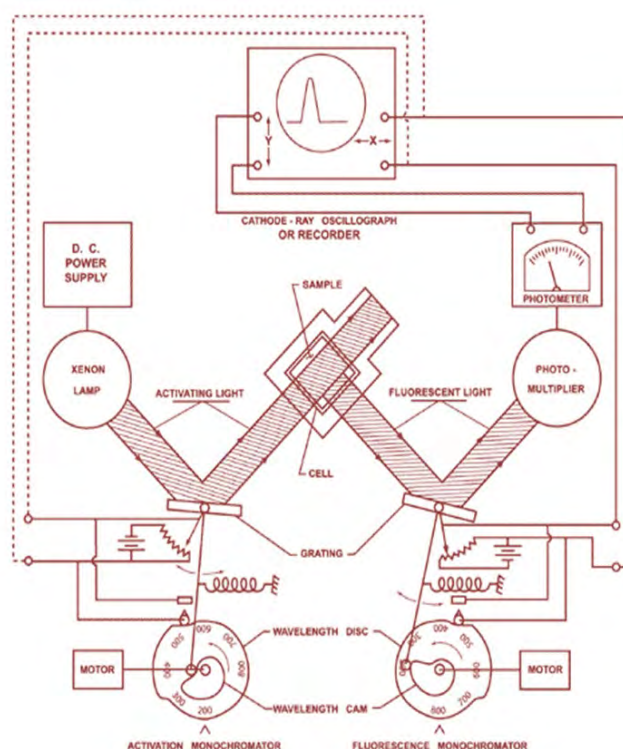
The role of iproniazid and MAOIs

The action mechanism of iproniazid as a MAO inhibitor was described, as already mentioned, by E. Albert Zeller’s group in 1952. Initially, this action mechanism was interpreted as being closer to that of the psychostimulants than that of the other antidepressants. However, it was observed that acute administration of MAOIs to experimental animals or to healthy individuals provoked practically no modification of their behaviour, except in the case of tranylcypromine, which has stimulative effects

similar to those of amphetamines. On the other hand, as occurred with TCAs, the MAOIs antagonized, at an experimental level, the effects of reserpine and the tetrabenazine, and boosted the effects of amphetamine, of hexobarbital, of 5-hydroxytryptophan and of DOPA [82].

Coinciding with the clinical introduction of iproniazid, the mid-1950s saw the introduction, in the context of neuropsychopharmacological research, of an analytical technique that greatly contributed to speeding up our understanding of how psychoactive drugs work, and in turn of the physiopathology of mental disorders: spectrophotofluorimetry (Fig. (8)) [3]. Thanks to this technique, it was possible to begin detecting changes in the levels of monoamines in the brain and of their metabolites through direct research. Furthermore, the observations carried out with reserpine between 1955 and 1957 (depletion of serotonin in the nervous system, or modifications in levels of noradrenaline in different tissues) in countries such as the United States, Britain, Switzerland, Spain or Sweden, permitted considerable progress in knowledge of the physiology of the autonomic and central nervous systems [94]. Bernard Brodie's group at the NIH, using spectrophotofluorimetry, as developed in the same laboratory by Robert Bowman and Sidney Udenfriend [95], discovered that the administration of reserpine to rabbits brought about a depletion of brain levels of serotonin, and more importantly, that the sedative and other effects of this substance remitted as the serotonin returned to its normal levels [96]. Two years later, this same team correlated the appearance of depressive symptoms with the depletion of serotonin deposits after administration of reserpine [21]. Moreover, when the animals were given a MAOI (iproniazid) after the administration of reserpine, there was no modification of the sedative effect induced by this agent [97], whereas if administration of iproniazid preceded that of reserpine, there was neither depletion of serotonin nor the effects of the reserpine, though the animals displayed hyperactivity and signs of increased sympathetic nerve activity [98]. In the words of Pletscher [99], "these experiments with the iproniazid-reserpine combination also supported the hypothesis that the action of the psychotropic drugs is mediated by biogenic amines, and that biogenic amines play a role in the functioning of the brain".

Fig. (8). Schematic drawing of the Aminco-Bowman spectrophotofluorometer.



Thus, it could be confirmed that the administration of reserpine reduced the levels of serotonin [100] and noradrenaline [101] in the brain, while the administration of iproniazid increased them. This, combined with the clinical observations that iproniazid induced euphoric conditions in some tuberculosis patients [36], and reserpine induced depression in some hypertensive patients [102], allowed the postulation of the initial hypothesis that inhibition of MAO and the resulting increase in serotonin and noradrenaline in the brain was responsible for the stimulant effect on mood (antidepressant effect) of iproniazid [103]; these factors also lent support to the theory that alterations of mood were mediated by modifications of the levels of serotonin, noradrenaline, or both [20]. This theoretical approach, eminently pharmacocentric, opened the door for the first time to an understanding of the neurobiological bases of depressive disorders. But it would be during the 1960s that monoaminergic theories of depression flourished – theories that postulated a functional deficiency of noradrenergic or serotonergic neurotransmission in certain brain areas as the essential cause of these pathologies [89].

The role of imipramine and TCAs

In the 1960s, the precise mechanism through which imipramine and other TCAs worked as antidepressants remained unclear. While the initial studies carried out with imipramine showed that the drug had multiple pharmacological actions, it could not be determined which of them was responsible for the positive effect on mood alterations. Among these actions, it was observed how imipramine antagonized and reversed the sedation, hypothermia, ptosis and diarrhoea induced by reserpine in rats, but how, in turn, the pharmacological actions of reserpine were not confined to the depletion of noradrenaline and serotonin, but rather included parasympathomimetic effects, the effect of imipramine on the disorders induced by reserpine did not provide the key to unlocking the mysteries of the way this antidepressant drug functioned [3,82].

However, such studies did help to produce a series of pharmacological models of the antagonism of reserpine, which in turn helped in the quest for new antidepressant agents with imipraminic effects [45]. One of those developed was desipramine, the demethylated metabolite of imipramine itself. This imipramine metabolite did indeed make a greater contribution to forming the hypothesis that the effect of imipraminic antidepressants was mediated by their action at the level of noradrenergic neurotransmission, thanks to the discovery that the reversal of the effects of reserpine by desipramine did not occur in those animals in which a selective depletion of catecholamines had been induced through administration of α -methylparatyrosine (AMPT), a selective antagonist of tyrosine-hydroxylase [94]. But this model also increased confusion about the action mechanism of antidepressants and the pathogenic mechanism of the illness, since the notion that depression was the result of a chemical imbalance, in which noradrenaline deficiency played a certain role, was called into question after it was demonstrated that administration of AMPT did not produce relapses in patients treated successfully with imipramine, or that it is tryptophan, precursor to serotonin, and not phenylalanine, precursor of noradrenaline, that triggers the antidepressant effect of MAOIs [104].

In Spain, the group led by Francisco G. Valdecasas at the University of Barcelona also studied this topic. A series of experiments with guanethidine, bretylium, amphetamine and tyramine suggested an inhibiting effect of noradrenaline uptake by

demethylimipramine [105], which has been one of the basic mechanisms employed over the last 50 years for the study of new antidepressants. Subsequently, it was demonstrated that demethylimipramine was capable of antagonizing the response to tyramine, at the vascular level and in the deferent behaviour of the rat, indicating that TCAs also inhibited the reuptake of this indirect sympathicomimetic amine [106].

Monoaminergic theories of depression

Thanks to the discovery and subsequent therapeutic use of TCAs and MAOs, the 1960s saw the flourishing of monoaminergic theories of depression [107], which postulated a functional deficiency of noradrenergic or serotonergic neurotransmission in certain brain areas as a primary cause of these pathologies [89], as we shall discuss presently. These findings equipped psychiatry, for the first time in its history, with a series of biological bases similar to those available in other areas of internal medicine.

Catecholaminergic hypothesis

The “catecholaminergic hypothesis” was the first to be postulated, based on the observations mentioned above about the effects of the antidepressants recently discovered: the inhibitory action of iproniazid on MAO [18], the blocking of synaptic reuptake of noradrenaline by imipramine [108], and the fact that reserpine, an alkaloid that produces an emptying of noradrenaline in nerve endings, caused depressive symptoms in a high percentage of patients on being used as an antihypertensive [109]. This hypothesis on the biological mechanism of depression, presented by Joseph J. Schildkraut (Fig. (9)) of the Massachusetts Mental Health Center (Boston) in a classic work published in 1965, suggested that this pathology was due to a fall in noradrenaline level in the intersynaptic cleft: “some depressions, if not all, are associated with an absolute or relative deficit of catecholamines, particularly noradrenaline, in important adrenergic receptors in the brain. Contrariwise, elation may be associated with an excess of such amines” [110]. To date, Schildkraut’s article is still the most cited in the entire history of the *American Journal of Psychiatry*. In support of this theory, Schildkraut *et al.* [111] also highlighted the fact that lithium salts, effective in the treatment of the manic

phases of bipolar disorders, reduced cerebral levels of noradrenaline, an effect opposite to that observed with TCAs.

Fig. (9). Joseph Jacob Schildkraut (1934-), Professor of Psychiatry at the University of Harvard and Director of the Neuropsychopharmacology Laboratory at the Massachusetts Mental Health Centre (Boston). In his article entitled *The Catecholamine Hypothesis of Affective Disorders*, published in 1965, he postulated the noradrenergic hypothesis of depression.



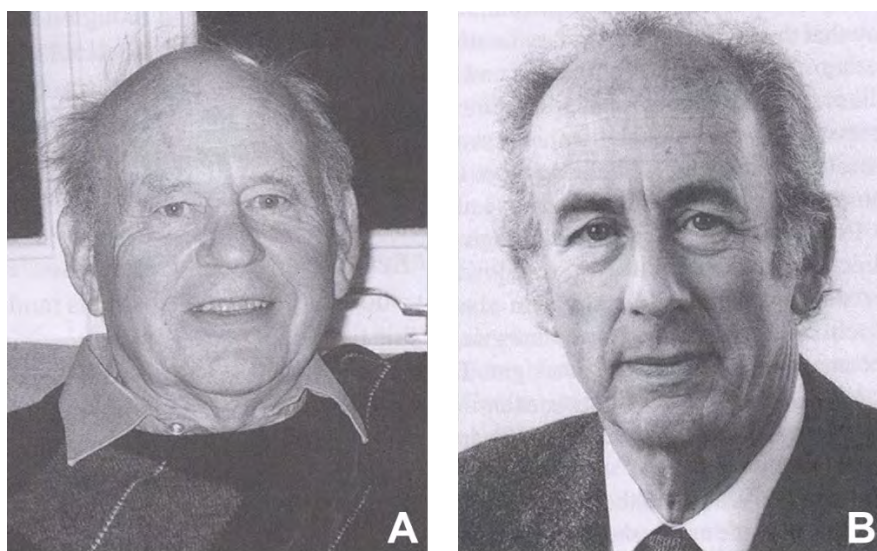
This so-called “noradrenergic hypothesis of depression” set off an avalanche of studies on the role of the noradrenergic system in the genesis of affective and other psychiatric disorders.

Serotonergic hypothesis

At the same time, there began to develop a “serotonergic hypothesis” of depression. Since 1952, thanks to the work of Betty Twarog, a researcher in Professor John Welsh’s laboratory at Harvard, it had been known that serotonin was a brain neurotransmitter [112]. For their part, the efforts of Brodie’s group, mentioned above, in relation to reserpine and the tissular depletion of serotonin, including in the brain [20], were complemented by those of other groups, such as that led by Alec J. Coppen (Fig. (10A)) of the Neuropsychiatric Research Institute, which belonged to the Medical Research Council of London. Coppen’s group demonstrated that the administration of tryptophan, a precursor of serotonin, to depressed animals boosted the therapeutic effects of MAOIs

[104]. Another important group was that of Dutch psychiatrist Herman M. van Praag (Fig. (10B)), of the Department of Biological Psychiatry at Groningen University. Van Praag, working initially with the biochemist Bart Leijnse, concluded that there were reasons to acknowledge a relationship between MAO inhibition and antidepressant action, and between serotonergic dysfunctions and the appearance of certain types of depression [113].

Fig. (10). The serotonergic hypothesis of depression is based largely on the pioneering work of Alec James Coppen (1923-), at the Neuropsychiatric Research Unit of the UK Medical Research Council (MRC), and Herman M. van Praag (1929-), at the Department of Biological Psychiatry of the University of Groningen (The Netherlands).



However, this serotonergic hypothesis was postulated without a clear demonstration of neurobiochemical correlates at a central level [89], but rather on the basis of studies of variables related to peripheral serotonergic dysfunction, basically at platelet level [107]. The definitive extrapolation of these hypotheses to CNS functioning did not take place until the introduction of more modern techniques. Thus, in 1968, Arvid Carlsson and colleagues at the University of Gothenburg (Sweden) described for the first time how TCAs blocked the reuptake of serotonin at a brain level [114], permitting Izyaslav P. Lapin and Gregory F. Oxenkrug to postulate, in 1970, the serotonergic theory of depression, as opposed to the catecholaminergic hypothesis, based on a deficit of serotonin at an inter-synaptic level in certain brain regions [115]. Finally, it would be confirmed that TCAs (and electroconvulsive therapy) improved the efficiency of

serotonergic transmission, above all that which was mediated by 5-HT_{1A} receptors, either through sensitization of post-synaptic receptors or through desensitization of pre-synaptic receptors, which usually reduce the release of serotonin in the synaptic cleft or inhibit the frequency of discharge of serotonergic neurones [116]. With all of these experimental observations it could also be concluded that a fall in synaptic levels of serotonin, in certain brain areas, was one of the biochemical causes of depressive disorders.

FLUOXETINE AND SELECTIVE SEROTONIN REUPTAKE INHIBITORS

As already mentioned, the incorporation of TCAs and MAOIs into the antidepressant arsenal was the fruit of coincidence and of the observational skills of some researchers, both basic and clinical. However, the scientific value of these drugs, in the framework of the pharmacology of mental disorders, is of crucial importance, since they provide highly relevant data on the action mechanisms of pharmacological agents at the synaptic transmission level and, by extension, throw light on the aetiology of the antidepressant effect, opening the way for the development of new, much more specific drugs.

In contrast to the case of the way these substances were introduced into the clinical context, the selective serotonin reuptake inhibitors (SSRIs) constitute the first family of psychoactive drugs developed in line with a procedure of rational and directed design [117], that is, following a strategy planned in advance, which involved seeking a drug capable of acting on a specific *locus* of action (the serotonin reuptake pump, in this case), avoiding, moreover, other non-essential *loci* (e.g., different neuroreceptors) and the associated potential undesirable effects.

Fluoxetine was the first SSRI to be synthesized and developed, by the US firm Eli Lilly (Indianapolis, Indiana), and is considered the prototypical molecule of this family of antidepressants, becoming, indeed, the world's most widely prescribed antidepressant. The first publication on fluoxetine dates from 1974. The 15 August issue of the prestigious journal *Life Sciences* included the article by Wong et al. entitled "*A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine*", which described the actions of the new molecule on amine reuptake systems and postulated its potential utility for the study of the serotonergic function and

of certain mental disorders [118]. Twelve years later, the drug came onto the pharmaceutical market in Belgium, and in 1987 (12 December) it was approved for sale as an antidepressant by the FDA. Fluoxetine is, moreover, the most written-about drug – together with chlorpromazine – in the history of pharmacology, being the subject of well over 25,000 scientific publications.

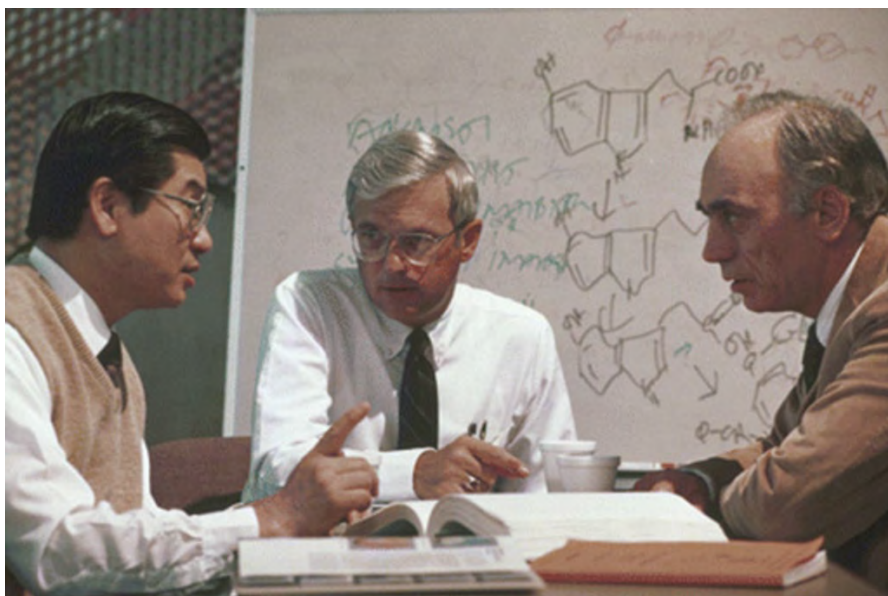
A triumph for the policy of the rational design of psychoactive drugs: the discovery of fluoxetine

The story of the synthesis and development of fluoxetine [119] begins with the studies carried out in the 1960s on the action mechanisms of TCAs. At the end of that decade, the serotonergic hypothesis of depression began gaining momentum among researchers after studies demonstrated the powerful inhibition of cerebral reuptake of serotonin exercised by imipramine and other, tertiary derivatives [120] –an inhibition that was much more powerful in the case of clomipramine (a molecule with a chloride group added to the triple ring of imipramine). Clinical evidence also supported this serotonergic hypothesis, such as a decrease in levels of serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the rhombencephalon of depressive patients who had committed suicide [121] and reduced concentration of 5-HIAA in the cerebrospinal fluid of depressive patients [122]. Moreover, treatments with precursors of serotonin, such as tryptophan or 5-hydroxytryptophan, showed antidepressant effects [89], while the incorporation of new technologies, such as preparations of rat brain synaptosomes, enabled Lilly Research Laboratories, among other things, to determine the high-affinity kinetics in the uptake of serotonin [123].

The development of fluoxetine, from a historical perspective, can be dated from 1971, when a prestigious pharmacologist with experience in serotonin research, Ray W. Fuller (Fig. (11)) joined Lilly. Fuller soon began trying to make the directors of the company aware of the importance of these new neurotransmitters in the genesis of affective disorders, though there was some initial reluctance from Lilly to embark upon research in this direction. That same year, Solomon H. Snyder from Johns Hopkins University – one of the founding fathers of modern biological psychiatry –, was honoured by Lilly Research Laboratories and invited to give a lecture. The theme he chose was

neurotransmission, and his lecture highlighted the great utility for biological research of so-called brain “synaptosomes”, procedure that he himself developed, which would subsequently be applied in the development of fluoxetine [119]. The insistence of Fuller, supported by the biochemist David T. Wong (Fig. (11)) resulted in the formation of a “serotonin-depression study team”, made up of Fuller, Wong, the organic chemist Bryan B. Molloy (Fig. (11)) and Robert Rathbun, and which would be the driving force behind the development of the new antidepressant [1,124].

Fig. (11). David T. Wong (1936-) (left), biochemist at Lilly Research Laboratories and leader of the research group that developed and introduced fluoxetine, seen here at his laboratory in Indianapolis (USA). Bryan B. Molloy (1939-2004) (right), research chemist at Lilly Research Laboratories and responsible for the synthesis, among other phenoxyphenylpropylamine derivatives, of fluoxetine, in 1972. In the centre, Ray W. Fuller (1935-1996).



This group, led by Wong, devoted its research efforts in the early 1970s to obtaining molecules capable of selectively inhibiting the reuptake of serotonin, as potential antidepressant agents, and which would lack the cardiotoxicity and anticholinergic properties of TCAs. The work of Molloy and Rathbun was pioneering in this regard. Having observed that diphenhydramine and other antihistamines were capable of inhibiting the reuptake of monoamines [125] and of blocking, to the same extent as imipramine and amitriptyline, the ptosis induced by tetrabenazine in mice [126] –a standard test of antidepressant activity–, Molloy synthesized a series of phenoxyphenylpropylamines as analogues of diphenhydramine. One of these substances,

LY-14939 (later known as nisooxetine), was studied by Rathbun and Richard Kattau, who observed that it was as powerful as TCAs in reversing hypothermia induced by apomorphine in mice. Moreover, both nisooxetine and desipramine antagonized the hypothermia induced by reserpine in mice [127], and were powerful inhibitors of noradrenaline reuptake in brain synaptosomes, though nisooxetine scarcely blocked the reuptake of serotonin and dopamine [128]. Wong considered that small chemical modifications of the phenoxyphenylpropylamine compounds could provide selective serotonin reuptake inhibitors, and hence chose 55 derivatives of this series and 2 naphthalenoxide analogues to test the power of reuptake inhibition in the three monoamines *in vitro*. On 8 May 1972 a member of Wong's team, Jon-Sin Horng, tested fluoxetine oxalate (LY-82816), and on 24 July of that same year it was found that fluoxetine chlorhydrate (LY-110140) was the most powerful and selective inhibitor of serotonin uptake in the entire series [118], with a potency for inhibiting the uptake of serotonin 6 times greater than N-methyl-phenoxyphenylpropylamine, the father compound of the series, while its potency was 100 times smaller in the uptake of noradrenaline. Precisely the p-trifluoromethyl radical of the phenoxy ring of fluoxetine chlorhydrate was confirmed as the key element in the great potency and selectiveness of this drug for serotonin reuptake. Moreover, the affinity of fluoxetine for different neuroreceptors was seen to be very low [129], which explained the scarcity of adverse effects associated with it, especially compared to the range of side effects typical of TCAs (constipation, urine retention, blurred vision, orthostatic hypotension, sedation, memory disorders, dizziness, etc.).

The clinical introduction of fluoxetine

In relation to the clinical development of fluoxetine, it should be mentioned that after the synthesis of the SSRIs and the corresponding experimental safety studies, there began in Indianapolis and Chicago a series of clinical trials which, despite promising results, were never published, perhaps because of the company's commercial policies. Moreover, the first clinical publication on this drug was of a negative nature, since it reported the appearance of a severe dystonic condition in a patient treated with this antidepressant [130].

Nevertheless, in 1980 Lilly decided to commit themselves definitively to the new molecule, entrusting the clinical research task to John Feighner, who carried out his studies at his private psychiatric clinic in La Mesa (California). In 1983, the first positive results began to appear: fluoxetine was as effective an antidepressant as the classical tricyclic drugs, and moreover, showed far fewer adverse effects [124]. Feighner [131] began talking of a “New Generation of Antidepressants”. Between 1984 and 1987 clinical trials with fluoxetine multiplied, and finally, in December 1987, the FDA definitively approved its clinical use, under the trade name Prozac®.

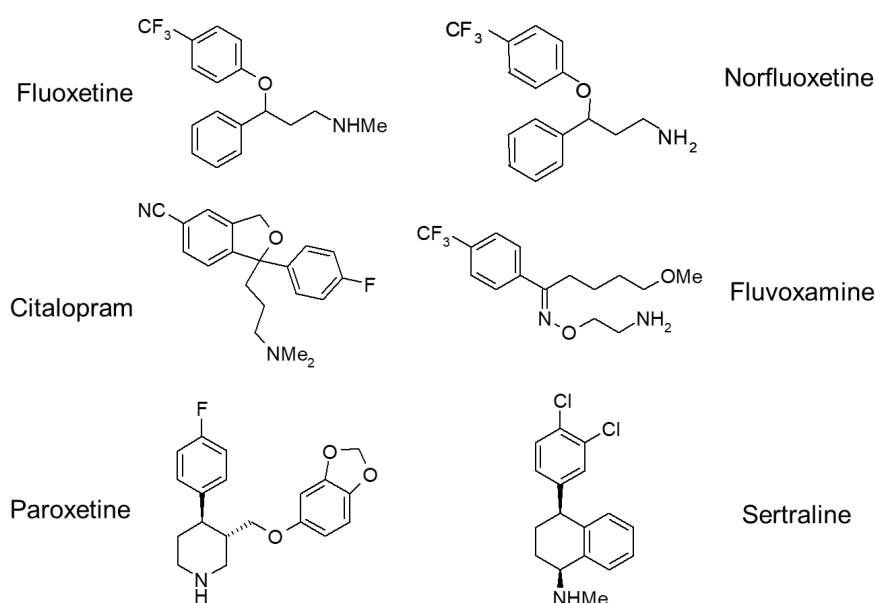
Numerous clinical trials subsequently confirmed that the antidepressive efficacy of fluoxetine was similar to that of TCAs in outpatient major depression and superior to that of placebo [132]. The efficacy of fluoxetine was also confirmed in patients with major depression and melancholia [133], dysthymias [134] and different degrees of inpatient depression [135]. All such conditions were included, in the early 1990s, by two researchers at the McLean Hospital, in a category called “Disorders of the Affective Sphere” [136]. Thus, perspectives for the use of fluoxetine were highly promising. Indeed, growth of fluoxetine use has been the most rapid in the history of psychotropic drugs: in 1990, three years after its introduction in the USA, it was already the most widely prescribed drug by North American psychiatrists, and in 1994 it sold more than any other drug worldwide, except Zantac® [63]. Furthermore, as occurred with Miltown®, Prozac® became established within the cultural scene of the nineties, making the front pages of popular newspapers and periodicals, such as the *New York Times* (“With Millions Taking Prozac, A Legal Drug Culture Arises”, 1993), or *Newsweek* (“How A Treatment For Depression Became As Familiar As Kleenex And As Socially Acceptable As Spring Water”, 1994), and becoming the main protagonist of a best seller (*Listening to Prozac*, 1993) by Peter D. Kramer [137], Professor of Psychiatry at Brown University.

The incorporation of new SSRIs

In the wake of the article by Wong et al. [118], a large quantity of selective serotonin reuptake inhibitors, of highly diverse chemical origin, began appearing in the scientific literature. Six of them, including fluoxetine (duloxetine, tomoxetine, nisoxetine, dapoxetine, fluoxetine and norfluoxetine), owed their existence to the research efforts of

Wong's group [119]. The first SSRI to be marketed was zimelidine, in 1982, by Astra Pharmaceuticals (Södertälje, Sweden). However, this drug was rapidly withdrawn from the market (just the following year) due to problems of hypersensitivity (fever, myalgias, increased levels of aminotransferases and, above all, various cases of neurological complications) [138]. Subsequently, and within a relatively short period, four more drugs from this family (Fig. (12)) were made available to physicians, each one developed by a different pharmaceutical company; citalopram (Lundbeck), fluvoxamine (Solvay), paroxetine (AS Ferrosan, Novo Nordisk) and sertraline (Pfizer). Fluvoxamine was first marketed in 1983 in Switzerland, citalopram in 1989 in Denmark, sertraline in 1990 in the UK and paroxetine in 1991 in Sweden.

Fig. (12). Chemical structure of selective serotonin reuptake inhibitors (SSRIs).



Pharmacological contributions of fluoxetine

In vivo neurochemical studies also confirmed the specificity of fluoxetine in the inhibition of serotonin reuptake, thus reinforcing the serotonergic hypothesis of depression. Among the results of research in this context it is also important to highlight the reduction of serotonin reuptake *ex vivo* by rat brain synaptosomes treated with fluoxetine [128] or the blocking of toxicity induced by neurotoxics, such as *p*-chloroamphetamine (*p*-CA), at the level of the membrane transporter responsible for the reuptake [139]. Despite the lack of

techniques for determining serotonin concentration in the synaptic cleft, various indirect tests permitted confirmation of an increase in extraneuronal concentrations of this neurotransmitter, such as a cytofluorimetric technique called “fading”, which reveals that fluoxetine increases the extracellular serotonin concentration in areas of the brain raphe area in rats [140], or *in vivo* voltimetric techniques, confirming a slight and prolonged increase of the signal in the corpus striatum of the rat as a result of fluoxetine, as well as its prevention of a rapid and intense increase in the signal after administration of p-CA, a competitor for the transporter of the reuptake pump of this amine [141]. Finally, through push-pull cannulation in the nucleus accumbens of the rat, a seven-fold increase in serotonin concentration was observed in the first hour after intraperitoneal injection of fluoxetine [142].

However, despite the excellent results obtained at a biochemical level, fluoxetine was not effective in some models of tests carried out on experimental animals and used in pre-clinical screening of potential antidepressants, such as those related to avoidance of hypothermia induced by reserpine or apomorphine, whose result was negative with fluoxetine [127], or to the incapacity to reduce mobility, in the forced swimming test in rats [143].

In any case, all the data mentioned here indicate that fluoxetine has not only constituted an extremely important therapeutic tool for treating different mental disorders, but indeed, as Fuller and Wong [144] rightly claim, it “has represented a valuable pharmacological instrument for the study of serotonergic transmission mechanisms and the physiological functions of serotonergic brain neurones”.

NEW LINES OF ANTIDEPRESSANT DRUGS DEVELOPMENT

Currently, a priority goal for psychopharmacology is to discover the precise nature of the circuits responsible for the modifications of neuronal functioning that lead to depression, as well as the adaptation mechanisms triggered by antidepressants, for correcting and normalizing the behavioural, cognitive, affective and neurovegetative alterations observed in these conditions. For this purpose, research should not be limited to the classical aminergic mechanisms (reuptake and metabolization) or the more modern ones

(receptor mechanisms), but should rather explore other sources of knowledge constantly being provided by biochemistry, molecular biology and genomics. In line with this approach, and despite the fact that the latest antidepressants introduced into clinical practice maintain the same aminergic action mechanism, the future of antidepressant therapy appears to be trying to turn towards extraneuronal non-aminergic mechanisms or mechanisms that modulate the intraneuronal biochemical pathways.

The most recent additions to the antidepressant therapeutic arsenal

Despite the considerable clinical advantages of SSRIs, based largely on their better tolerance and safety profile and greater convenience, there are a series of problems encountered in antidepressant therapy that have yet to be resolved. It suffices to mention the delay in the onset of antidepressant response or the percentage, estimated at around 30%, of patients who do not respond to treatment [145]. Such problems, among others, have justified research efforts in the quest for new antidepressants, and which have led, in the last 15 years, to the clinical introduction of new drugs, with different pharmacodynamic properties. Notable among these are venlafaxine, duloxetine, nefazodone, mirtazapine and reboxetine. However, these drugs, despite belonging to four new families of antidepressants [146], continue to share an action mechanism that revolves around the enhancement of aminergic functioning: inhibitors of noradrenaline and serotonin reuptake (venlafaxine, duloxetine, milnacipram), antagonists of serotonergic 5-HT₂ receptors (nefazodone), specific noradrenergic and serotonergic antidepressants –NaSSA (mirtazapine)– and selective inhibitors of noradrenaline reuptake (reboxetine, atomoxetine) (see Table 1).

The incorporation into the antidepressant arsenal of these new families of drugs has brought progress in some cases, and in others disappointment, with regard to the treatment of depression. As positive events we can consider the introduction of venlafaxine, mirtazapine and reboxetine. On the other hand, nefazodone –actually withdrawn from the market due to safety issues– and the selective and reversible inhibitors of MAO (RIMA) have not had the desired results [147].

New integrated approaches in aetiopathogenic theories of depression

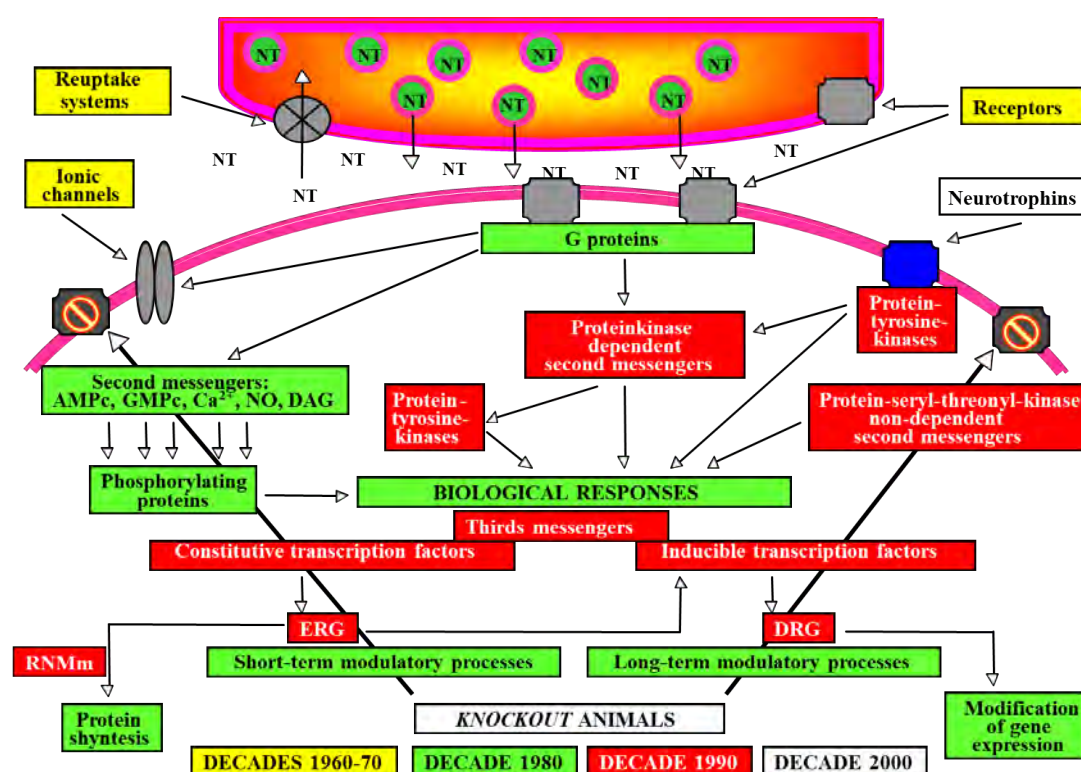
Despite the important advance represented by the monoaminergic hypotheses in relation to the aetiopathogeny of mental disorders and the action mechanism of antidepressants, a feeling soon emerged that these theories reflected only a small part, probably an initial part, of this action mechanism [1]. This realization led, in the 1980s, to the theory of receptor adaptation. According to this theory, the persistent activation of receptors, as a consequence of the increase in serotonin and noradrenaline in the synaptic cleft, led them (adrenergic 5HT₂ and β) to downregulate, a phenomenon that coincided in time with the onset of the therapeutic effect of the antidepressant [148]. However, the fact that this regulation phenomenon was not universal to antidepressants and that, furthermore, the blockers of these receptors lacked antidepressant effect –and could even induce depression in some people [149]– called into question the possibility that this receptor-adaptation mechanism was not the sole factor responsible for the therapeutic effect of antidepressants.

More recent theories [150] defend a “dysregulation” model, which would involve not just a single neurotransmitter pathway; rather, there would be alteration of several, including the noradrenergic, the serotonergic and even the dopaminergic pathway. In line with these postulates, Delgado and Moreno [151] proposed an aetiological model in which depression would result from a dysfunction of different brain areas, notably the frontal cortex, the hippocampus, the amygdala and the basal ganglia, which, in turn, would be modulated by different monoaminergic neurotransmission systems. According to this theory, numerous factors, notably stress, could influence the correct functioning of these areas, in either a selective or a generalized way, which concurs with the classic postulates of a heterogeneous aetiology of depressive disorders. Appended to this hypothesis should be the possible existence of marked alterations in the intraneuronal pathways of signal transduction, which would also situate the source of depressive disorders in the sphere of molecular dysfunctions.

New targets in the quest for antidepressants: from synaptic pharmacology to intraneuronal pharmacology

As pointed out earlier, in the 1960s and 70s the majority of studies that set out to demonstrate the effects of drugs on the CNS focused on extracellular aspects of synaptic transmission (Fig. (13)), basically involving the interaction of the neurotransmitter with its receptor. This interaction was the consequence of acting on the inhibition of the systems of reuptake (TCAs and SSRIs) and metabolism (MAOIs), which increased the levels of monoamines in the synaptic cleft, thus facilitating their action on the receptor. However, these events occur rapidly, and are detectable from the first administration of the antidepressant drug, though the therapeutic effect does not begin until after a few weeks of treatment. These correlates suggested that the cited antidepressant effect occurs after a series of adaptations at a neuronal level, as a consequence of the chronic administration of these drugs [152] (Table 2).

Fig. (13). Historic advances in the understanding of the neurobiology of neurotransmission systems and of the action mechanisms of psychotropic drugs, including the intracellular systems of transduction of external signals.



NT (neurotransmitter); NO (nitric oxide); DAG (diacylglycerol); ERG (early response genes); DRG (delayed response genes).

Thus, it became more and more obvious that the union of the neurotransmitter and the receptor represented only the beginning of the effects of neurotransmitters on their neuronal targets. In fact, it became clear over the last decade that these neurotransmitter substances regulated cell functioning (downregulation of receptors, protein synthesis, release of neurotransmitters, etc.), through the activation of biochemical pathways of intraneuronal messengers (G proteins, second messengers, such as AMPc or intracellular calcium and phosphorylating proteins), which eventually induced modifications in the gene expression of neurones, responsible for a wide range of biological responses (Fig. (13)) [152]. Moreover, though, neurones possess a high quantity of tyrosine-kinase proteins encrusted in their cell membrane, which act as receptors for neurotrophins and other growth factors (Fig. (13)), and this complicates even further the understanding of the diffusion of nerve information.

Table 2. Pre- and post-receptor mechanisms in the central nervous system modified by chronic administration of monoaminergic antidepressants.

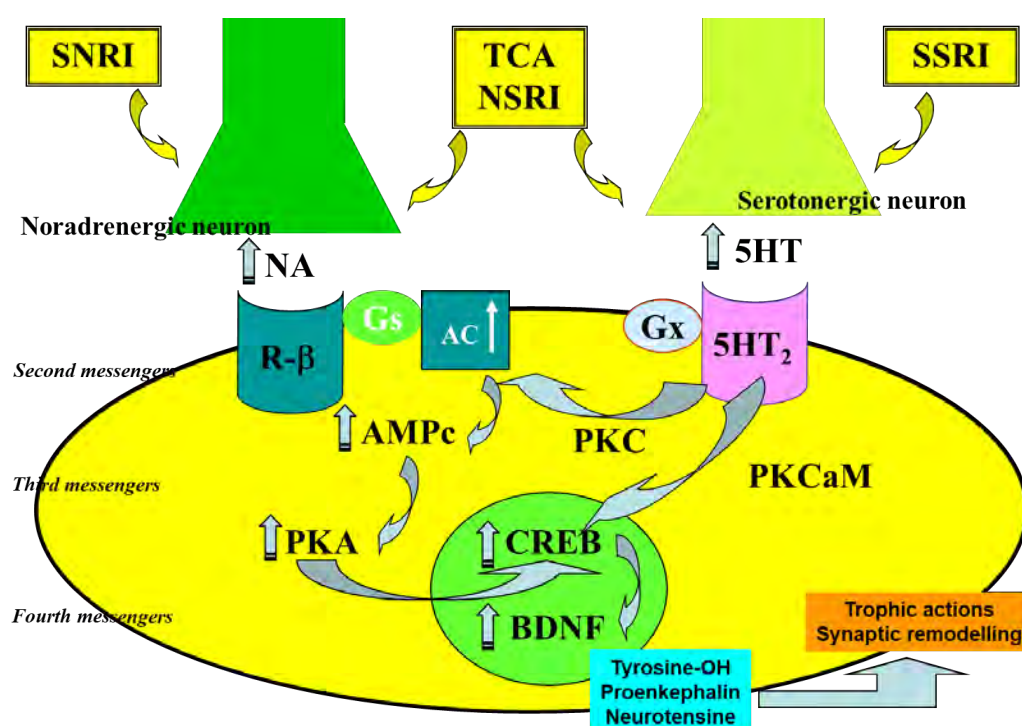
-
- Synaptophysin
 - Proteins G
 - cAMP
 - Protein-kinase A (PKA)
 - Protein-kinase C (PKC)
 - Protein-kinase dependent on Ca^{2+} and calmodulin
 - cAMP-dependent protein associated with microtubules (MAP₂)
 - CREB Protein
 - Fos RNAm protein
 - Neurotrophins (BDNF)
-

CREB (*cAMP response element binding protein*); BDNF (*brain derived neurotrophic factor*).

Thus, the increase of monoamines in the synaptic cleft triggers a series of intracellular neurochemical changes which, as recently postulated, have a decisive influence on the therapeutic effect of antidepressants. The intracellular effects of antidepressants have made it possible to propose the hypothesis that these drugs, after increasing the action of monoamines, the first messengers, on their corresponding receptors, and regardless of the transduction pathway of the second messengers triggered (AMPc, diacylglycerol –DAG–, etc.), would have a point of convergence in the protein-kinases (PKA, PKC, PKCaM),

considered as third messengers, which would control the genetic expression, through the phosphorylation of transcription factors that could be considered as fourth messengers (Fig. (14)) [152,153]. According to this hypothesis, SSRIs, TCAs and selective noradrenaline reuptake inhibitors (SNRI) would have a common intracellular mechanism widely removed from the point of action in the synaptic cleft, which would modulate, through modifications of gene expression, the synthesis of certain substances, such as proenkephalin, neurotensin, BDNF (brain-derived neurotrophic factor) or enzymes, such as tyrosine-hydroxylase, which, in sum, would provoke changes of functional adaptation, trophic actions or synaptic remodelling, tending to offset the possible anomalies present in depression. All of this unquestionably constitutes an enormous advance for our understanding of what could be the beginning of the psychopharmacology of this new millennium, capable of moving on from a superficial and synaptic psychopharmacology, until could be called intracellular psychopharmacology [152].

Fig. (14). Effect of the different families of antidepressants on intraneuronal molecular mechanisms and end point of convergence at the genetic level.



TCA (tricyclic antidepressants); NSRI (noradrenaline and serotonin reuptake inhibitors); SNRI (selective noradrenaline reuptake inhibitors); SSRI (selective serotonin reuptake inhibitors); NA (noradrenaline); 5HT (serotonin); G (G proteins); AC (adenylate-cyclase); PKA (protein-kinase A); PKC (protein-kinase C); PKCaM (kinase dependent on calcium and calmodulin); CREB (cAMP response element binding protein); BDNF (brain derived neurotrophic factor).

In any case, the scientific evidence accumulated over the last decade appears to confirm that there is no unitary biochemical mechanism to explain the antidepressant effect of all the substances currently available. Hence the movement of research on the action mechanism of antidepressants in other directions, as well as efforts to find new *loci* of antidepressant action. Thus, research is in progress on the role of neurotrophic factors (neurotrophins and BDNF), of corticotrophin releasing hormone (CRH) and glucocorticoids, of excitatory amino acids and of the NMDA (N-methyl-D-aspartate) receptor, as well as on other possible targets (opioid system, interleukins, P substance, somatostatin, Y neuropeptide, melatonin, nitric oxide, and so on).

CONCLUSIONS

The clinical introduction of psychotropic drugs in the 1950s constitutes one of the great medical advances of the 20th century, and the importance of the event has been compared with the discovery of antibiotics and vaccines. Gayral [154] refers to the “revolution of psychopharmacology” as the second revolution of psychiatry, arguing that the introduction of psychoanalysis was the first. For his part, J. Allan Hobson, neurophysiologist at the University of Harvard, remarks in his book *The chemistry of conscious states*, in reference to the introduction of psychoactive drugs in the 1950s, that “... the development of drugs that interacted with the brain’s chemical systems is the most important advance in the history of modern psychiatry” [155]. Moreover, from the clinical and public health points of view, the net result of this introduction was a “powerful social change in the conceptualisation and acceptance of mental illness, including through the media, in the organization of mental health services, in the development of the specialty and nosology of psychiatry, in the dynamics of high technology economies” [91].

Iproniazid, in spite of its short psychiatric life, and imipramine deserve a privileged place in the history of psychopharmacology and psychiatry, since not only did they open the door to the specific treatment of mood disorders –lending great prestige to the psychiatry of the time, improving everyday clinical practice and increasing patients’ quality of life–, they also made it possible to develop the first serious hypotheses on the biological nature of these affective disorders [1,22,27,79,82,99], the monoaminergic theories of depression, around which scientific discussion revolved in the specialized journals in the 1960s and

1970s [89]. Psychoactive drugs in general, and iproniazid and imipramine in the particular case that concerns us here, thus permitted the gradual definition of the neurochemical process underlying mental illness, and the generation of a physiopathological theory on it, permitting the advent of so-called “biological psychiatry”. We are talking, then, about an approach that could be considered “pharmacocentric”, with far-reaching heuristic implications for psychiatry [3]. This situation emerged as unique in the history of medicine, since a large quantity of aetiological hypotheses were based on the action of a series of drugs whose application to psychiatric pathologies resulted, in many cases, as today, from the intervention of chance. With iproniazid and imipramine, depression ceased to be an illness of the mind to become an illness of the brain [82].

Even so, and excluding the clinical introduction of fluoxetine and the rest of the SSRIs in the 1990s, there have been scarcely any substantial advances in the pharmacology of depressive disorders over the last 50 years. In this regard, it should be borne in mind that one of the most important challenges facing research today, in the field of Neurosciences, is an understanding of the molecular mechanisms responsible for intraneuronal communication and those through which cells manifest their phenotype in response to environmental signals. Detailed knowledge of these mechanisms could provide us, in the future, with much more specific and safer pharmacological tools for treating different neurological and psychiatric conditions, among the depressive disorders.

ABBREVIATIONS

AC = adenylate-cyclase

AMPT = α -methylparatyrosine

APA = American Psychiatric Association

BASF = Badische Anilin und Soda Fabrik

BDNF = brain derived neurotrophic factor

CINP = Collegium Internationale Neuro-Psychopharmacologicum

CNS = Central Nervous System

CREB = cAMP response element binding protein

CRH = corticotrophin releasing hormone

DAG = diacylglycerol

DOPA = 3,4-dihydroxy-phenylalanine

DRG = delayed response genes
ERG = early response genes
FDA = Food and Drugs Administration
5-HIAA = 5-hydroxyindole acetic acid
5-HT = serotonin
MAO = monoamine-oxidase
MAOIs = monoamine-oxidase inhibitors
NA = noradrenaline
NaSSA = specific noradrenergic and serotonergic antidepressants
NIH = National Institutes of Health
NMDA = N-methyl-D-aspartate
NO = nitric oxide
NSRI = noradrenaline and serotonin reuptake inhibitors
NT = neurotransmitter
p-CA = *p*-chloroamphetamine
PKA = protein-kinase A
PKC = protein-kinase C
PKCaM = kinase dependent on calcium and calmodulin
RIMA = reversible and selective inhibitors of MAO
SNRI = selective noradrenaline reuptake inhibitors
SSRI = selective serotonin reuptake inhibitors
TCA = tricyclic antidepressants

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HIPÓTESIS Y OBJETIVOS

Las hipótesis que marcan el inicio y el desarrollo de la presente tesis doctoral son las siguientes:

- 1.- El papel de la serendipia en el descubrimiento de nuevos antidepresivos y reguladores del humor pudo ser muy relevante durante las dos primeras décadas de la era psicofarmacológica (décadas de 1950 y 1960) y parece estar disminuyendo desde entonces.
- 2.- La adscripción de la influencia de la serendipia en el descubrimiento e introducción clínica de los fármacos es muy controvertida, según los distintos autores que se han ocupado de este análisis, posiblemente por la ambigüedad semántica del término “serendipia”.
- 3.- La introducción y aplicación de nuestra definición operativa de serendipia y nuestros cuatro patrones diferentes de atribuibilidad fortuita de los descubrimientos, en el ámbito de la farmacología, dará luz a este controvertido fenómeno.

En consecuencia, y para validar las hipótesis de partida, los objetivos generales que se plantean en esta tesis doctoral son los siguientes:

- 1.- Describir detalladamente el proceso histórico que condujo al descubrimiento de los fármacos antidepresivos y estabilizadores del estado de ánimo.
- 2.- Analizar el verdadero papel de la serendipia en el descubrimiento, desarrollo e introducción clínica de los fármacos antidepresivos.
- 3.- Analizar el verdadero papel de la serendipia en el descubrimiento, desarrollo e introducción clínica de los agentes reguladores del humor.
- 4.- Aplicar nuestra definición operativa de serendipia al proceso histórico del descubrimiento de todos los fármacos antidepresivos y eutimizantes.
- 5.- Identificar el patrón de imputabilidad serendípica atribuible a cada uno de los fármacos antidepresivos y reguladores del humor introducidos en clínica hasta la actualidad.
- 6.- Generar planteamientos sobre el futuro del papel de la serendipia en el descubrimiento de nuevos agentes farmacológicos.

MATERIAL Y MÉTODOS

Archivos y documentos sobre la historia de la psicofarmacología

El material empleado en la presente tesis doctoral procede de diferentes archivos y fondos documentales, procurando siempre trabajar con los manuscritos originales que contienen la información farmacológica y clínica inicial sobre los fármacos antidepresivos y reguladores del humor. Para ello, se han manejado las siguientes fuentes:

- 1) Bases de datos primarias del ámbito biomédico para la localización de artículos científicos: *EMBASE*, *SCOPUS*, Web of Science (WoS).
- 2) Recursos documentales proporcionados por las compañías farmacéuticas distribuidoras de los agentes farmacológicos estudiados.
- 3) Documentación accesible a través de la Red Internacional de Historia de la Neuropsicofarmacología (INHN), bajo la dirección de Thomas A. Ban (Vanderbilt University).
- 4) La serie de entrevistas *The Psychopharmacologists* de David Healy (Arnold – Oxford University Press), en las que se recogen las declaraciones, comentarios e impresiones de los responsables históricos de los principales descubrimientos en el ámbito de la psicofarmacología durante el siglo XX.

5) La colección de Historia de la Psicofarmacología del Colegio Internacional de Neuropsicofarmacología (CINP) (Collegium Internationale Neuro-Psychopharmacologicum), coordinada por Thomas A. Ban, David Healy y Edward Shorter y publicada por Animula Publishing House.

6) La colección privada de documentos del profesor López-Muñoz sobre la historia de la psicofarmacología, que asciende a más de 2000 registros.

Criterios operativos de serendipia

El grupo de investigación liderado por el doctorando propuso en 2012 la estandarización de la acepción de serendipia en relación con los descubrimientos científicos, mediante una definición operativa y funcional basada en cuatro patrones diferentes de imputación serendípica en el proceso de descubrimiento de los fármacos (López-Muñoz et al., 2012), en concordancia siempre con la definición original propuesta por Walpole.

Estos 4 patrones son los siguientes (Figura 17):

- a) Patrón I: engloba los descubrimientos puramente fortuitos o azarosos.
- b) Patrón II: incluye aquellos hallazgos casuales, en algunos casos realizados en animales de laboratorio, que secundariamente conducen a descubrimientos clínicos planificados y sin intervención del azar.
- c) Patrón III: integrado por descubrimientos que carecen de influencia de la serendipia en un primer momento, pero que posteriormente conducen a hallazgos fortuitos.
- d) Patrón IV: corresponde a descubrimientos puramente no fortuitos, que ocurren fuera del ámbito de la serendipia, es decir, del azar o del accidente no buscado. Este patrón incluye descubrimientos que surgieron, al margen de la serendipia, de programas de investigación sistemáticos diseñados específicamente para desarrollar racionalmente medicamentos eficaces en diferentes patologías.

Por tanto, se podría decir que, dentro de estos criterios operativos, existen patrones serendípicos puros (patrón I), patrones mixtos, donde la serendipia juega su papel en un determinado momento, pero no explica, por sí sola, el hallazgo final (patrones II y III) y patrones no serendípicos, donde nunca intervino este fenómeno (patrón IV).

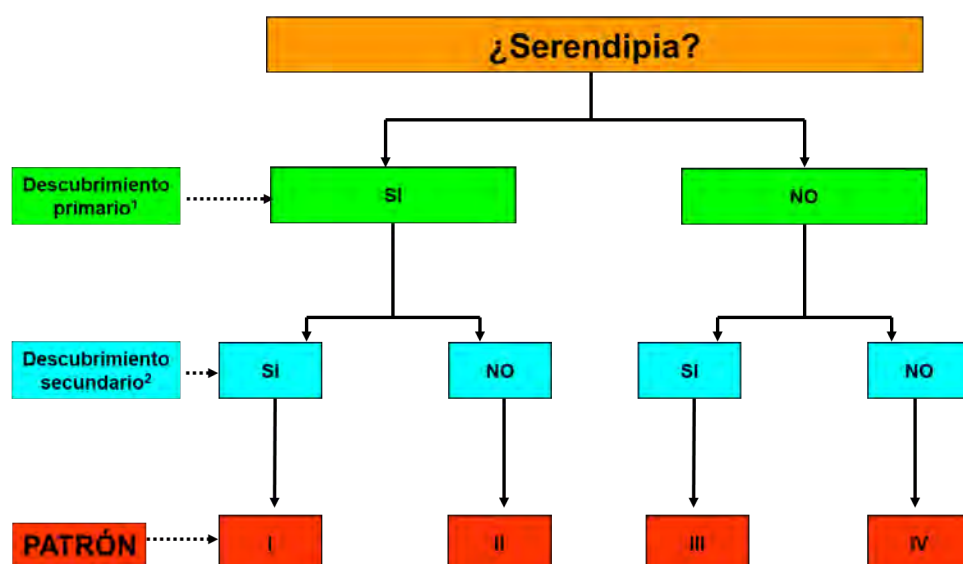


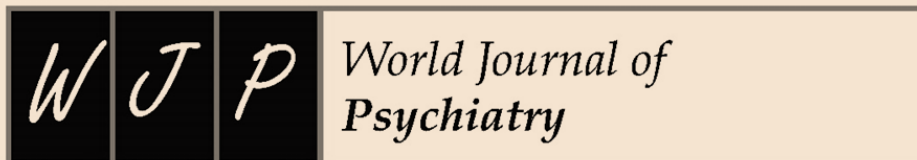
Figura 17: Esquema mostrando los cuatro patrones de imputación serendípica en el descubrimiento de los agentes farmacológicos (López-Muñoz et al., 2012).

1 Habitualmente, aunque no siempre, corresponden a descubrimientos en el animal de laboratorio.

2 Descubrimientos relativos a eficacia clínica.

RESULTADOS Y DISCUSIÓN

DOCUMENTO 2



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MINIREVIEWS

Role of serendipity in the discovery of classical antidepressant drugs: Applying operational criteria and patterns of discovery

Francisco López-Muñoz, Pilar D'Ocón, Alejandro Romero, José A Guerra, Cecilio Álamo

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Abstract

The role played by serendipity in the origin of modern psychopharmacology has proven to be controversial in scientific literature. In its original meaning (Walpole), serendipity refers to discoveries made through a combination of accidents and sagacity. We have implemented an operational definition of serendipity based on finding something unexpected or unintended, regardless of the systematic process that led to the accidental observation, and we have established four different patterns of serendipitous attributability. In this paper, we have analyzed the role of serendipity in the discovery and development of classical antidepressant drugs, tricyclic antidepressants and monoamine oxidase inhibitors as well as heterocyclic, "atypical" or "second generation" antidepressants. The discovery of the antidepressant properties of imipramine and iproniazid, the prototypes of tricyclic antidepressants and monoamine oxidase inhibitors, respectively, fits the mixed type II pattern; initial serendipitous discoveries (imipramine was an antipsychotic and iproniazid was an anti-tuberculosis agent) led secondarily to non-serendipitous discoveries. But the other

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Role of Serendipity in the Discovery of Classical Antidepressant Drugs: Applying Operational Criteria and Patterns of Discovery

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ABSTRACT

The role played by serendipity in the origin of modern psychopharmacology has proven to be controversial in scientific literature. In its original meaning (Walpole), serendipity refers to discoveries made through a combination of accidents and sagacity. We have implemented an operational definition of serendipity based on finding something unexpected or unintended, regardless of the systematic process that led to the accidental observation, and we have established four different patterns of serendipitous attributability. In this paper, we have analyzed the role of serendipity in the discovery and development of classical antidepressant drugs, tricyclic antidepressants and monoamine oxidase inhibitors, as well as heterocyclic, "atypical" or "second generation" antidepressants. The discovery of the antidepressant properties of imipramine and iproniazid, the prototypes of tricyclic antidepressants and monoamine oxidase inhibitors, respectively, fits the mixed type II pattern; initial serendipitous discoveries (imipramine was an antipsychotic and iproniazid was an anti-tuberculosis agent) led secondarily to non-serendipitous discoveries. But the other components of these two families of drugs were developed specifically as antidepressants, modifying the chemical structure of the series leaders, thereby allowing all of them to be included in the type IV pattern, characterized by the complete absence of serendipity. Among the heterocyclic drugs, mianserin (originally developed as an antihistamine) also falls into the type II pattern.

Key Words: Serendipity; Antidepressants; Imipramine; Iproniazid; Psychopharmacology; History of neurosciences

Core Tip: In this paper, we have analyzed, for the first time, the role of serendipity in the discovery and development of classical antidepressant drugs through our operational definition of serendipity. We have assigned each of the classic antidepressants its corresponding pattern of serendipitous attributability, according to four different patterns.

INTRODUCTION

The era of modern psychopharmacology began in the late 1940s, with the publication of the antimanic effects of lithium by Australian psychiatrist John F.K. Cade^[1]. However, it was in the 1950s that what has come to be known as the “psychopharmacological revolution”^[2] came into being, with the introduction of the large families of pharmacological agents that are still in use today: typical neuroleptics or antipsychotics, benzodiazepine anxiolytics and the two large groups of classic antidepressants; tricyclics (TCAs) and monoamine oxidase inhibitors (MAOIs)^[3]. All of these psychotropic drugs drastically changed the state of psychiatric care, starting from a fundamentally empirical therapeutic approach, which, nevertheless, allowed for a gradual understanding of some of the neurobiological bases of mental illnesses and how to treat them.

Year 1957 should be regarded as a key date in modern psychiatry, as this was the year when the first two specifically antidepressant drugs in history were introduced into clinical practice, belonging to two completely different pharmacological families and two completely different geographical areas of research: iproniazid, an MAOI agent and the result of a research process developed in the United States, and imipramine, the prototypical representative of the TCA family, developed and studied in Europe^[4]. Prior to the clinical introduction of these antidepressant agents, the therapeutic tools used to manage affective disorders were extremely limited^[5]. At the beginning of the 20th century, chloral hydrate, barbiturates, amphetamines and opiate derivatives were used in agitated melancholic patients, and during the first half of the century, excluding biological treatments (insulin comas, chemical and electrical shock therapies, and “sleep cures”), there were only a few non-specific chemical preparations available to doctors, such as dinitrile succinate, malonic nitrite and lactic acid, all of which had rather unsatisfactory antidepressant results^[6,7], confirmed in the few clinical studies carried out. But, this was also due, in part, to Freudian ideas prevalent until the 1950s, that depressive syndromes

had only psychodynamic, not biological, causes, meaning that these patients could not benefit from treatment with pharmacological agents^[8,9].

In the specific field of antidepressant drugs, TCAs - agents that ushered in a new era in the treatment of depression - are still the benchmarks today, especially in clinical research, and have the same efficacy rates as other antidepressants that have appeared since then. However, unlike TCAs, which continue to be used in clinical practice, although not as a first line of treatment, the use of MAOIs has largely fallen off, due primarily to their adverse effects and problems of interactions with other psychostimulant drugs and tyramine-rich foods, which can lead to tragic hypertensive crises, although atypical depressions are still candidates for treatment with these drugs. During the 1970s, new heterocyclic antidepressants appeared, known at the time as “atypical” or “second generation” antidepressants (maprotiline, mianserin, trazodone, viloxazine, nomifensine), the main characteristic of which was that they were more selective in their action on monoaminergic transmission systems. All of these drugs can be categorized as traditional antidepressants (Table 1).

Table 1. Classification of classical monoaminergic antidepressants according to action mechanism and historical perspective on their clinical introduction.

FAMILY	Mechanisms of action	Acronym	Prototype substance	Period
Tricyclic antidepressants	5-HT and NA reuptake inhibitors with blocking action of diverse receptors	TCA	Imipramine	1957-1980
Monoamine oxidase inhibitors	Irreversible MAO inhibitors	MAOI	Phenelzine	1958-1965
Heterocyclic or “second generation” antidepressants	NA reuptake inhibitors with blocking action of diverse receptors		Maprotiline	1967-1980
	Antagonists of α_2 auto-receptors		Mianserine	1970-1980
	DA and NA reuptake inhibitors		Nomifensine	1970-1980
	5-HT reuptake inhibitor and antagonist of 5-HT ₂ receptors		Trazodone	1970-1980

5-HT (serotonin); NA (norepinephrine); DA (dopamine).

TCAs (tricyclic antidepressants); MAOIs (monoamine oxidase inhibitors).

Finally, in the late 1980s, a new series of drug families were introduced into clinical practice, including selective serotonin reuptake inhibitors (SSRIs), which were widely

used and accepted. These drugs offered considerable advantages over their predecessors, particularly in terms of safety and tolerability, and opened up the field of antidepressant therapy to non-psychiatrists. The first SSRI was zimelidine, which was withdrawn from the market, but we can say that the period of “modern” antidepressants began with the successful clinical introduction of fluoxetine^[10].

Serendipity may have played a crucial role in the process of discovering classic psychotropic drugs during the 1950s^[11,12], although opinions in scientific literature in recent decades are rather contradictory, possibly due to a lack of consensus on what is meant by serendipity. In the specific field of science, this concept has traditionally been associated with those discoveries or findings of a fortunate and unexpected nature, fortuitous events or accidental encounters (“happy accident”, “pleasant surprise”, etc.), although its meaning has also been linked to the very concept of chance, randomness or coincidence.

The differences in opinion about the role of serendipity or chance discoveries in science may lie in the semantic ambiguity of the term “serendipity”, the origin of which can be traced to correspondence between the English writer, politician and historian Horace Walpole, 4th Earl of Oxford, and the British diplomat Sir Horace Mann. One epistle in this fluid correspondence, which refers to the classic Persian tale *The Three Princes of Serendip*, contains the two components that should make up the concept of serendipity: accidents and sagacity^[13]. Therefore, it is sagacity that marks the difference between serendipitous discovery and the absence of discovery in the presence of relevant accidental information. But isn't sagacity a basic and indispensable component of the scientific mentality itself? If the answer is yes, this element must be present irrespective of whether the phenomena observed in the scientific discovery were foreseen or not. However, we have postulated that there is a structural difference in this approach; sagacity always precedes and leads observation in non-serendipitous discoveries, but in serendipitous discoveries, sagacity manifests itself after the unexpected observation has been made. However, even this assessment leads to interpretative problems, as once scientists have made their discovery, they tend to explain them as a consequence of perfectly planned working hypotheses, even when they take place in a completely random way.

Thus, from a conceptual point of view, we can conclude that serendipitous discovery is the discovery of something unsought, regardless of the systematic process that led to the accidental observation. Viewed in this light, serendipity is undoubtedly a key factor in the creative process in the arts and humanities^[14,15]. However, it can also be seen as an integral part of the development of social sciences and, of course, of biomedical sciences in general and psychopharmacology in particular.

Kubinyi^[16] briefly analyzed the discoveries of different pharmacological agents in which serendipity was somehow involved, and Hargrave-Thomas et al.^[17] confirmed that 24% of all commercially available drugs were positively influenced by serendipity during their development, particularly psychopharmaceuticals. In this sense, the discovery of most of the psychopharmacological agents that revolutionized the care of mental illnesses during the 1950s has not escaped this conceptualization either^[13]. However, although the researchers responsible for these discoveries have themselves reported that chance was a key factor in their findings, the role of serendipity in the early days of psychopharmacology is still far from being established.

To address this point further, we have established an operational definition of serendipity, based on four different patterns of attributability^[13,18], which allows us to reflect on the actual role that serendipity played in the findings that shaped the origins of modern psychopharmacology. In this paper, following this approach, we will look at the role played by serendipity in the discovery of the classic antidepressant drugs.

PATTERNS OF SERENDIPITOUS ATTRIBUTABILITY

In previous papers^[13,18], we have proposed a standardized definition for the term serendipity in the field of science, given the semantic ambiguity of this concept. This "operational" definition would establish that serendipity is the discovery of something not sought. Moreover, we have proposed a working definition of serendipity^[13,18] based on four different patterns of serendipitous imputation in the drug discovery process (Figure 1):

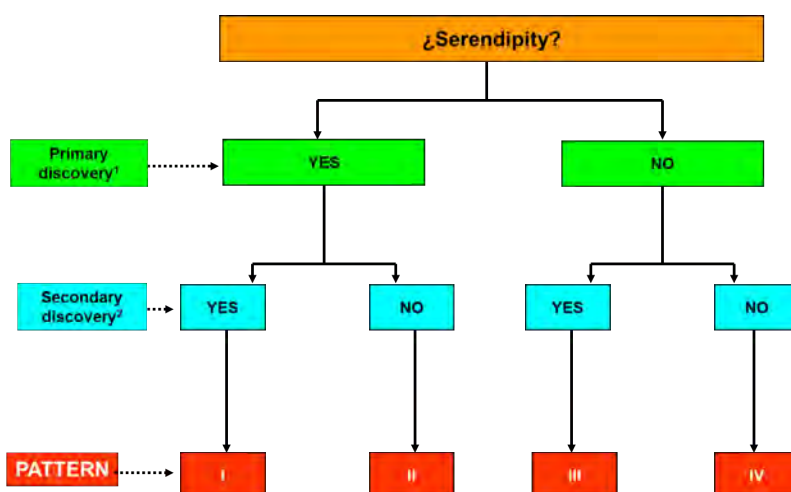
- 1) The first pattern, which would encompass pure serendipitous discoveries, was more frequent in the first half of the 20th century.

2) The second pattern, which is a variant of the previous one, would correspond to those initial serendipitous discoveries that secondarily lead to non-serendipitous discoveries.

3) The third pattern would include non-serendipitous discoveries that are secondarily partnered with serendipitous discoveries.

4) And the fourth pattern of non-serendipitous discoveries, in line with our operational definition of finding something unsought, has become more and more frequent since the second half of the last century. In the latter pattern, beyond serendipity, drugs evolved out of systematic research programs specifically designed to develop effective drugs for different pathological conditions.

Figure 1: Diagram of the four patterns of serendipitous attribution in the discovery of pharmacological agents.



¹ They usually, but not always, relate to findings in laboratory animals.

² Findings relating to clinical efficacy.

Mixed discoveries (patterns II and III) were very common towards the middle of the 20th century (coinciding with the so-called "golden decade" of psychopharmacology, in the 1950s), and were characterised by initial serendipitous discoveries (in some cases in laboratory animals) leading secondarily to non-serendipitous discoveries, and vice versa.

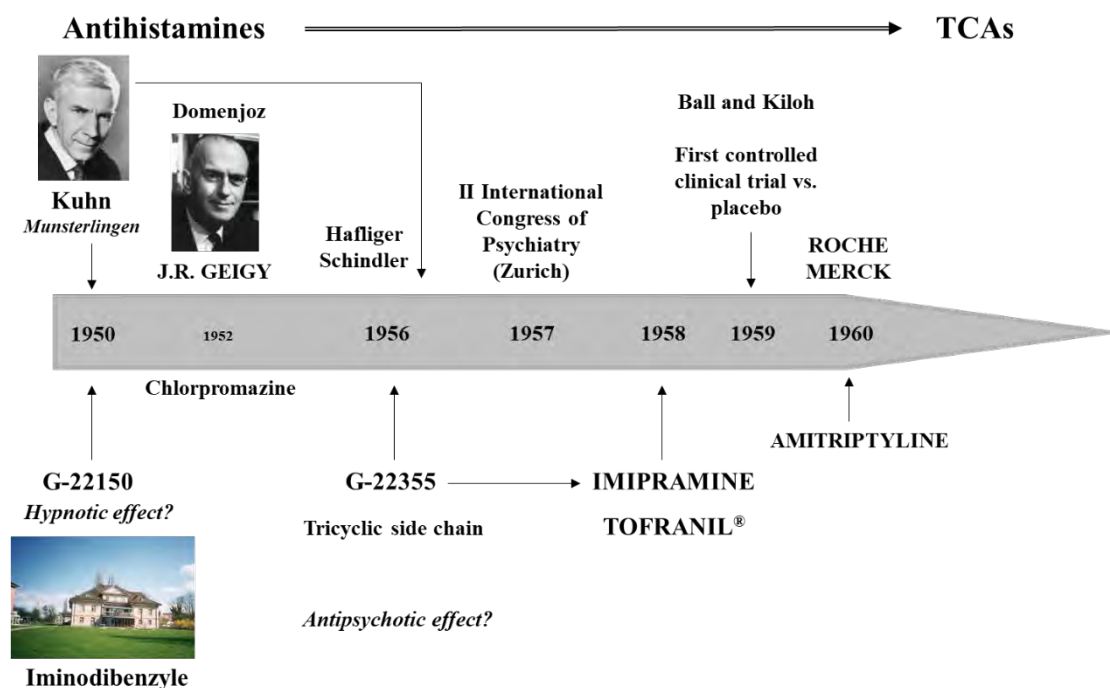
Prior to applying the attributability criteria, a detailed historical study of the development process of each of the antidepressant drugs analyzed was carried out, using the original articles in which the first pharmacological and clinical data on these drugs were published. This was done using most important databases in this field (Medline, Embase,

Scopus), the documentation services of the pharmaceutical companies that have marketed these drugs, and the documentation available in the Network for the History of Neuropsychopharmacology (INHN), coordinated by Thomas A. Ban (Vanderbilt University), the series of interviews entitled *The Psychopharmacologists*, by David Healy (Arnold - Oxford University Press), the *History of Psychopharmacology* collection of the CINP (Collegium Internationale Neuro-Psychopharmacologicum), coordinated by Thomas A. Ban, David Healy and Edward Shorter and edited by Animula, and the documentary background on the history of psychopharmacology by Prof. López-Muñoz.

SERENDIPITY IN THE PROCESS OF DISCOVERY OF CLASSICAL ANTIDEPRESSANT DRUGS

Discovery of the antidepressant properties of imipramine and TCAs

The history of the clinical introduction of the first antidepressant drug (from the family of tricyclic agents), imipramine, was part of a search for antipsychotic drugs^[19,20], following the therapeutic success reported with the clinical introduction of chlorpromazine^[21] and reserpine, an alkaloid from *Rauwolfia serpentina*^[22] in 1952 (Figure 2). See López-Muñoz et al.^[23-25] for details. These developments intensified the search for substances with similar properties by pharmaceutical companies. Accordingly, the pharmaceutical company J.R. Geigy (Basel) dusted off some phenothiazine substances that it had initially tried to develop, unsuccessfully, as dyes^[8] and later on as antihistamines and hypnotics, in the hope that they might have some other psychiatric benefit^[8,9,26].

Figure 2: Historical process of the discovery of tricyclic antidepressants during the 1950s.

TCAs (tricyclic antidepressants).

In this context, the Swiss psychiatrist Roland Kuhn, deputy medical director at the Cantonal Psychiatric Clinic in Münsterlingen (near Lake Constance), who had already studied the hypnotic and neuroleptic properties of certain Geigy phenothiazine agents^[26,27], asked the Swiss company for new compounds from the phenothiazine family to test them in his psychotic patients. In early 1956, Kuhn received a preparation called G-22355, a substance with the same side chain as chlorpromazine, which had been synthesized by Franz Häfliger and Walter Schindler in 1948 from promethazine by replacing the sulfur bridge of phenothiazine with an ethylene bridge^[28]. The substance had been registered in 1951 under US license number 2554736^[29].

Kuhn's extensive clinical research in 1956 soon showed that the agent G-22355 had no appreciable neuroleptic activity. Even patients who had previously been treated with chlorpromazine developed more severe psychotic symptoms not schizophrenic, and became clinically disturbed and agitated^[30]. However, Kuhn observed that three patients diagnosed with depressive psychosis showed a pronounced improvement in their general condition in just a few weeks. The antidepressant effect of this substance, later named imipramine, was therefore completely unexpected and its discovery entirely accidental.

In this regard, the possibility that this substance could have a therapeutic antidepressant effect was first raised by Kuhn in a written communication to Geigy dated February 4, 1956^[31].

Subsequently, a further 37 patients with depressive disorders received this drug, demonstrating its particular efficacy in treating depressive disorders^[26,32,33]: “The patients appear, in general, more animated, their voices, previously weak and depressed, now sound louder; they are more communicative, the lamentations and sobbing have disappeared. The depression, which had manifested itself through sadness, irritation and a sensation of disaffection, now gave way to friendly, joyous and accessible feelings”^[32]. Kuhn presented his results at the 2nd International Congress of Psychiatry in Zurich in September 1957 to an audience of just 12 people, using the data obtained from the clinical follow-up of these 40 depressed patients. The proceedings of the conference were published in the August issue of the *Schwizerische Medizinische Wochenschrift*^[32]. However, the following year, Kuhn republished his data (with a larger sample of patients) in the *American Journal of Psychiatry*^[33], thereby making his discovery internationally known. In this paper, Kuhn extensively described the pharmacological effects, data on efficacy and the adverse effects of imipramine, and provided recommendations for its clinical use, dosage and duration of treatment. In this work, Kuhn stated that “the patients got up in the morning voluntarily, they spoke in louder voices, with greater fluency and their facial expression became more lively. They began to do some individual activities, they once more sought to make contact with other people, they began to train on their own, to participate in games, to become happier, and to recover their ability to laugh”^[33].

Geigy introduced imipramine to the local Swiss market at the end of 1957, under the trade name of Tofranil®. It was subsequently introduced in the rest of the European market in the spring of 1958^[8,29], and represented a giant step forward in the treatment of depression, being the first representative of a new family of drugs, known as imipraminic or TCAs.

Kuhn had the sagacity to recognize an antidepressant drug when looking for an antipsychotic drug. Kuhn himself commented: “Chance admittedly had something to do with the discovery of imipramine. Chance was not decisive, however... to this had to be added a measure of intellectual achievement that was able to “invent” something

completely new, something hitherto unknown, namely a new disease... Göthe put the sense of the matter in a nutshell when he wrote: ‘Discovery needs luck, invention, intellect – neither can do without the other’”^[34]. Something similar pointed more than a century ago the great Louis Pasteur: “In the realm of scientific observation, luck is granted only to those who are prepared” (cit.^[35]).

The discovery of the antidepressant properties of imipramine is a representative example of how a serendipitous finding, the observation of schizophrenic patients treated with this drug looking for an antipsychotic effect, leads to a planned and non-serendipitous discovery, i.e., the antidepressant effect. Therefore, the antidepressant effect of imipramine would fit into the type II pattern of our serendipitous attributability criteria. This pattern of a mixture of serendipitous and non-serendipitous findings was possibly the most common during the early stages of modern psychopharmacology. But it is precisely this dual quality that has been a major source of controversy in attributing serendipity to psychopharmacological discoveries.

Despite the remarkable success of imipramine, the next TCA, amitriptyline, was not introduced to the market until 1961. This molecule was also investigated as an antipsychotic by the pharmaceutical company Merck and Co. For this, they made modifications in the central ring of the thioxanthene family, and in this way, they got the first compound of the dibenzocycloheptadiene group ^[36]. Merck commissioned Frank J. Ayd Jr., one of the American pioneers in the study of chlorpromazine, to conduct clinical research on this new compound. But Ayd tried it as an antidepressant, following in the wake of imipramine. Ayd treated 130 patients at Baltimore Square Hospital with amitriptyline and found that the antidepressant effect was similar to that of imipramine. The Food and Drugs Administration (FDA) approved amitriptyline for marketing as an antidepressant on April 7, 1961, and it received the trade name Elavil®. This molecule would retain some of the tranquillizing effects of thioxanthenes, thus displacing imipramine in the treatment of patients with agitated or anxious depression.

The introduction of amitriptyline, the second tricyclic agent, by Merck and Co. increased the confidence in these drugs of both general practitioners and specialists. Thanks to the commercial strength of these two pharmaceutical companies and a marketing agreement between them (the joint marketing of both products, Elavil® Merck and Tryptizol® Roche,

worldwide, except in the USA, where it was only marketed by Merck), amitriptyline quickly became the most prescribed antidepressant at the time.

Simultaneously, Hoffmann-La Roche and H. Lundbeck and Co. had succeeded in synthesizing amitriptyline, by modifying the chemical structure of imipramine accordingly, although due to the priority of their application, Roche received the European marketing rights under the name Saroten[®][37].

The discovery of the antidepressant properties of imipramine and its commercial success led to the development of a number of compounds with similar structures and activities (now called “me-too” compounds) in order to identify specific comparative advantages^[38]. This subsequently became quite common practice in the field of pharmacological therapeutics. As a result, a number of TCAs were developed during the 1960s. In 1963, nortriptyline was approved in Britain under the name Allegron[®], while in the USA it was approved by the FDA in November 1964, when desipramine (J.R. Geigy), the principal urinary metabolite of imipramine, was also approved; in 1966, trimipramine was introduced in Britain and other European countries under the name Surmontil[®]. These agents were followed by other TCAs: in 1966 by protriptyline (called Concoridin[®] in Europe and Vivactil[®] in the USA), in 1967 by iprindole (Prondol[®]), in 1969 by dothiepin (Prothiaden[®]), an agent not approved in the USA, doxepin^[39], introduced onto the European market by Galenus (Aponal[®]), a subsidiary of Boehringer, and in the USA by Pfizer (Sinequan[®])[40], and clomipramine (Anafranil[®]), introduced in Europe in 1970, which was not approved in the United States.

All components of the TCA series were developed specifically as antidepressant agents, following in the wake of imipramine and modifying its chemical structure, so they can all be included in the type IV pattern of our serendipitous attribution criteria, in which neither chance nor sagacity played a part (Table 2).

Table 2: Attribution of serendipity in the discovery of classical antidepressant drugs.

Group / Family	Drug	ATC code	Date of discovery (psychiatric introduction)	Effect / primary properties ^a	Effect / secondary properties ^b	Pattern of discovery
TCAs	Imipramine	N06AA02	1951 (1957)	S	NS	II
	Amitriptyline	N06AA09	1958 (1961)	NS	NS	IV
	Trimipramine	N06AA06	1964 (1966)	NS	NS	IV
	Butriptyline	N06AA15	1964	NS	NS	IV
	Desipramine	N06AA01	1964	NS	NS	IV
	Clomipramine	N06AA04	1963 (1970)	NS	NS	IV
	Nortriptyline	N06AA10	1963 (1967)	NS	NS	IV
	Protriptyline	N06AA11	1967	NS	NS	IV
	Iprindole	N06AA13	1967	NS	NS	IV
	Doxepin	N06AA12	1969	NS	NS	IV
	Dibenzepin	N06AA08	1970	NS	NS	IV
	Maprotiline*	N06AA21	1967 (1973)	NS	NS	IV
	Dosulepin	N06AA16	1977	NS	NS	IV
	Amineptine	N06AA19	1978	NS	NS	IV
	Amoxapine	N06AA17	1980	NS	NS	IV
	Quinupramine	N06AA23	1983	NS	NS	IV
MAOI	Lofepamine	N06AA07	1989	NS	NS	IV
	Iproniazid	N06AF05	1952 (1957)	S	NS	II
	Isocarboxazid	N06AF01	1959	NS	NS	IV
	Phenelzine	N06AF03	1960	NS	NS	IV
	Tranlycypromine	N06AF04	1961	NS	NS	IV
OCA	Nialamide	N06AF02	1988	NS	NS	IV
	Trazodone	N06AX05	1966 (1973)	NS	NS	IV
	Nomifensine	N06AX04	1977	NS	NS	IV
	Mianserin	N06AX03	1966 (1979)	S	NS	II

^a Usually, but not always, they correspond to discoveries in laboratory animals.

^b Discoveries related to clinical efficacy.

NS (non-serendipitous discovery); S (serendipitous discovery).

TCAs (tricyclic antidepressants); MAOIs (monoamine oxidase inhibitors); OCA (other classical antidepressants).

*Maprotiline is the first tetracyclic antidepressant and is included in the group of “second generation antidepressants”.

Antidepressant drugs were classified by the Anatomical Therapeutic Chemical (ATC) classification system controlled by the World Health Organization Collaborating Centre for Drugs Statistics Methodology (WHOC). This system classifies the active ingredient of a drug into groups according to the organ or system on which they have their effect.

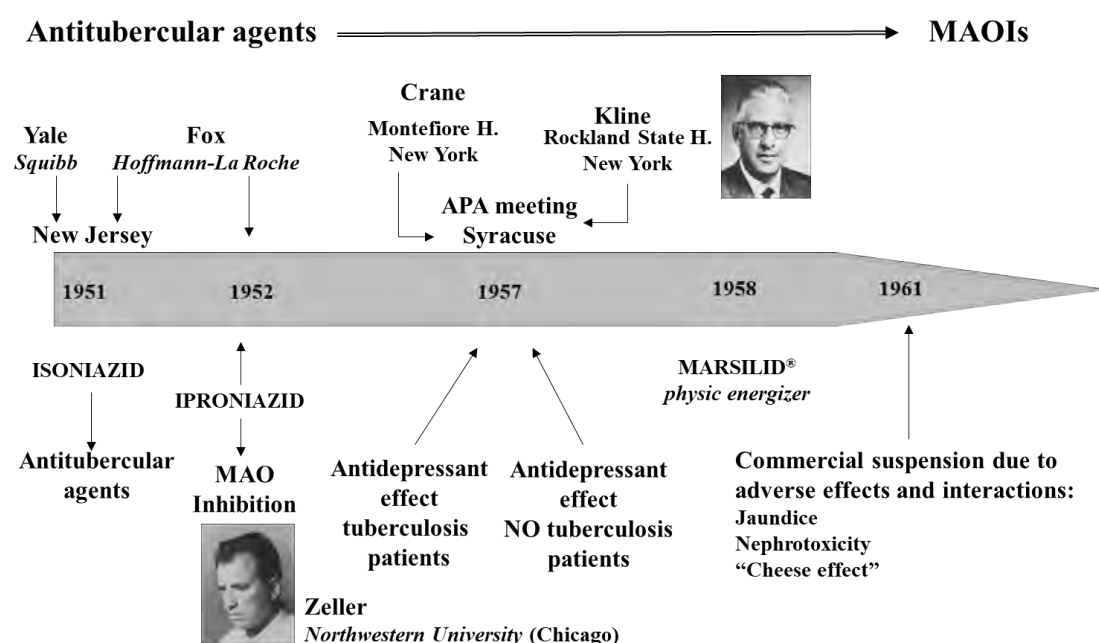
https://www.whocc.no/atc_ddd_index/?code=N06AX&showdescription=no

Discovery of the antidepressant properties of iproniazid and non-selective MAOIs

The origin of the first specific antidepressant drugs, MAOIs, can be traced back to hydrazide anti-tuberculosis agents, which had been used since the early 1950s^[5,41] (Figure 3). In 1952, Irving J. Selikoff and Edward Robitzek began to study the clinical effects of iproniazid at Sea View Hospital on Staten Island (New York). They observed that,

compared to isoniazid, iproniazid had a greater stimulatory power on the central nervous system, an effect initially interpreted as a secondary effect of the preparation^[42]. The psychological changes observed in tuberculosis patients treated with iproniazid were particularly striking^[5,8,43]; these patients showed increased vitality, even a desire to leave the hospital, and a gradual increase in social activity. In other types of patients treated with iproniazid, such as patients with rheumatoid arthritis or cancer, similar psychostimulant effects were also observed^[44].

Figure 3: Historical process of the discovery of monoamine oxidase inhibitors during the 1950s.



But the adverse effects of iproniazid, observed in the first clinical trials with tuberculosis patients, were more frequent than in the case of isoniazid, so it was abandoned, except for specific cases, such as that of David M. Bosworth, Director of the Department of Orthopedics at St. Luke's and Polyclinic Hospital (New York), who continued to defend the use of iproniazid in bone tuberculosis^[45]. But a few astute clinicians saw a "primary effect" in the psycho-stimulant type of "secondary effect" discussed above, which could be useful in other types of patients, mainly of a psychiatric nature. This was the case of Jackson A. Smith (Baylor University, Waco, Texas), who, evaluating the "tranquillizing" effect of iproniazid, observed that, of a group of eleven patients treated for two weeks with this drug, two of them experienced a certain improvement (increased appetite,

weight gain, increased vitality and improved sleep)^[46]. The same was true of Gordon R. Kamman, of the University of Minnesota (Twin Cities)^[47] and Carlos Castilla del Pino of the University of Cordoba in Spain, who described the euphoriant and mood-elevating effects of hydrazide therapy in tuberculosis patients^[48]. Some studies were even published assessing the mood elevating effect of isoniazid in psychiatric patients^[49-51]. In fact, one of these researchers, Max Lurie (Cincinnati), may have coined the term “antidepressant”, precisely to describe the effect that this drug had on depressed patients^[52].

The year 1957 was fundamental in the history of hydrazide drugs as antidepressants, as the first data on the effects of iproniazid on depression were presented at a meeting of the American Psychiatric Association (APA) in Syracuse in April of that year. Although its use was much more limited than isoniazid, George Crane of Montefiore Hospital in New York reported improvement in the mood of 11 out of 20 tuberculosis patients with concomitant depression^[53], as did Frank Ayd, an intern at Taylor Manor Hospital in Baltimore^[54]. However, these researchers never mentioned iproniazid as an “antidepressant” agent.

Meanwhile, Nathan S. Kline and his colleagues (Harry P. Loomer and John C. Saunders), from Rockland State Hospital (Orangeburg, New York), who were aware of the work of Charles Scott's team at Warner-Lambert Research Laboratories (Morris Plains, New Jersey), particularly the ability of iproniazid to prevent reserpine-induced immobility in mice^[55], were the first psychiatrists to assess the efficacy of iproniazid in non-tuberculous depressed patients (chronic psychotic depression), when they performed the same procedures on humans as Scott had done on animals. For their study, they recruited 17 severely inhibited patients with schizophrenia and 7 patients with depression from Kline's private practice and gave them a dose of iproniazid 50 mg, 3 times a day. Their results revealed the stimulating effect of iproniazid on depressed patients; 70% of the patients treated with this drug experienced a great improvement, including increased mood, increased appetite, and increased interpersonal skills, interest in the environment and in themselves. These same effects were already provided at the Syracuse Meeting, although they were not released until a few years later, when they were published^[56].

In 1957, Kline published the first neuropsychiatric experiments with iproniazid (previously reported at the APA Annual Meeting in Syracuse), during a meeting of the

Committee on Appropriations of the United States Senate in May^[57], proposing the term “physic energizer” to designate the activity of this drug^[58]. Two years later, Werner Janzarik proposed, at a symposium held in Montreal, the use of the term “thymereithics”, i.e., compounds that act by increasing the stimulatory effects, to refer to all those drugs with effects similar to the new MAOIs.

Although iproniazid was only authorized (with the trade name of Marsilid) for the treatment of tuberculosis patients, its use in depressive patients was massive and only one year after the Syracuse Meeting, it has been estimated that more than 400,000 patients with depression were treated with iproniazid^[59]. This opened the door to a group of specifically antidepressant drugs, later known as MAOIs, as, thanks to the research of Ernst Albert Zeller's team at Northwestern University Medical School (Chicago, Illinois), it was known in 1952 that iproniazid was able to inhibit MAO^[60]. Despite all this, iproniazid was withdrawn from the US market in 1961 following allegations that it induced a number of cases of jaundice and nephrotoxicity.

Serendipity played an important role in the discovery of iproniazid^[11]. Thanks to the sagacity of healthcare professionals dedicated to the care of tuberculosis patients, it was realized that certain “secondary effects” of anti-tuberculosis medication of a psychostimulant nature, which appeared by chance, could be useful in psychiatric patients diagnosed with depressive disorders. Therefore, this would fall under a type II pattern under our serendipitous attribution criteria.

Iproniazid soon gave way to other agents with much higher MAO inhibitory potency^[61], such as Hoffman-LaRoche's isocarboxazid (Marplan[®]), marketed in 1959, phenelzine developed by Warner-Lambert (Nardil[®])^[62], which became available in 1960, and tranylcypromine (Smith, Kline & French) (Parnate[®])^[63,64], which entered the market in 1961, as well as other hydrazine derivatives (nialamide, mebanazine and pheniprazine) and indole derivatives (etryptamine)^[65,66]. The origin of this agent, synthesized in 1948 by Alfred Burger and William L. Yost, is part of the search for new analogues of amphetamines (trans,dl-2 phenylcyclopropylamine sulphate)^[67], although its MAOI activity was discovered much later, in 1959 by Smith, Kline & French Laboratories^[63,68]. Indeed, the fact that tranylcypromine was not a hydrazine derivative aroused some clinical

interest, and it was speculated that it could have a better hepatic safety profile than that of other MAOIs known to date^[69].

But tranylcypromine was also withdrawn from the US market in 1964, albeit for other safety reasons, when an increase in the number of drug-related hypertensive crises, some of them linked to intracranial subarachnoid hemorrhages, was reported, although it was reintroduced in the same year at the request of specialists and is still in use today. Thanks to the contributions of Barry Blackwell, then a resident consultant in psychiatry at the Maudsley Hospital in London, it was confirmed that these crises were triggered by the concomitant consumption of certain cheeses, given their high tyramine content, hence the term “cheese effect”^[70]. The link between the hypertensive crises described by Blackwell and the consumption of tyramine-rich foods is also a clear example of the phenomenon of “serendipity” in psychiatry, according to Blackwell himself^[71]. A hospital pharmacist in Nottingham, called G.E.F. Rowe, read an article published by Blackwell in 1963 in *The Lancet* on tranylcypromine and its adverse effects^[70], and noted that the symptomatology described was alarmingly similar to that experienced by his own wife when she consumed certain cheeses. These episodes were described in detail in a letter Rowe sent to Blackwell, who was alerted to this dangerous association. Many other foods (yeast products, chicken liver, snails, pickled herring, red wines, some varieties of beer, canned figs, beans, chocolate and cream products, etc.) were subsequently found to contain indirectly acting amines (mainly tyramine), which could also cause hypertensive episodes in patients treated with MAOIs.

After the use of iproniazid as an antidepressant, the other agents in this family were incorporated into the antidepressant therapeutic arsenal thanks to recognition of their MAO inhibitory effect, meaning that they would fall into the type IV pattern under our serendipitous attribution criteria, where chance no longer played a role (Table 2).

Heterocyclic or “second-generation” antidepressants

During the 1960s, many changes were made to the dibenzazepine structure of imipramine in order to obtain new antidepressants with superior efficacy and/or an improved adverse effect profile. As a result, the tetracyclic, heterocyclic or “second generation antidepressants”^[36], such as maprotiline (Ludiomil®), marketed by Ciba-Geigy in Europe

and Japan in 1972^[8], mianserin (Tolvon[®]), nomifensine (Merital[®]) and trazodone (Desyrel[®]), were developed. Compared to the classic TCAs, which had a very unspecific mechanism of action (serotonin -5-HT- and norepinephrine -NA- reuptake inhibition with blocking action of diverse receptors)^[72], these drugs had a slightly cleaner pharmacodynamic profile.

The first tetracyclic antidepressant was maprotiline, developed as an antidepressant by Max Wilhelm and Paul Schmidt in 1967 at Ciba. However, the four rings of its chemical structure are not fused together as is the case with other tetracyclic antidepressants. Clinical trials of this agent were also conducted by Kuhn^[73]. By contrast, nomifensine is a tetrahydroisoquinoline antidepressant that is not chemically related to TCAs, MAOIs or heterocyclic antidepressants. It is a dopamine (DA) and NA reuptake inhibitor developed as an antidepressant in the 1960s by Hoechst AG. The pharmacological effects of nomifensine were similar to those of TCAs in animal models of depression, but with a much lower rate of sedation^[74]. However, it was withdrawn from the market in 1986 due to safety concerns (immune related hemolytic anemia), including some cases of dependence, given its similar mechanism of action to psychoactive drugs such as cocaine.

As far as trazodone is concerned, it is now known to have a dual mechanism of action, whereby it inhibits the serotonin transporter and blocks the 5-HT₂ serotonin receptors (both the 5-HT_{2A} and 5-HT_{2C} receptors). But, like TCAs, it also exerts an antagonistic effect on α_1 - and α_2 -adrenergic receptors and histamine H₁ receptors, with almost no anticholinergic effects^[75]. It was discovered in Italy in 1966 at Angelini Research Laboratories by Guiseppe Palazzo and Bruno Silvestrini^[76] and developed as a second generation antidepressant following the then current “mental pain” hypothesis, which postulated that clinical depression was associated with a reduced pain threshold^[77]. Trazodone was patented and marketed in many countries around the world from 1973 and approved by the FDA as the first non-TCA, non-MAOI antidepressant in 1981. These three compounds can be included in our type IV pattern of attributability, as serendipity was not involved in their discovery and development.

However, the development of mianserin is another example of serendipitous influence. As part of a research program carried out by Organon International, B.V. in Oss (The Netherlands), mianserin (a tetracyclic piperazino-azepine) was synthesized in 1966 by

Willem J. van der Burg's group^[78], with the aim of confirming whether the antihistamine properties of phenbenzamine and the anti-serotonergic activity of cyproheptadine could be combined in a chemical structure that could be potentially useful for treating asthma, migraine or allergic diseases such as hay fever.

Early pharmacological studies confirmed that mianserin was capable of antagonizing the effects of serotonin in different samples of various animal tissues^[79], including human blood vessels, and also exhibited antihistamine properties^[80]. These findings led to the launch of a pilot study in 1969, which was not published, in which the tetracyclic compound was administered to ten asthmatic patients, compared to an untreated control group. Patients who received mianserin had significantly fewer night-time asthma attacks. However, this line of research was not continued, as a number of central adverse effects, mainly sedation, were also described^[81]. Nevertheless, another study in Ireland, also in 1969, found that mianserin had a marked positive effect in improving mood in some subjects, and they began to call mianserin the “good mood pill”. This observation about the hypothetical antidepressant properties of mianserin spurred on the clinical development of the molecule^[81]. A number of experimental studies carried out using computer analyses of EEG recordings, and comparative pilot trials with amitriptyline confirmed the antidepressant efficacy of this drug^[82], which was presented as the first representative of a new generation of antidepressants (heterocyclic antidepressant compounds). Clinical trials over the next few years revealed antidepressant efficacy similar to that of classical TCAs, but superior to that of other “second generation” agents such as nomifensine or trazodone^[81].

As in the case of the two group-leading agents of TCAs and MAOIs, mianserin falls within the type II pattern under our serendipitous attribution criteria, i.e., an initial serendipitous discovery, when looking for an antihistamine drug, leading secondarily to a non-serendipitous discovery - an antidepressant agent (Table 2).

NOTES FOR DIALOGUE

Serendipity is a phenomenon that has been regularly and constantly referred to when analyzing the great discoveries that supported the birth of modern psychopharmacology. But, as previously mentioned, the real role of serendipity in these processes has not been

sufficiently well defined, possibly due to differences in opinion among authors, given the semantic ambiguity of the term “serendipity”^[83], and the degree of importance attributed at any given time to the two elements that make up the concept of serendipity: sagacity and unforeseen accidents. For this reason, our group^[13,18] advocates the original meaning of the term, as the discovery of something unexpected or not intentionally sought, in line with favors only the prepared mind” (cit.^[35]).

In fact, in the field of psychopharmacology, contrary to what has been postulated, pure serendipitous discoveries are rather rare, and most of them are of a mixed nature. Some authors refer to these patterns as “pseudo-serendipity”^[84] or discoveries that are “serendipity analogues”^[85].

These mixed serendipitous discoveries usually consist of a pattern that starts from an initial serendipitous observation and culminates in an intentionally sought-after discovery. For this reason, some authors and scholars may fall into the interpretative error of ascribing merit to chance or luck alone, seeing the results of research processes as a mere continuation of the initial serendipitous findings, rather than as two manifestly different events. The cases presented in this paper on the discovery of the two families of classical antidepressants are proof of this: TCAs and MAOIs. Many other discoveries during the 1950s are included within this type II serendipitous attribution pattern that we have defined (initial serendipitous discoveries, in some cases made in laboratory animals, leading secondarily to non-serendipitous discoveries), such as the discovery of the antipsychotic properties of chlorpromazine and clozapine, and the experimental tranquillizing properties of meprobamate and its subsequent anxiolytic effect in clinical trials. However, the clearest example was the discovery of the lethargic effect of lithium salts in guinea pigs and their subsequent antimanic effect in humans. Most authors consider the discovery of the antimanic effects of lithium to be purely serendipitous. However, Cade himself pointed out that the link between his casual observation of the lethargic effect in guinea pigs and the subsequent confirmation of the antimanic efficacy of lithium salts was far from obvious^[86]. For more information on the historical development of these drugs, see the work of our group^[19,20,23,25,41,87-89].

There are also examples of mixed serendipitous discoveries in reverse, included in our type III pattern (non-serendipitous discoveries partnered secondarily with serendipitous

discoveries). The most representative example of this group would have to be barbiturates and their intended hypnotic effects, which made the later serendipitous discovery of their anticonvulsant and antiepileptic effects possible^[90].

But although serendipity does not usually work alone, there are also cases of pure serendipitous discoveries (type I pattern of attributability), such as the discovery of the anticonvulsant and mood stabilizing effects of valproic acid and valproate, respectively, or the discovery of the psychotropic effects of lysergic acid diethylamide (LSD). Similarly, other discoveries in the field of psychopharmacology during the golden decade of the 1950s should be included under the type IV pattern, namely non-serendipitous discoveries, in line with our operational definition of an unintended finding. Notable here is the discovery of the anxiolytic effect of chlordiazepoxide, the first benzodiazepine agent^[91], and the antipsychotic effect of haloperidol and reserpine^[24,92,93].

The clinical introduction of psychotropic drugs during the 1950s can be considered one of the great advances in medicine of the 20th century, and a major part of this breakthrough can be attributed to the discovery of the antidepressant effects of iproniazid and imipramine^[3], a process in which serendipity played an essential role. But it is worth highlighting another series of contributions to the progress of biological psychiatry in addition to this great clinical contribution^[3]. Firstly, from a strictly pharmacological point of view, the development of imipramine led to the introduction of new methods for assessing the antidepressant activity of different substances^[94]. Secondly, the discovery and subsequent therapeutic use of TCAs and MAOIs played a major role in developing the first etiopathogenic theories on affective disorders^[95]. During the 1960s, catecholaminergic theories of depression blossomed, postulating a functional impairment of brain noradrenergic neurotransmission as the primary cause of affective disorders, based on observations made on the effects of newly discovered antidepressant drugs, such as the blocking of synaptic reuptake of NA by imipramine^[96]. Later, in 1968, Carlsson et al.^[97] described, for the first time, how imipramine was able to block the reuptake of serotonin in brain pathways, thereby laying the groundwork for the “serotonergic hypothesis” of depression.

However, the story of these two families of antidepressants evolved in completely different ways. Consequently, while TCAs continue to be used in clinical practice in an

important way and constitute first-line tools in clinical research, MAOIs have suffered a large reduction in their use, except in the specific case of atypical depressions, largely due to their problems of interactions with other psychostimulant drugs and with tyramine-rich foods, which can lead to tragic hypertensive crises. However, despite this divergence, the importance of imipramine and iproniazid in the history of psychopharmacology is paramount.

CONCLUSION

It is clear that, during the 1950s and 1960s, serendipity played an important role in the process of building modern psychopharmacology in general, and the first groups of families of antidepressant drugs in particular, giving way, in later decades, to another way of understanding scientific research in this field, namely the systematic and rational planning of projects to be developed. In recent decades, psychopharmacology is moving away from the influence of serendipity towards new scientific approaches, although this is a gradual process^[98], as can be seen with the serendipitous introduction of ketamine into the antidepressant arsenal. In any event, the results of this work confirm that serendipity should be understood as more of an eminently scientific construct than a literary curiosity.

In the words of the discoverer of vitamin C, Albert Szent-Györgyi, “discovery consists of seeing what everybody has seen and thinking what nobody has thought”^[99].

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DOCUMENTO 3



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Original Article

Did Serendipity Contribute to the Discovery of New Antidepressant Drugs? Historical Analysis Using Operational Criteria

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Abstract

Objective: Given their great importance, as one of the most prescribed types of therapeutic drugs worldwide, we have analyzed the role of serendipity in the discovery of new antidepressants, ranging from selective serotonin reuptake inhibitors to more contemporary developments. **Methods:** We carried out a historical analysis of the discovery of new antidepressants, resorting to the original articles published on their development (initial pharmacological and clinical information) and applied an operational criterion of serendipity developed by our group. **Results:** Selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline, and escitalopram), selective dopamine and noradrenaline reuptake inhibitors (bupropion), noradrenaline and serotonin reuptake inhibitors (venlafaxine, milnacipram, duloxetine, and desvenlafaxine), selective noradrenaline reuptake inhibitors (reboxetine), noradrenergic and specific serotonergic antidepressants (mirtazapine), melatonergic agonists (agomelatine), and serotonin modulators and stimulators (vortioxetine, vilazodone, tianeptine) correspond to the type IV pattern. Moclobemide, a reversible monoamine oxidase inhibitor, corresponds to the type II pattern, for which the initial serendipitous findings (i.e., the chance discovery of the inhibitory effects of monoamine oxidase (MAO) whilst being studied for their antihyperlipidemic properties) led to subsequent non-serendipitous discoveries (clinical antidepressant efficacy). Ketamine, a glutamatergic modulator, corresponds to the type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using). **Conclusion:** The majority of new antidepressants adhere to a type IV pattern, characterized by a rational and targeted design process where serendipity played no part, except moclobemide (type II pattern) and ketamine (type III pattern).

Keywords: antidepressants; history of medicine; psychopharmacology; serendipity

Main Points

1. Serendipity is a phenomenon que requires the convergence of accident and sagacity.
2. In pharmacology, purely serendipitous discoveries (type I pattern of imputability) are relatively rare. This pattern has not been found in the discovery of any of the new antidepressants.
3. The development of new antidepressants, from selective serotonin reuptake inhibitors (SSRIs) to the present, has been characterized by a pattern IV, based on rational and systematic research programs and where there is no intervention of serendipity.
4. Moclobemide can be classified under the type II pattern, wherein initial serendipitous findings (the chance discovery of MAO inhibitory effects in a molecule being studied for its antihyperlipidaemic properties) led to subsequent non-serendipitous discoveries (clinical antidepressant efficacy).

sequent non-serendipitous discoveries (clinical antidepressant efficacy).

5. Ketamine follows a type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using).

1. Introduction

The 1950s, renowned in the field of pharmacology as the "golden decade" of psychotropic drugs, ushered in the introduction of the primary groups of agents still used today in treating mental disorders: antipsychotics, anxiolytics and antidepressants [1]. These psychotropic drugs drastically altered psychiatric patient care and provided insight into the neurobiological underpinnings of mental illnesses for the



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Did Serendipity Contribute to the Discovery of New Antidepressant Drugs? Historical Analysis using Operational Criteria

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ABSTRACT

Objective: Given its great importance, as one of the most prescribed therapeutic groups worldwide, in this paper, we have analyzed the role of serendipity in the discovery of new antidepressants, spanning from selective serotonin reuptake inhibitors to the contemporary developments. **Methods:** We have carried out a historical analysis of the discovery of new antidepressants, resorting to the original articles published on their development (initial pharmacological and clinical information) and we have applied an operational criteria of serendipity developed by our group. **Results:** Selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline, and escitalopram), selective dopamine and noradrenaline reuptake inhibitors (bupropion), noradrenaline and serotonin reuptake inhibitors (venlafaxine, milnacipram, duloxetine, desvenlafaxine), selective noradrenaline reuptake inhibitors (reboxetine), noradrenergic and specific serotonergic antidepressants (mirtazapine), melatonergic agonists (agomelatine) and serotonin modulators and stimulators (vortioxetine, vilazodone, tianeptine) correspond to a type IV pattern. Moclobemide, a reversible monoamine oxidase inhibitor, corresponds to the type II pattern, for which the initial serendipitous findings (i.e., the chance discovery of the inhibitory effects of monoamine oxidase (MAO) whilst being studied for their antihyperlipidemic properties) led to subsequent non-serendipitous discoveries (clinical antidepressant efficacy). Ketamine, a glutamatergic modulator, corresponds to the type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using). **Conclusion:** The majority of new antidepressants adhere to a type IV pattern, characterized by a rational and targeted design process where serendipity played no part, except moclobemide (type II pattern) and ketamine (type III pattern).

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1. Introduction

The 1950s, renowned in the field of pharmacology as the "golden decade" of psychotropic drugs, ushered in the introduction of the primary groups of agents still used today in treating mental disorders: antipsychotics, anxiolytics and antidepressants.¹ These psychotropic drugs drastically altered psychiatric patient care and provided insight into the neurobiological underpinnings of mental illnesses for the first time in the history, an approach often referred to as "pharmacocentric".²

The two main families of antidepressant drugs discovered during this period, tricyclics (TCAs)³ and monoamine oxidase inhibitors (MAOIs),⁴ exhibited significant efficacy in managing affective disorders.^{1,5} However, their substantial clinical contributions were overshadowed by therapeutic challenges primarily associated with tolerability and safety profiles. Consequently, a major challenge in psychopharmacology was overcoming these drawbacks, a feat realized in the 1980s with the clinical introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs). SSRIs revolutionized depression therapy,⁵ offering undeniable advantages over classical antidepressants, particularly in terms of safety and tolerability. While zimelidine was the first SSRI introduced, it was subsequently withdrawn from the market, the "new" or "modern" antidepressant era began with the clinical introduction of fluoxetine⁶ paving the way for new antidepressant families (see Table 1).

These new drug families, similar to classical drugs in terms of their mechanisms of action, primarily modulate monoaminergic neurotransmission at a synaptic level.^{2,5} Nonetheless, additional antidepressant drug families targeting different neurotransmitter pathways, such as glutamatergics or melatonergics, have also been introduced into clinical practice.

Table 1. Classification of new antidepressants according to action mechanism and historical perspective on their clinical introduction.

FAMILY	Acronym	Prototype substance	Period
Selective 5-HT reuptake inhibitors	SSRI	Fluoxetine	1975-1990
Reversible MAO inhibitors	RIMA	Moclobemide	1975-1990
Selective DA and NA reuptake inhibitors	SDRI	Bupropion	1975-1990
NA and 5-HT reuptake inhibitors	NSRI	Venlafaxine	1980-2000
Selective NA reuptake inhibitors	SNRI	Reboxetine	1980-2000
Noradrenergic and specific serotonergic antidepressants	NaSSA	Mirtazapine	1980-2000
Melatonergic agonists		Agomelatine	1990-2010
Glutamatergic modulators		Esketamine	1970-2020
Serotonin modulators and stimulators	SMS	Vortioxetine	2000-2020

5-HT, serotonin; MAO, monoamine oxidase; DA, dopamine; NA, norepinephrine; SSRI, selective serotonin reuptake inhibitor; RIMA, reversible monoamine oxidase inhibitors; SDRI, selective dopamine and noradrenaline reuptake inhibitor; NSRI, noradrenaline and serotonin reuptake inhibitor; SNRI, selective inhibitors of noradrenaline reuptake; NaSSA, specific noradrenergic and serotonergic antidepressants; SMS, serotonin modulators and stimulators.

Serendipity is a phenomenon frequently invoked when examining scientific discoveries, including those in pharmacology. Serendipitous discovery is understood as the revelation of something unforeseen, independent of the systematic process leading to the accidental observation.⁷ However, the attribution of this phenomenon remains highly contentious, likely due to the semantic ambiguity surrounding the term "serendipity",⁸ which has been employed with a wide array of meanings. Traditionally associated with concepts like chance, fortune, randomness, or coincidence ("happy accident", "pleasant surprise", etc.), we adopt the approach proposed by the introducer of this term, the English writer, politician and historian Horace Walpole, 4th Earl of Oxford, in his commentary on the classic Persian tale *The Three Princes of Serendip* (1557).⁹ Walpole suggested that serendipity requires the convergence of accident and sagacity, with sagacity being the factor conditioning a serendipitous discovery in the presence of a significant accidental event.⁷ This is evidenced by the book *Serendipity. Accidental discoveries in Science*.¹⁰

Hargrave-Thomas et al.¹¹ noted that 24% of all commercially available drugs at the time were positively influenced by serendipity during their development, particularly psychopharmacological agents. Confirming this, we found that the discovery of most psychotropic drugs during the 1950s occurred under these parameters of serendipitous influence, including classical antidepressant drugs.^{7,12,13} To this end, we have established

an operational definition of serendipity based on four different attributability patterns,^{7,12} allowing us to clarify its role in drug discovery. This paper, following our established approach, examines the role of serendipity in the discovery of new or modern antidepressant drugs.

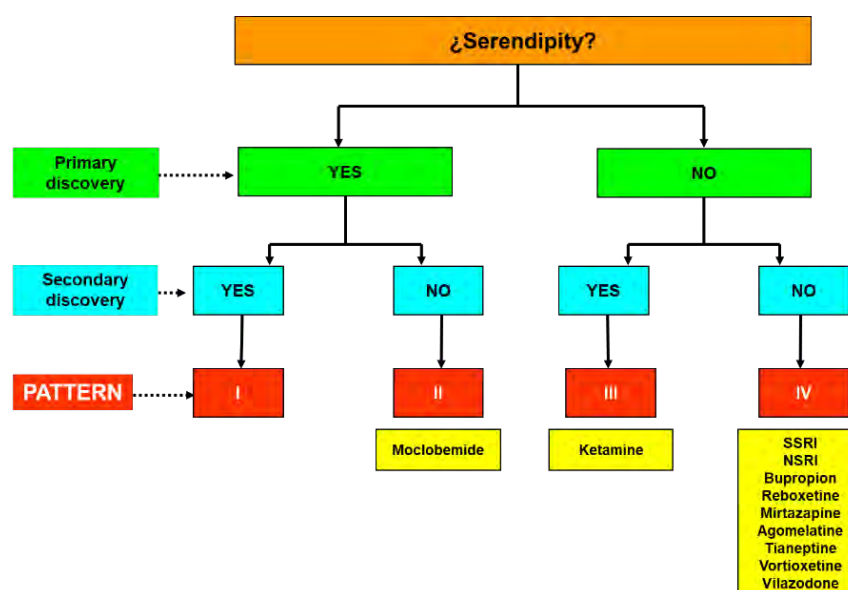
2. Methods

2.1. Operational Criteria of Serendipity

In previous research, we have employed a functional characterization of serendipity,^{7,12,13} which involves identifying four distinct patterns of attributing serendipity within the drug discovery process (Figure 1. Ref. ^{7,13}):

- a) Pattern I, encompasses purely serendipitous discoveries.
- b) Pattern II, a modification of the former pattern, delineates chance findings initially leading to planned discoveries devoid serendipitous origins.
- c) Pattern III, comprises discoveries lacking serendipity but subsequently leading to serendipitous findings.
- d) Pattern IV, corresponds to purely non-serendipitous discoveries, occurring outside the realm of chance or unintended accident. This pattern includes discoveries of pharmacological drugs within rational and systematic research programs specifically tailored to produce agents with specific effects on a given pathology.

Figure 1: Diagram of the four patterns of serendipitous attribution in the discovery of pharmacological agents and their application to new antidepressant drugs.



SSRI (selective serotonin reuptake inhibitors); NSRI (noradrenaline and serotonin reuptake inhibitors).
Figure adapted from the original created by the authors.^{7,13}

2.2. Archives and documents on the history of psychopharmacology

Before applying the attributability criteria, we accessed the original manuscripts containing the initial pharmacological and clinical information on new antidepressant drugs from the various sources:

- Primary databases in the biomedical field (Medline, Embase, Scopus).
- Documentation resources provided by the pharmaceutical companies distributing the new antidepressants.
- Documentation accessible through the International Network for the History of Neuropsychopharmacology (INHN), under the guidance of Thomas A. Ban (Vanderbilt University).
- David Healy's *The Psychopharmacologists* series of interviews (Arnold – Oxford University Press).
- The History of Psychopharmacology collection of the International College of Neuropsychopharmacology (CINP) (*Collegium Internationale Neuro-*

Psychopharmacologicum), coordinated by Thomas A. Ban, David Healy and Edward Shorter and published by Animula.

f) Prof. López-Muñoz's collection of documents on the history of psychopharmacology.

3. Results

3.1. Selective serotonin reuptake inhibitors (SSRIs)

The first SSRI synthesized and developed was fluoxetine, considered the prototype molecule of this antidepressant family. Its development stemmed from 1960s studies on TCAs which supported the serotonergic hypothesis of depression by demonstrating the potent inhibition of 5-HT uptake by imipramine and similar agents.¹ A lecture on "synaptosomes" technique, given in 1971 by Solomon H. Snyder from Johns Hopkins University later influenced fluoxetine's development. That same year, pharmacologist Ray W. Fuller, an expert in 5-HT research, and biochemist David T. Wong formed a "serotonin-depression study team", which also included organic chemist Bryan Molloy and pharmacologist Robert Rathbun.¹ In the early 1970s, this team focused on developing molecules that selectively inhibited 5-HT uptake, aiming to create antidepressants without the cardiotoxicity and anticholinergic properties of TCAs.¹ They noted that diphenhydramine and other antihistamines could inhibit monoamine uptake, leading them to synthesize a series of phenoxyphenylpropylamines, including nisoxetine.¹⁴ Among the 55 derivatives in this series, fluoxetine hydrochloride (LY-110140) was identified in 1972 as the most potent and selective 5-HT uptake inhibitor.¹⁵ Fluoxetine's structure, particularly the p-trifluoromethyl group, was key to its efficacy and selectivity, resulting in fewer adverse effects compared to TCAs.¹⁶ Despite indirect testing methods, studies suggested an increase in extraneuronal 5-HT concentrations.¹ The first publication on fluoxetine appeared in 1974, highlighting its potential utility in studying serotonergic functions and mental disorders.¹⁵ Fluoxetine's clinical development began in 1980, with initial studies conducted at John Feighner's private psychiatric clinic in La Mesa (California). By 1983, results demonstrated fluoxetine's efficacy as an antidepressant with significantly fewer side effects compared to TCAs, marking the advent of a "New Generation of Antidepressants".¹⁷ Extensive clinical trials between 1984 and 1987 culminated in its approval by the US Food and Drug Administration (FDA) in December 1987.

Following fluoxetine, other SSRIs were introduced, including zimelidine, marketed in 1982, which was withdrawn due to adverse effects (hypersensitivity issues, including fever, myalgias, increased levels of aminotransferases and notably, various cases of neurological complications linked to Guillain-Barré syndrome).¹⁸ The rest of the SSRIs were marketed later through targeted research strategies. Fluvoxamine was developed by Hendricus B.A. Welle and Volkert Claassen¹⁹ in the mid-1970s at Belgium, and marketed in Switzerland in 1983. Citalopram was synthesized in 1972 by chemist Klaus Bøgesø²⁰ and it was first marketed in Denmark in 1989. Paroxetine, a phenylpiperidine derivative, was discovered in 1975 and patented in the US in 1977. The patent was subsequently transferred in 1980 and was first marketed in Sweden in 1991.²¹ Sertraline's development began in 1977, led by pharmacologist Kenneth Koe and chemist Willard Welch.²² This SSRI was launched in the UK in 1990. Finally, in 1997 began the development of escitalopram, (S)-enantiomer of the racemate citalopram.²⁰ In 2002, escitalopram was launched in Europe and the US and subsequent clinical studies confirmed its superiority over escitalopram, particularly in patients with severe depression.²³

The development of SSRIs marked a shift in psychopharmacology towards rational, directed drug design rather than serendipitous discovery, aligning with our type IV pattern of serendipitous attribution (Table 2).

Table 2: Attribution of serendipity in the discovery of new antidepressant drugs.

Group / Family	Drug	ATC code	Date of discovery (psychiatric introduction)	Effect / primary properties	Effect / secondary properties	Pattern of discovery
SSRIs	Fluoxetine	N06AB03	1972 (1987)	NS	NS	IV
	Citalopram	N06AB04	1972 (1989)	NS	NS	IV
	Paroxetine	N06AB05	1973 (1991)	NS	NS	IV
	Sertraline	N06AB06	1979 (1990)	NS	NS	IV
	Fluvoxamine	N06AB08	1978 (1983)	NS	NS	IV
	Escitalopram	N06AB10	1988 (2002)	NS	NS	IV
RIMA	Moclobemide	N06AG02	1972 (1992)	S	NS	II
SDRI	Bupropion	N06AX12	1969 (1985)	NS	NS	IV
NSRI	Venlafaxine	N06AX16	(1993)	NS	NS	IV
	Milnacipran	N06AX17	(1996)	NS	NS	IV
	Duloxetine	N06AX21	1986 (2004)	NS	NS	IV
	Desvenlafaxine	N06AX23	(2008)	NS	NS	IV
	Levomilnacipran	N06AX28	(2013)	NS	NS	IV
SNRI	Reboxetine	N06AX18	1984 (1997)	NS	NS	IV
NaSSA	Mirtazapine	N06AX11	1989 (1994)	NS	NS	IV
MA	Agomelatine	N06AX22	1998 (2009)	NS	NS	IV
GM	Esketamine	N06AX27	1962 (2019)	NS	S	III
	Tianeptine	N06AX14	1981 (1989)	NS	NS	IV
SMS	Vortioxetine	N06AX26	2002 (2013)	NS	NS	IV
	Vilazodone	N06AX24	2004 (2011)	NS	NS	IV

NS (non-serendipitous discovery); S (serendipitous discovery).

SSRI (selective serotonin reuptake inhibitors); RIMA (reversible monoamine oxidase inhibitors); SDRI (selective dopamine and noradrenaline reuptake inhibitors); NSRI (noradrenaline and serotonin reuptake inhibitors); SNRI (selective inhibitors of noradrenaline reuptake); NaSSA (specific noradrenergic and serotonergic antidepressants); MA (melatonergic agonists); GM (glutamatergic modulators); SMS (serotonin modulators and stimulators).

Antidepressant drugs were classified by the Anatomical Therapeutic Chemical (ATC) classification system controlled by the World Health Organization Collaborating Centre for Drugs Statistics Methodology (WHOCC). This system classifies the active ingredient of a drug into groups according to the organ or system on which they have their effect.

https://www.whocc.no/atc_ddd_index/?code=N06AX&showdescription=no

3.2. Reversible monoamine oxidase inhibitors (RIMAs)

The development of reversible and selective monoamine oxidase A (MAO-A) inhibitors, with moclobemide as the prototype, emerged from efforts to improve the safety profile of

classical MAOIs. Moclobemide (Ro 11-1163), a benzamide derivative of morpholine, was first synthesized in 1972 by Pierre-Charles Wyss in Basel (Switzerland).²⁴ This synthesis was part of a research programme focused on developing new lipid-lowering agents without antiviral activity. Despite failing to exhibit significant hypolipidemic effects and yielding negative screenings, moclobemide was found to possess intriguing monoamine oxidase (MAO) inhibitory activity in rat studies, prompting a shift towards its development as an antidepressant.²⁴ *In vitro* studies evidenced moclobemide to be a weak but highly selective MAO-A inhibitor, with a relatively short enzyme inhibition period of 8 to 10 hours.²⁵ Furthermore, its safety profile was significantly better than that of classical MAOIs, with rare instances of problematic hypertensive crises.²⁶

Clinical trials began in 1977, and moclobemide was introduced into clinical practice in the UK and Europe in 1992 as the first drug of the new RIMA class. Although it was marketed in various countries and used as a first-line treatment in Finland and Australia, it was never approved in the US.

The serendipitous discovery of moclobemide, originally intended as an antihyperlipidemic, led to its development as a leading example of the new class of antidepressants. This development fits within the type II pattern of our serendipity attribution criteria (Table 2).

3.3. Other monoamine reuptake inhibitors

Over the past four decades, numerous new antidepressant drugs have been developed to enhance the basic and clinical profiles of SSRIs. These new drug families, with diverse pharmacodynamic properties, primarily act on the central nervous system (CNS) by modulating monoamine neurotransmission.⁵ This includes NSRIs (venlafaxine, duloxetine, milnacipram, desvenlafaxine, levomilnacipram); SDRIs (bupropion); and SNRIs (reboxetine).

Bupropion, originally known as amfebutamone, is a chlorpropionophenone derivative primarily inhibiting dopamine (DA) reuptake, with minimal effect on 5-HT transporters.²⁷ Developed by Nariman Mehta in 1969,²⁸ bupropion was introduced to the US market in 1985 but withdrawn in 1986 due to seizure risks, which were later linked to dosage.

Reintroduced in 1989 with a maximum daily dose of 450 mg, sustained-release (SR) and extended-release (XL) formulations were approved by the FDA in 1996 and 2003, respectively, to improve patient's adherence to treatment.²⁹ Reboxetine, the first, SNRI, was developed at Italy in the mid-1980s and approved in Europe in 1997.³⁰ Another potent and selective SNRI is atomoxetine. Initially developed as an antidepressant, it proved more efficacious for the treatment of attention-deficit/hyperactivity disorder (ADHD) and was FDA-approved for this indication in 2002.

Venlafaxine, the first NSRI, was designed to inhibit both 5-HT and norepinephrine (NA) reuptake (with three times greater selective for 5-HT than NA), proving effective with minimal action at other receptors.³¹ By optimizing of ciramadol, an opiate analgesic lead, through a three-step synthesis, reducing its chiral centres from three to one, and incorporating an alkylamine pharmacophore, venlafaxine was introduced to the US market in 1993. In 1997, the XL formulation of venlafaxine was also approved for depression.³² To mitigate potential drug interactions in patients with varying metabolizing capabilities, desvenlafaxine was developed, the primary active metabolite of venlafaxine (O-desmethyl metabolite),³³ and was approved in the US in 2008.³¹ Duloxetine emerged from observations made during research on the molecule LY227942, whose (+)-enantiomer exhibited twice the potency inhibiting 5-HT reuptake compared to the (-)-enantiomer. This antidepressant was introduced to the market in 2004.³⁴ Finally, milnacipran, a cyclopropane derivative with 5-HT and NA reuptake inhibitory properties, was approved for use in France in 1996.³⁵ Levomilnacipran, the levorotatory enantiomer of milnacipran, was commercialized in 2013.³⁶

The development of these drugs was based on rational hypotheses rather than serendipity, reflecting a type IV pattern of drug discovery (Table 2).

3.4. Noradrenergic and specific serotonergic antidepressants (NaSSA)

Mirtazapine, known as ORG 3770, is a tetracyclic piperazine-azepinet derived from the antidepressant mianserin. It chemically differs from mianserin by the addition of a nitrogen atom in one of the rings.³⁷ This atypical tetracyclic antidepressant blocks α_2 adrenoceptors, 5-HT₂ and 5-HT₃ receptors. By antagonizing somatodendritic α_2 autoreceptors and heteroreceptors located in the pre-synapses, it enhances the firing rate

of the neurons and neurotransmitter release.³⁸ Additionally, its blockade of 5-HT₂ and 5-HT₃ receptors helps to moderate some of the known serotonergic adverse effects and improves pharmacological efficacy.³⁹ The initial data on mirtazapine were published in 1989, and its clinical introduction occurred in the Netherlands in 1994.

As the discovery process of mirtazapine as an antidepressant did not rely on serendipity at any stage, this development aligns with our type IV pattern (Table 2).

3.5. Melatonergic agonists

The hypothesis that led to the discovery of the first melatonergic agent, agomelatine, was based on the manipulation of the circadian rhythm, which is often disrupted in depressive patients.⁴⁰ Consequently, a series of naphthalene derivatives were synthesized, and their ability to displace [¹²⁵I]-melatonin in the pituitary gland was investigated.⁴¹ Concurrently, electrophysiological studies were conducted, revealing that one of the derivatives, S20098, acted as an agonist of melatonin receptors. This molecule was selected for further development and named agomelatine.⁴² Subsequent studies confirmed that this agent could normalize circadian rhythms in a dose-dependent manner⁴³ and pharmacological screenings for antidepressant properties yielded positive results.⁴⁰ The receptor profile of agomelatine is different from other antidepressant drugs. Agomelatine acts as an agonist of the MT₁ and MT₂ melatonin receptors,⁴⁴ while also functioning as an antagonist of the 5-HT_{2C} receptors.⁴⁵ Moreover, it does not inhibit the reuptake of monoamines and lacks the capacity to block other receptors. With its properties as a melatonergic receptor agonist, agomelatine can be regarded as an agent capable of synchronizing distorted rhythms.

Following successful testing of agomelatine in various animal models of depression, the first clinical trial of agomelatine was launched in 2002 by Henri Lôo *et al.*⁴⁶ (Hôpital Sainte Anne, Paris), confirming its antidepressant efficacy compared to paroxetine. In March 2006 clinical trials began in the US. However, development for the US market was discontinued in October 2011. Agomelatine was approved for clinical use in Europe in 2009. Despite numerous studies confirming the clinical efficacy of agomelatine in treating depression,⁴⁵ no further melatonergic drugs have been developed.

The development of agomelatine followed a systematic research program specifically designed to obtain a drug with a melatonin-like profile, devoid of serendipity (type IV pattern of serendipity) (Table 2).

3.6. *Glutamatergic modulators*

Ketamine (CI-581), a short-acting derivative of phencyclidine, was synthesized in 1962 by Calvin Lee Stevens.⁴⁸ It was initially used as a dissociative anaesthetic from 1970⁴⁹ and gained attention for its use in the Vietnam War.⁵⁰ Despite its clinical potential, ketamine began being abused recreationally as "Special K" in the mid-1990s, leading to its classification as a Schedule III of the Controlled Substance Act in 1999. Interest in its antidepressant effects emerged in the 1970s,^{50,51} but clinical research was delayed for more than two decades by its association with recreational use.¹ A until the first pilot study in 2000 demonstrated that intravenous ketamine at subanaesthetic doses improved depressive symptoms in major depression patients 72 hours after administration,⁵² leading to a surge in studies confirming its efficacy for treatment-resistant major depression, bipolar disorder and suicidal ideation.⁵³ Ketamine primarily functions as a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor.⁵⁴ Its antidepressant effects are also attributed to other mechanisms such as α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated signalling, increased DA levels in the prefrontal cortex and nucleus accumbens.⁵⁵ Following the discovery that, esketamine, the S enantiomer of ketamine, was higher NMDA receptor affinity,⁵¹ a double-blind clinical trial showed its rapid antidepressant effects in treatment-resistant depression after intravenous infusion.⁵⁶ Subsequently, the possibility of administering low doses of esketamine intranasally was explored⁵⁷ and was approved by the FDA and European Medicines Agency (EMA) in 2019 for use in resistant depression in combination with an SSRI or SNRI, with administration monitored in clinical settings.⁵⁸ Despite its benefits, esketamine has a higher incidence of dissociative effects and potential abuse risk due to its hallucinatory properties.⁵⁹

Tianeptine, discovered by the French Society of Medical Research in the 1960s and patented by researchers Antoine Deslandes and Michael Spedding in 1981,⁶⁰ differs from traditional TCAs, as amineptine, by not affecting 5-HT reuptake.⁶¹ Instead, it has a weak action on μ -opioid receptors and modulates glutamatergic mechanisms.⁶² Although

initially developed for major depressive disorder, its US development was discontinued in 2012.⁶³ Tianeptine was later marketed as a nootropic supplement but faced scrutiny due to high abuse potential and legal concerns.⁶⁴ This led to the coining of the term "gas station heroin". Since 2023, products containing tianeptine have been gradually withdrawn.

Ketamine has garnered significant attention in psychiatric research as a prototype for a new generation of antidepressants following the discovery of its profound and rapid effects on depressive symptoms. However, it stands as a clear example of serendipity resulting from a non-serendipitous discovery (type III pattern) (Table 2). Originally developed as an anaesthetic agent, its antidepressant efficacy was stumbled upon coincidental when improvement in depressive symptoms was observed in individuals using the substance as a drug of abuse.

3.7. Serotonin modulators and stimulators (SMS)

Vortioxetine is a bis-aryl-sulfanyl amine and piperazine derivative, whose rationale and synthesis (Lu AA21004) was detailed in 2002.⁶⁵ It was introduced into the US market in 2013. This compound represents a new class of antidepressants known as SMS or "multi-modal", due to its high binding affinity and complementary mechanisms of action on several 5-HT receptors and 5-HT transporters. Specifically, vortioxetine acts as a 5-HT_{1A} receptor agonist, 5-HT_{1B} receptor partial agonist, 5-HT_{3A} and 5-HT₇ receptor antagonist, and a potent 5-HT reuptake inhibitor.⁶⁶ Additionally, vortioxetine exhibits significant affinity for DA and NA transporters, being 3 to 12 times more selective for 5-HT transporters, respectively.⁶⁷

Vilazodone received approval medical use in the US in 2011. Classified as a SMS or serotonin partial agonist/reuptake inhibitor (SPARI), vilazodone possesses SSRI properties and acts as an activator of the 5-HT_{1A} receptor.⁶⁸

The development of SMS drugs was driven by rational planning based on an understanding of the role of serotonergic neurotransmission in affective disorders, with minimal reliance on serendipity (type IV pattern of serendipity) (Table 2).

4. Discussion

As articulated by Albert Szent-Györgyi, the discoverer of vitamin C, "a discovery consists of seeing what everybody has seen and thinking what nobody has thought" (p. 57).⁶⁹ Therefore, in line with the original conceptualization, we contend that "*serendipity*" pertains to the discovery of something unexpected or not deliberately sought,^{7,12} i.e., a finding that arises without the observer anticipating it.

In pharmacology, purely serendipitous discoveries (our type I pattern of imputability), are relatively rare, contrary to popular belief. Most discoveries exhibit a mixed character (Patterns II and III), blending serendipitous and non-serendipitous elements. Typically, this follows a consistent pattern that starts with an initial serendipitous observation, often encountered in laboratory-based animal research, which subsequently prompts deliberate investigations in a clinical setting (our Pattern II). These circumstances contribute to the existence of the aforementioned discrepancies among authors. Some interpret these findings solely through the lens of chance, positing that the results of clinical trials represent a *continuum* of the initial serendipitous findings and should be regarded as part of a unified discovery rather than separate events. Other authors refer to these patterns as "pseudoserendipity"¹⁰ or "serendipity analogous" discoveries.⁷⁰

However, it is evident that serendipity, to varying degrees, played a fundamental role in the initial decades of modern psychopharmacology, particularly in the discovery of the first two families of antidepressant drugs (TCAs and IMAOs).^{3,4,13} This process yielded revolutionary outcomes in the realm of mental health, influencing various aspects of socio-health reality. These include the progressive phenomenon of "deinstitutionalization" in psychiatry and the involvement of primary care into mental health services, both mitigating the historical stigmatization associated with psychiatric care. Moreover, this "revolution" spurred scientific advancements, including the formulation of initial biological hypotheses concerning the genesis of mental illnesses, particularly affective disorders.^{2,71} At the nosological level, the introduction of these drugs contributed, to some extent, to shaping new diagnostic criteria. Furthermore, the emergence of classic psychotropic drugs enhanced clinical research by facilitating the synthesis of numerous drugs for mental disorder treatment.

The development of new drugs for affective disorders benefited significantly from the tenets of monoaminergic theories of depression, which dominated scientific discourse in specialized journals during the 1960s and 1970s following the discovery of imipramine and iproniazid. These theories posited a functional deficiency in noradrenergic or serotonergic neurotransmission^{2,5} in specific brain regions as a primary cause of these pathologies,⁷² paving the way for new families of antidepressant drugs characterized by modulating monoaminergic functionalism.

Hence, the findings of our study appear to affirm that since the 1980s, the development of new antidepressant agents have followed a different dynamic, marked by a systematic and deliberate pursuit of outcomes, with minimal reliance on serendipity (our Pattern IV). Some authors have underscored the role of serendipity in contemporary scientific research in this field. Donald Klein,⁷³ in his article *The Loss of Serendipity in Psychopharmacology*, partly attributes the relative dearth of innovation in psychopharmacology over the past five decades to the absence of serendipity. He advocates for fostering serendipity through structured research environments.⁷³ In our editorial, we identified several "anti-serendipity" factors that may explain this phenomenon outlined by Klein; a) the scientific shift towards rational drug design grounded in translational research; b) reduced time for researchers to observe and engage with patients; and c) pharmacology's reliance on clinical trials employing double-blind, placebo-controlled designs as the primary method for demonstrating drug efficacy.⁷⁴ Additionally, other authors highlight more specific factors, such as advances in genetic and diagnostic imaging techniques, including nuclear magnetic resonance, combinatorial and computational chemistry, X-ray crystallography, etc.⁷⁵

Over the past four decades, the discovery and identification of new chemical entities (NCE) have predominantly focused on elucidating the molecular targets with which these agents interact. This approach, often termed "targetophilia", by some authors, adopts a reductionist perspective that emphasizes the specific sites of drug action.⁷⁶ This paradigm has prevailed in the development of new antidepressant drugs, leading to a practical decline in serendipitous discoveries within this process, as evidenced by the findings of our study. Nonetheless, certain exceptions have been noted, such as in the cases of moclobemide and ketamine. Serendipity played a pivotal role in the discovery of the

antidepressant properties of both drugs, as previously mentioned, thereby categorizing them within our type II and III patterns of imputability, respectively.

Despite the considerable clinical advantages of new antidepressants, which are largely attributed to their improved tolerance, safety profile, and greater convenience, several challenges persist in antidepressant therapy. Notable among these challenges are the delayed onset of antidepressant response and the estimated percentage of non-responsive patients, which stands at around 30%.⁷⁷ Additionally, inadequate antidepressant response affects 40-50% of patients. This may be influenced by the convergent pharmacodynamic properties of these new antidepressants, which often enhance aminergic function: Examples include NSRI (venlafaxine, duloxetine, milnacipram), NaSSA (mirtazapine), SDRI (bupropion), and SNRI (reboxetine, atomoxetine).⁵ Moreover, some recent antidepressants target non-aminergic receptors, albeit not entirely selectively. For instance, agomelatine, a melatonergic agonist (MT₁ and MT₂) also blocks 5-HT_{2A} receptors, thereby facilitating the release of DA and NA in the prefrontal cortex.⁷⁸ The antidepressant arsenal has further expanded with vortioxetine, characterized as SMS or "multi-modal", given its impact on the functionalism of several monoamines. Its primary mechanism involves a combination of SSRI, 5-HT₃ receptor antagonism and 5-HT_{1A} receptor agonism, thus, affecting monoaminergic pathways as well. Lastly, tianeptine is an antidepressant with a complex mechanism involving glutamatergic functionalism, along with esketamine, which influences opioidergic and DA release in the nucleus accumbens and prefrontal cortex. Therefore, these latter antidepressants also engage monoaminergic mechanisms.⁶²

Depression is a complex pathology characterized by pathophysiological mechanisms that extend beyond solely aminergic pathways. As a result, research into the mechanisms of action of antidepressants has begun to explore alternative directions. These include investigations into neurotrophic factors such as neurotrophins and brain-derived neurotrophic factor (BDNF), corticotrophin releasing hormone (CRH), glucocorticoids, and various other potential targets as the opioid system, interleukins, substance P, somatostatin, neuropeptide Y, melatonin, nitric oxide, among others. Moreover, studies are delving into intraneuronal molecular signal communication pathways. Therefore, the quest for antidepressants with clinical profiles distinct from conventional ones involves a deeper exploration of depression's pathogenesis and the use of pathophysiological

findings as potential therapeutic targets. In this evolving landscape, serendipity may once again emerge as a relevant factor.

Conclusion

The discovery of the majority of new antidepressants adhere to a type IV pattern, characterized by a rational and targeted design process where serendipity played no part. This is the case of SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline, and escitalopram), SDRI (bupropion), NSRIs (venlafaxine, milnacipram, duloxetine, desvenlafaxine), SNRI (reboxetine), NaSSA (mirtazapine), melatonergic agonists (agomelatine), and SMS (vortioxetine, vilazodone, tianeptine). However, there are two exceptions: moclobemide and ketamine. Moclobemide, a RIMA, can be classified under the type II pattern, wherein initial serendipitous findings (such as the chance discovery of MAO-A inhibitory effects in a molecule being studied for its antihyperlipidaemic properties) led to subsequent non-serendipitous discoveries (clinical antidepressant efficacy). Ketamine, a glutamatergic modulator, follows a type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using ketamine).

Since the 1980s, psychopharmacology has been evolving outside the influence of serendipity, but this phenomenon eventually becomes apparent, as has happened in the case of ketamine. However, the results of this work are limited by the data provided by the discoverers themselves in their scientific articles and in their memoirs. In addition, the scientific construct of the serendipity phenomenon itself has varied over time and its role has been interpreted differently by each researcher. Fortunately, the operational criteria of serendipity developed by our group has allowed us to address this issue in a fairly objective and satisfactory way.

MAIN POINTS

- Serendipity is a phenomenon que requires the convergence of accident and sagacity.

- In pharmacology, purely serendipitous discoveries (type I pattern of imputability) are relatively rare. This pattern has not been found in the discovery of any of the new antidepressants.
- The development of new antidepressants, from SSRIs to the present, has been characterized by a pattern IV, based on rational and systematic research programs and where there is no intervention of serendipity.
- Moclobemide can be classified under the type II pattern, wherein initial serendipitous findings (the chance discovery of MAO-A inhibitory effects in a molecule being studied for its antihyperlipidaemic properties) led to subsequent non-serendipitous discoveries (clinical antidepressant efficacy).
- Ketamine follows a type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using).

Availability of Data and Materials: All data analyzed in the current study is included in the manuscript.

Author Contributions: Conception–FL-M; Design–FL-M; Supervision–FL-M, PD'O, AR, DDB, CÁ; Materials–FL-M; Data Collection and/or Processing–FL-M; Analysis and/or Interpretation–FL-M, PD'O, AR, DDB, CÁ; Literature Review–FL-M; Writing–FL-M; Critical Review–FL-M, PD'O, AR, DDB, CÁ. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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DOCUMENTO 4



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Review

A History of the Pharmacological Treatment of Bipolar Disorder

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Abstract: In this paper, the authors review the history of the pharmacological treatment of bipolar disorder, from the first nonspecific sedative agents introduced in the 19th and early 20th century, such as solanaceae alkaloids, bromides and barbiturates, to John Cade's experiments with lithium and the beginning of the so-called "Psychopharmacological Revolution" in the 1950s. We also describe the clinical studies and development processes, enabling the therapeutic introduction of pharmacological agents currently available for the treatment of bipolar disorder in its different phases and manifestations. Those drugs include lithium salts, valproic acid, carbamazepine, new antiepileptic drugs, basically lamotrigine and atypical antipsychotic agents (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, cariprazine and lurasidone). Finally, the socio-sanitary implications derived from the clinical introduction of these drugs are also discussed.

Keywords: bipolar disorder; pharmacological treatment; mood stabilizer drugs; lithium; antiepileptic drugs; antipsychotic drugs

1. Introduction

Bipolar disorder is a mental pathology that has been known since ancient times and has its origin in the concept of "mania," a term that comes from the Greek "*μανία*," meaning "madness" or "frenzy" [1]. The father of medicine, Hippocrates, already qualified mania as a subtype of mental illness. The term can even be found in the early Ancient Greece literature, as in Homer's *Iliad*, referring to the uncontrolled anger of Achilles against Agamemnon [2]. Philippe Pinel [3] established a series of categories of this type of madness (mania with delirious and non-delirious states) and throughout

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ABSTRACT

In this paper, the authors review the history of the pharmacological treatment of bipolar disorder, from the first nonspecific sedative agents introduced in the 19th and early 20th century, such as solanaceae alkaloids, bromides and barbiturates, to John Cade's experiments with lithium and the beginning of the so-called "Psychopharmacological Revolution" in the 1950s. We also describe the clinical studies and development processes, enabling the therapeutic introduction of pharmacological agents currently available for the treatment of bipolar disorder in its different phases and manifestations. Those drugs include lithium salts, valproic acid, carbamazepine, new antiepileptic drugs, basically lamotrigine and atypical antipsychotic agents (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, cariprazine and lurasidone). Finally, the socio-sanitary implications derived from the clinical introduction of these drugs are also discussed.

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1. Introduction

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Until relatively recent dates, bipolar disorder had not received properly deserved scientific and social recognition as it enjoys today [8]. Due to “scientific negligence,” compared to other psychiatric disorders—for example, major depression or schizophrenia—the lack of knowledge about its etiopathogenesis, the erroneous underestimation of its prevalence and the status of therapeutic pseudo-orphanage had not been amended until almost two decades ago [9]. In fact, until the mid-1990s, before valproate’s anti-manic efficacy of was demonstrated, the only drug available for treating those patients was lithium salts.

From a current scientific research perspective, bipolar disorder is an emerging pathology [9]. From a clinical perspective, it presents an important morbidity/mortality [10]. The

well-known epidemiological studies Epidemiological Catchment Area Study (ECA) in 1981 and National Comorbidity Survey (NCS) in 1991 estimated the prevalence of bipolar disorder in about 1% of the population and it is currently estimated that its prevalence throughout the lifespan is between 1% and 2% of the population over 20 years of age [11]. It is a serious mood disorder of a chronic nature, characterized by the constant or irregular appearance of alternative episodes of mania/hypomania with euthymia/depressive episodes [12]. Traditionally, a difference has been made between bipolar disorder type I, which is characterized by the presence of, at least, a manic or mixed episode in combination with depression; and bipolar disorder type II, characterized by one or more depressive episodes, with at least one episode of hypomania lasting longer than four days, with bipolar disorder type II being more frequent than type I. Cyclothymic disorder has a recurrent and chronic course, with greater symptomatic oscillation but of less severity than that observed in bipolar disorder types I and II. Between 15–50% of cyclothymic patients usually progress to either bipolar disorder type I or, mainly, to type II [13]. Nevertheless, nowadays a tendency exists to consider this pathology from a broader context, including all those cases with less obvious and apparent clinical manifestations. This way of approaching the disease, called “bipolar spectrum,” implies prevalence ranging from 2.8% to 6.5% of the population [10,14–16].

Bipolar disorder, largely due to its chronic and recurrent course, poses an important burden for the patient, the family and the society and its treatment is essential to avoid the main complications of the disease. In developed countries, bipolar disorder is ranked among the top 10 causes of disability [17]. According to the World Health Organization (WHO), bipolar disorder is the fourth cause of neuropsychiatric disability in people aging 15–44 years. Additionally, the use of health resources that bipolar patients make is greater than that of patients with depressive or chronic medical conditions [18]. One should also bear in mind that the most serious complication of bipolar disorder is suicide. Between 25–50% of patients with bipolar disorder attempt suicide, with prevalence of 32.4% and 36.3% for bipolar disorder type I and type II, respectively [19]. It is in the depressive phase that most attempts and completed suicides occur. Other important burdens associated with bipolar disorder are increased mortality from medical causes, substance abuse (mainly alcoholism), comorbidity with other psychiatric disorders such as anxiety, behaviour and eating disorders and chronic affective symptoms. To note, bipolar disorder

patients have enormous economic burden of this disorder, estimated in the USA to be about \$31 billion in direct costs and \$120 billion in indirect costs [20].

Until the discovery of lithium's antimanic effect, the pharmacological tools used in clinical practice had limited efficacy, not only in this type of patient but in the entire field of mental pathology [21]. This was in part a result of the inheritance and influence of Benedict Agustin Morel, a degenerationist who considered that the cause of mental disorders was hereditary transmission, implying their incurability [4]. Yet, during the first half of the 20th century, the first drugs used systematically in the treatment of manic patients were introduced, with barbiturates standing out among them. The antimanic efficacy of lithium salts was confirmed during the 1950s and in the late 1960s it was finally demonstrated in Europe that lithium was effective in the prophylaxis of manic-depressive episodes in bipolar disorder [22]. But the Food and Drugs Administration (FDA) of the United States resisted to authorize this drug for its antimanic indication until 1970 [23] and for its indication as maintenance/prophylactic treatment of manic-depressive episodes until 1978. Twenty-eight years later, in 1995, valproic acid, an anticonvulsant agent, was approved by the FDA for its antimanic indication. In parallel to valproic acid, carbamazepine, another antiepileptic drug, was developed for the treatment of patients with bipolar disorder. This drug has been authorized by numerous regulatory agencies in multiple countries and enjoys a good acceptance by psychiatrists worldwide. Finally, since 2000, different atypical antipsychotic drugs (AADs) have been authorized by the FDA for their antimanic (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, etc.) or antidepressant indication (quetiapine, lurasidone). Lamotrigine, a modern antiepileptic agent, has been authorized for the prevention of depressive episodes in bipolar disorder. Table 1 shows the most important historical milestones in the pharmacological treatment of bipolar disorder. Overall, the pharmacological treatment of bipolar disorder is complex and treatment guidelines exist for its different phases—manic episodes, depressive episodes and maintenance (or prophylaxis) periods. In this sense, polypharmacy combining drugs from different therapeutic groups and different mechanisms of action is the norm rather than the exception.

Table 1. Key milestones in the history of the pharmacological treatment of bipolar disorder.

Year	Important events
1817	Isolation of lithium (Arwedson and Berzelius)
1832	Synthesis of chloral hydrate (von Liebig)
1857	Introduction of bromides as hypnotic-sedatives (Locock)
1863	Synthesis of barbiturates (von Baeyer)
1868	Description of the sedative-hypnotic properties of <i>Solanaceae</i> alkaloids (Schroff)
1869	Use of chloral hydrate as a hypnotic (Liebreich)
1870	Use of chloral hydrate in manic patients (Elstun)
1880	Isolation of hyoscine or scopolamine (Ladenburg)
1881	Synthesis of valproic acid (Burton)
1903	Introduction of barbitol in medicine (Fisher and von Mehring)
1912	Marketing of phenobarbital
1915	Introduction of barbiturate sleep cures (Epifanio)
1920	Application of morphine and scopolamine “sleep cures” (Klaesi)
1943	Introduction of promethazine in psychiatry, for the treatment of manic symptoms (Daumézou)
1949	Introduction of lithium in the management of manic and schizophrenic disorders (Cade)
1954	First controlled clinical trial with lithium in manic patients (Schou)
1957	II World Congress of Psychiatry (Zurich): first classification of psychotropic drugs (Delay) International Symposium on Psychotropic Drugs (Milan): first specific scientific meeting on psychotropic drugs
1958	Foundation of the Collegium Internationale Neuropsychopharmacologicum
1960	Confirmation of the prophylactic effect of lithium salts in manic episodes (Schou)
1961	Synthesis of carbamazepine (Schindler) Foundation of the American College of Neuropsychopharmacology
1963	Discovery of the anticonvulsant effect of valproic acid (Carraz)
1966	First data on the antimanic effect of valproic acid (Lambert) First systematic study on the effectiveness of lithium in the USA (Wharton and Fieve)
1970	Demonstration of the prophylactic properties of lithium in manic-depressive psychosis (Schou) Approval of the clinical use of lithium (USA FDA)
1971	Use of carbamazepine as mood regulator (Takezaki and Hanaoka)
1973	Approval of chlorpromazine in the treatment of manic episodes (USA FDA) Publication of the book <i>Lithium: its role in psychiatric research and treatment</i> (Gershon and Yuwiler)
1978	Approval of lithium salts for the prevention of manic/depressive episodes (USA FDA) First study about the antimanic effects of carbamazepine in the West (Ballenger and Post)
1994	First controlled trial with divalproex in mania (Bowden) First publication on the efficacy of lamotrigine in bipolar disorder (Weisler)
1995	Approval of valproic acid as an antimanic drug (USA FDA)
1999	First controlled trial with olanzapine in manic episodes (Tohen)
2000	Approval of olanzapine in bipolar disorder (USA FDA)
2003	Approval of risperidone in bipolar disorder (USA FDA) Approval of the combination olanzapine-fluoxetine in depressive episodes of bipolar disorder (USA FDA) First controlled trials of lamotrigine on relapse prophylaxis in bipolar disorder (Bowden and Calabrese)
2004	Approval of lamotrigine for the prevention of depressive episodes of bipolar disorder (USA FDA) Approval of quetiapine, ziprasidone and aripiprazole in bipolar disorder (USA FDA) Approval of olanzapine for the prevention of new episodes of bipolar disorder (USA FDA)
2005	Approval of aripiprazole for the prevention of new episodes of bipolar disorder (USA FDA)
2007	Approval quetiapine for the prevention of new episodes of bipolar disorder (USA FDA)
2008	Approval of quetiapine in depressive episodes of bipolar disorder (USA FDA)
2009	Approval of asenapine in bipolar disorder (USA FDA) Approval of risperidone and ziprasidone for the prevention of new episodes of bipolar disorder (USA FDA)
2013	Approval of lurasidone in depressive episodes of bipolar disorder (USA FDA)
2015	Approval of cariprazine in bipolar disorder (USA FDA)

2. The Therapeutic Precedents of the Psychopharmacological Era

Until the clinical introduction of lithium salts, sedatives [24] were the main axis of pharmacological treatment of manic symptoms. During the second half of the 19th century, a time referred to by some authors as the “alkaloid period” [25], those agents were the most used sedatives. They were introduced into psychiatric care thanks to the isolation of morphine from opium in 1805 by Friedrich Wilhelm Sertürner [26]. In the book *Traité des Maladies Mentales*, published in 1865, Griesinger noted that anxious and agitated patients improve after receiving opium [27]. Hashish was also used as a sedative and its effects were studied in depth by Moreau de Tours [28]. But the most successful alkaloids in psychiatry were isolated essential chemicals of various components of the *Solanaceae* family (Figure 1), the plants known for their hallucinogenic effects. One of them was hyoscyamus, which was isolated in 1839 by chemists from the company E. Merck (Darmstadt, Germany) to show their sedative and hypnotic properties as described in 1868 by the Viennese pharmacologist Karl Schroff. Hyoscyamine was another alkaloid that became a popular ingredient in many cocktails in the latest years of the 19th century. Finally, in 1880, another hyoscyamine alkaloid—hyoscine—isolated by Albert Ladenburg in Germany. Hyoscine (called scopolamine in North America) was then also a widely used ingredient in psychiatric cocktails (such as the famous Hyoscine CoA, containing hyoscine, morphine and atropine), was often used in controlling highly excited and aggressive manic patients [29,30].

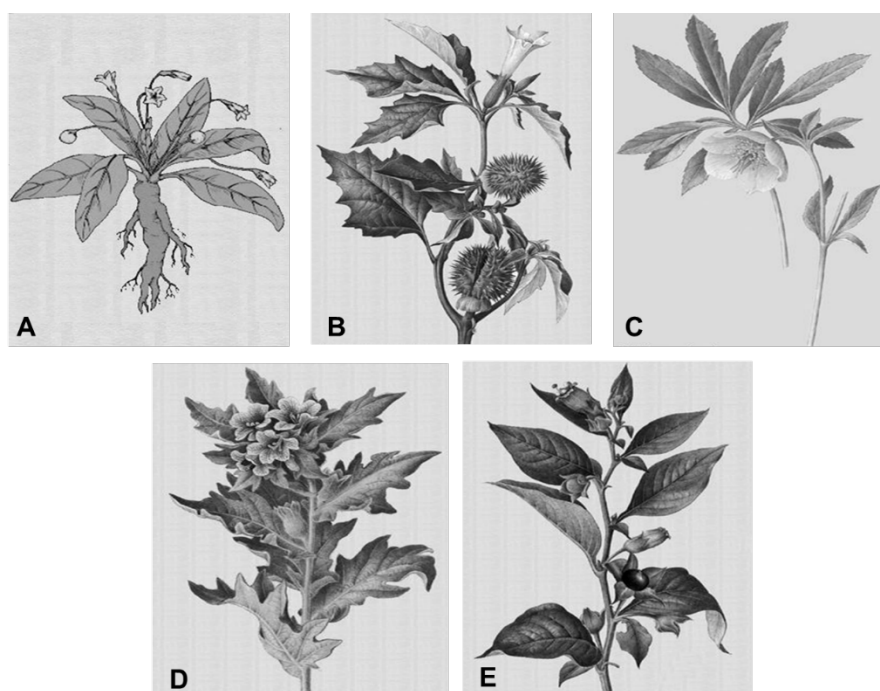


Figure 1. Illustrations of the most relevant plants in the *Solanaceae* family, from which several alkaloids were obtained to be used in psychiatric practice as sedatives prior to modern psychopharmacology: (A) Mandrake (*Mandragora officinalis*); (B) Stramonium (*Datura stramonio*); (C) Eléboro (*Helleborus niger*); (D) Hellebore (*Hyoscyamus niger*); (E) Belladonna (*Atropa belladonna*).

The advent of synthetic chemistry was another of the great milestones in pharmacology in the 19th century, because for the first time in history, synthesized substances instead of existing nature plants with biological activity were produced [31]. Choral hydrate was first produced psychopharmacaceutically [32]. Synthesized in 1832 by a chemist from Giessen, Justus von Liebig, it was not assessed as a hypnotic until 1869, by the pharmacologist Mathias Otto Liebreich. The following year, the American psychiatrist William J. Elstun reported that 5 patients (3 manic and 2 melancholic) from Indiana Hospital for the Insane improve after receiving chloral hydrate [33]. Soon chloral hydrate was replacing both morphine and solanaceous alkaloids because it could be conveniently given orally. Among its great contributions to the history of psychopharmacology, chloral hydrate was the first drug to make home treatment possible, without the need to have a patient admitted to a psychiatric institution [25].

Bromides were another therapeutic contribution in the 19th century [32]. Isolated in 1826 by the pharmacist from Montpellier, Antoine Balard, bromine was used as an iodine substitute as a food additive. It became popular in France, where they could already observe that bromine salt-induced sedation (“*invresse bromurique*”). Although first used

as antiepileptics, bromides in the second half of the 19th century were widely used as sedatives for this indication in 1857 by the London internist and Queen Victoria's obstetrician, Sir Charles Locock (Figure 2). Similarly, they were also used as one of the best remedies for controlling agitation in psychotic, manic and melancholic patients, as well as those affected by different phobias, which were favourably used in European asylums and mental hospitals. The use of bromides had extended until the early years of the 20th century [34].

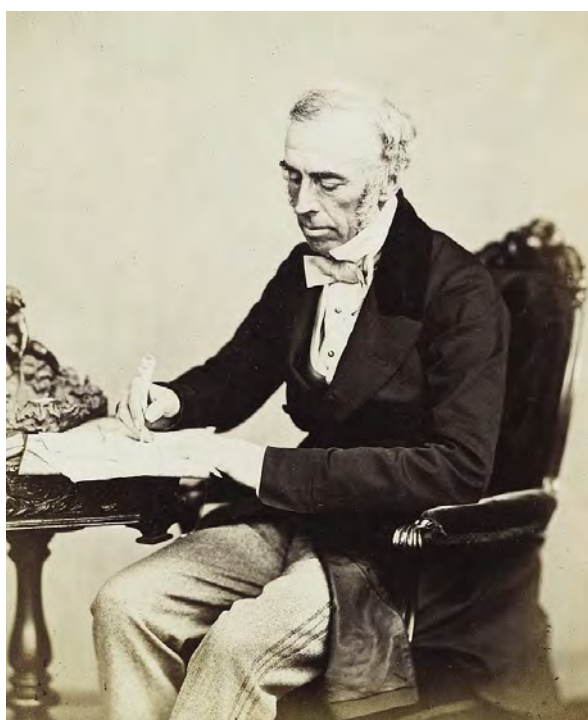


Figure 2. Portrait of Sir Charles Locock (1799–1875) dated 1862. Locock was an obstetrician, First Physician Accoucheur to the Queen Victoria and a member of the St. Albans Medical Club.

By the end of the century, new drugs with sedative activity were added to this therapeutic arsenal. Those drugs—codeine, papaverine, chloroform potion, chloral syrup, paraldehyde, carbamic acid, or hydrocyanic acid—were isolated in pharmacology laboratories. Even a treatment with adrenal cortex extracts was suggested, following the observation that serum cholesterol levels were increased in bipolar patients [35,36]. Subsequently, the introduction of some nonspecific chemical preparations included succinic dinitrile, malonic nitrite, or lactic acid, although delivering unsatisfactory results [37]. Another commonly used drug was sodium diphenylhydantoin (Dilantin[®]), tested by Kalinowsky and Putnam [38] but producing only limited success in cases of manic excitement.

Without a doubt, barbiturates had been the most widely used agents in treating manic patients during the first half of the 20th century and until the mid-1950s [39,40]. Chemically, those uranum compounds have a six-element ring structure, with a central nucleus of malonylurea. They were synthesized in 1863 by Adolf von Baeyer (Figure 3). Barbitol (diethyl-barbituric acid) was the first agent of this family introduced clinically as a hypnotic in Germany. It was marketed in 1903 by the company Bayer & Comp. (Elberfeld, Germany) under the name Veronal[®] (Emil Fischer and Joseph von Mehring), although it had been synthesized long before (1882) by Max Konrad and Max Guthzeit. This drug was presented itself as an anticonvulsant, then a sedative and, eventually a hypnotic. Veronal[®] was found to calm manic patients, restore sleep in melancholic patients and induce sleep in patients with insomnia [39,40]. Due to changes in chemical structure of the barbituric acid molecule, more than 2500 different barbiturates were synthesized but only about 50 of them have ever been on the market. One of the first such drugs and perhaps the most used later, was phenobarbital, marketed in 1912 by the company Bayer under the name of Luminal[®]. This long-acting drug, was widely used as an antimanic, anxiolytic and anticonvulsant; other barbiturates with short and intermediate action (such as secobarbital, amobarbital, pentobarbital, etc.) were initially used as hypnotics [39].



Figure 3. Adolf von Baeyer (1835–1917), discoverer of barbituric acid, in the centre with a hat in his hands, together with his team from the Chemistry Laboratory of the Munich Academy of Sciences, in 1893.

The hypnotic properties of some barbiturates were quickly used in treating psychotic and manic patients, as they induced a deep and prolonged sleep state [41]. The pioneer in the use of these techniques was the Italian psychiatrist Giuseppe Epifanio, assistant at the University Psychiatric Clinic of Turin. Published in 1915 in an Italian journal in the middle of World War I, this article did not get proper attention from the international scientific community [42]. The clinical introduction of those techniques is attributed historically to Jakob Klaesi, a psychiatrist at the University Clinic of Zurich (Figure 4A). Klaesi enjoyed great prestige at the time right after he proposed his sleep cures in 1920 [43]. These techniques consisted of premedication with morphine and scopolamine, as well as the subsequent use of so-called Somnifen[®], administered intravenously or subcutaneously (Figure 4B). That was a mixture of diethyl and dipropenyl-barbituric acid, prepared by the Swiss firm Hoffmann-LaRoche (Basel) in a process lasting at least 6–7 days. Another preparation of these characteristics was the so-called Cloetta or Cloettal mixture [44,45], using barbiturates rectally, amyl hydrate, alcohol, chloral hydrate, digitaline, paraldehyde and ephedrine. The main clinical indications of “sleep cures” were manic excitations and agitated depressions, although they were also tested in schizophrenia with less satisfactory results [41].



Figure 4. Jakob Klaesi (right) (1883–1980) with the Burghölzli Hospital psychiatric staff, including its director, Eugen Bleuler (centre), in a photograph taken around 1910 (A) and a container of Somnifen drops of the first third of the century 20th century, commercialized in Spain by F. Hoffmann-La Roche & Cie, Paris (B).

3. Lithium as an Antimanic Agent

Lithium is coined from the Greek “lithos,” meaning stone. Chemically, lithium is the simplest drug among those used in psychiatric therapy, as it is the lightest metal in nature.

The distribution of this metal in small quantities is wide, being detected in seawater, the water of rivers and springs, the organs of different animals, the remains of many plants and even in meteorites [46].

Lithium and mental disorders enjoy a long story. Although the great Greek, Roman and Arab classical authors did not specifically mention lithium in their medical works, the use of alkaline waters for the treatment of the mental illness known as “mania” dates from the time of Caelius Aurelianus, in the 5th century. In a section dedicated to the treatment of mania, this author wrote, “*utendum quoque naturalis aquis, ut sunt nitrosae*” (“natural waters, such as those of alkaline springs, must be used”). In 1817, this alkaline metal was isolated from a mineral known as petalite by the Swedes Johann August Arfwedson (Figure 5A) and Jöns Jakob Berzelius (Figure 5B) and they originally named it lithium. Since lithium has been incorporated into therapeutics, being used in treating different pathologies, both organic (gout and cancer, for example) and neurological (epilepsy) [47,48].

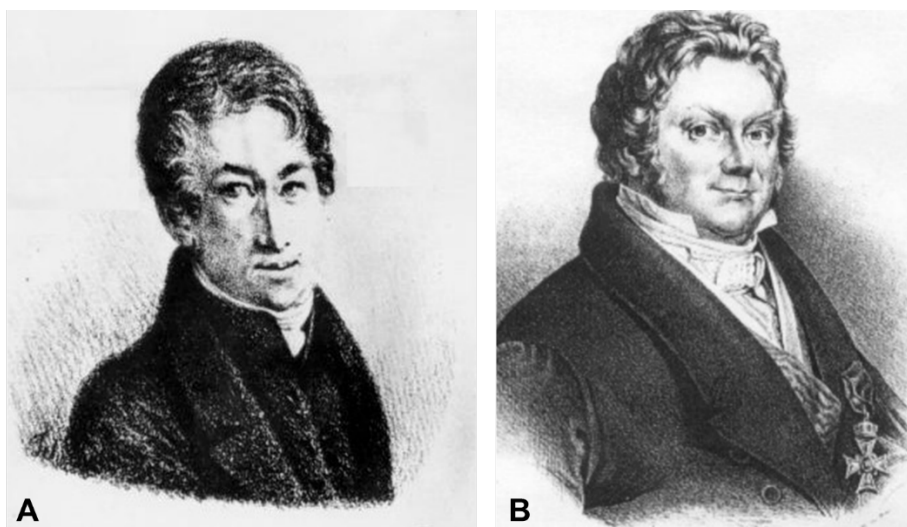


Figure 5. Mid-nineteenth century lithographs of the two Swedish chemists responsible for the discovery of lithium: Johann August Arfwedson (1792–1841) (A) and Jöns Jakob Berzelius (1779–1848) (B), Professor of Chemistry and Pharmacy at the Karolinska Institute. Both were members of the Royal Swedish Academy of Sciences.

In addition, one should consider the great popularity that, around the years of the turn of the century, the “intake of waters” gained, mainly in the USA. Thus, a series of products that supposedly contained lithium water were commercialized, using aggressive advertising stunts. Such is the case of Buffalo Lithia Water (“the best natural remedy for

excess uric acid in blood”), Tedyffrin Water (“cures dyspepsia, rheumatism, Bright’s disease and dissolves bladder stones”), or Manadnock Lithia Spring Water (“the most wonderful spring water known in the world”). Even a beer manufactured with lithium water (Lithia Beer), was marketed in Wisconsin and it was highly appreciated in those decades (Figure 6). All of those stated in their instructions that they were harmless and effective remedies for treating all kinds of nervous disorders [47]. But the decline in consuming lithium waters and, therefore, the popularity of lithium, took place at the end of the first decade of the 20th century, as the public came to know that these products only contained spectroscopically traces of lithium and, above all, due to the first cases of intoxication of cardiac patients, as a consequence of chronic use [49]. In *The Practitioner*, several cases of “cardiac depression and even dilation as a result of an excessive and continued consumption of lithium tablets” were reported in 1907 [50]. In spite of all this, in 1929, Charles Leiper Grigg (Howdy Corporation, St. Louis, MO, USA) invented the 7-UP Lithiated Lemon Soda, with the advertising claim of “an abundance of energy, enthusiasm, clear complexion and shining eyes,” referred to simply as 7-UP since 1936, although lithium was part of its composition until the 1940s, coinciding with the North American cases of toxicity discussed above [51].

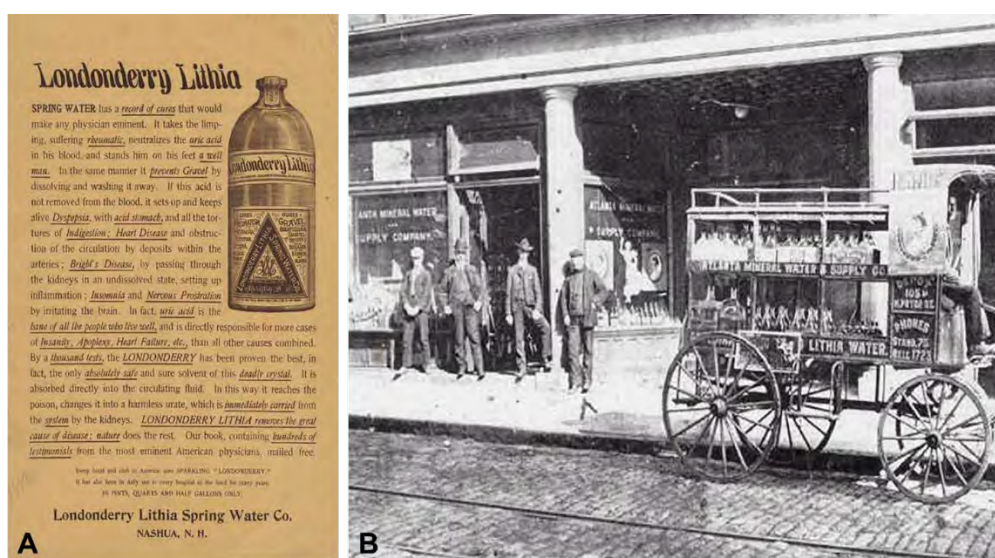


Figure 6. Two examples of the popularity of lithiated waters at the end of the 19th century: a commercial of Londonderry Lithia (Londonderry Lithia Spring Water and Co., Nashua, NH, USA), showing all its supposed therapeutic properties (A) and a photograph of the late 19th century of the head office and distribution system of Atlanta Mineral Water and Supply Co. (Atlanta, GA, USA) (B), advertising its Lithia Water.

In the mid-nineteenth century, the rise of the “uric acid diathesis” theory, proposed by Sir Alfred B. Garrod (Figure 7), played an important role in the introduction of lithium into pharmacological therapy [52]. In 1859, Alexander Ure, a surgeon at the Western Ophthalmic Institution (London), could dissolve a series of bladder stones in a lithium carbonate solution [47]. Almost at the same time, Garrod could verify, in the corpses of patients with gout, that when phalanges with deposits of uric acid were introduced in lithium, potassium or sodium carbonate solutions, the quickest dissolution of such deposits occurred in lithium carbonate. This theory was based on the observation that, in test tubes, lithium salts could dissolve urate deposits from cartilage. Hence, lithium was becoming widely used in treating kidney stones, rheumatism and gout [53]. In fact, in the United Kingdom, lithium was sporadically and unofficially used in treating gout until the 1970s [54].



Figure 7. Sir Alfred Baring Garrod (1819–1907), professor of Materia Medica and Therapeutics at King’s College Hospital and President of the Medical Society of London in 1860. He was knighted as “Sir Alfred Baring Garrod” and in 1890 was appointed “Physician Extraordinary” to Queen Victoria.

Similarly, some of mental disorders were hypothesized to be related to having high levels of urates, being referred to as “gout that affects the head” and “gouty mania”. Lithium treatments were also recommended in those patients [47]. It even came to be occasionally used in treating other psychiatric disorders. For example, the American general surgeon William Hammond (Bellevue Hospital in New York) (Figure 8A) used lithium bromide in treating acute mania, although he could not discern whether the effects observed were due to bromide or lithium [55]; and the Danish internist Carl G. Lange (University of Copenhagen) (Figure 8B) stated in 1886 that the use of a mixture containing lithium was

capable of preventing the so-called “periodic depression” [56]. On the other hand, in the British Isles, as Henderson and Gillespie [57] recalled that lithium waters were believed to have important virtues for treating mental illness. Even much earlier, Sir John Floyer, in his book *History of Cold Bathing* (1722), described that the success achieved in a case of mania with a lithium-based treatment. Still, all these events went completely unnoticed for many years.

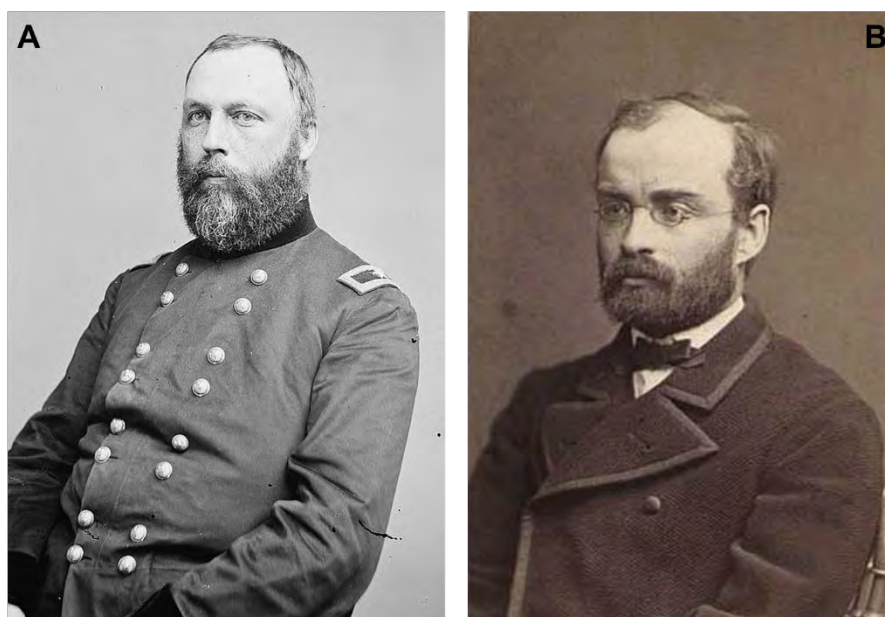


Figure 8. Pioneers in the use of lithium in the treatment of mental disorders: William Alexander Hammond (1828–1900) (A), Surgeon General of the United States Army, professor of anatomy and physiology at the University of Maryland School of Medicine, professor of Nervous and Mental Diseases at Bellevue Hospital and at the New York University; and Carl Georg Lange (1834–1900) (B), Danish physician who made contributions to the fields of neurology, psychiatry and psychology.

The interest in lithium came back in 1927, when the use of lithium bromide in the treatment of epilepsy was postulated. The key contribution was from David M. R. Culbreth, who observed that lithium bromide was the most sedative and hypnotic of all bromides [47]. Yet, it would not be until the end of the 1940s when lithium salts finally became part of the therapy of mental illnesses.

3.1. The Experiments of John Cade

As in many other events in biomedical research, chance played an important role in the introduction of lithium into the psychopharmacological arsenal [58,59]. Thanks to the

careful observation of Australian psychiatrist John F. Cade (Figure 9), who in 1949 was Senior Medical Officer, in the Victorian Department of Mental Hygiene of Australia (Superintendent in the Repatriation Mental Hospital of Bundoora, Victoria, Australia), he noted how patients with thyroid endocrine diseases presented themselves symptoms that were similar to the clinical manifestations of manic-depressive disorder, so that individuals with hyperthyroidism experienced symptoms similar to those seen in individuals in the manic phase, while the traits of thyroid hypofunction were resembling those of the depressive phase [60].

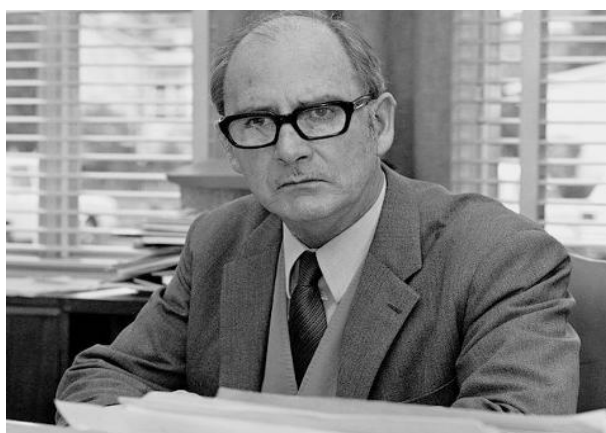


Figure 9. John Frederick Cade (1912–1980), authentic pioneer of modern psychopharmacology with his experiments on lithium.

Given this similarity, the Australian psychiatrist questioned whether at the origin of manic-depressive illness is a hormonal dysfunction or some toxin that was being excreted in the urine and so he designed a series of interesting animal research studies (Figure 10). Initially, he collected urine samples from manic and melancholic patients, as well as from healthy controls and after a process of concentration, he injected them intraperitoneally to guinea pigs, at different doses. Some animals which had been treated with high doses of urine suffered convulsive movements, prolonged unconsciousness and even died, which reaffirmed Cade's idea that the urine of these patients could have contained some sort of toxic substance. At first, he believed that this substance could be urea. But he observed that the urine of manic patients was markedly more toxic than the rest, even when the amount of urea or creatinine was similar between manic and non-manic patients. This study finding made Cade to think that another substance should exist to increase the toxicity of urea, such as uric acid.



Figure 10. The kitchen at Bundoora Repatriation Mental Hospital where John Cade conducted some of his lithium experiments.

To demonstrate this theory, Cade designed a study based on giving laboratory animals of a solution with urea and different concentrations of uric acid (Figure 11). Due to the poor solubility of this substance, Cade turned to lithium urate, a much more soluble salt and surprisingly found that the injection of this salt at 0.5% in the 8% urea solution protected the animals from the previously observed convulsive phenomena, resulting in complete survival. In addition, the animals did not respond to stimuli, not even painful ones and their mobility and appetite for food considerably have been decreased. These observations led Cade to investigate the effects in guinea pigs of the exclusive administration of lithium carbonate. Two hours after having received test drug, animals showed a state of lethargy, which was reversed another two hours later [47,48].

10/10/49.

1. Tan 9 white ♂, white L. rear paw. 10 oz.
2. Grey tan 9 W. ♂, 3 paws pink. R.R. paw black. 15 oz.
3. White ♂, black paws & ears. 13 oz.
4. B.T. ♀, R.R. quarter tan, L. rear quarter black. 7 oz.
5. Grey ♀ tan belly. 13 oz.

G.P. ① = 10 oz. 7.5 cc. 8% urea aa. { 16% urea
redissolved ppt from shake.
at 12.19 PM. 0.75 cc. / oz. body wt.
N.A.D. at 12.49 PM.
N.A.D. at 2.10 PM.

G.P. ③ = 13 oz. 16 1/4 cc. at 12.54 PM. 1.25 cc. / oz. body wt.
N.A.D. at 2.10 PM.

G.P. ④ = 7 oz. 12 1/4 cc. at 2.17 PM. 1.5 cc. / oz. body wt.

G.P. ② = 15 oz. 20 cc. of 8% urea aa. { 16% urea
supernatant lemon coloured
at 2.47 PM. fluid removed from ppt.
1.3 cc. / oz. This contains approx. 5% NaCl.
3.30 PM - nothing noteworthy - for sev. hrs. N.A.D. following P.M.

8.30 - tremulous & ataxic, myoclonic

Figure 11. Laboratory notes by Cade regarding the effects of the injection of different compounds and lithium salts to guinea pigs.

The results of these studies made Cade to think of the possible benefit that certain manic patients could experience after receiving those lithium salts. But before taking this step and following the great clinicians of the previous century and under the Hippocratic principle of *primum non nocere*, he had lithium citrate self-administered to assess its safety. Immediately after testing the absence of toxicity on himself—which is not illustrative, given his high level of tolerance to suffering after his having spent three years as a prisoner-of-war in the Japanese POW camp of Changi, Singapore, during World War II—he administered, on 29 March 1948, 1200 mg/day of lithium citrate, three times a day in divided dose, to a 54-year-old man, Mr. W. B. in manic excitement of five years of evolution. After a five-days treatment, the patient was evidentially improved. He left the hospital four months later, with a daily ambulatory treatment of 300 mg of lithium carbonate, twice a day, because this salt caused less nausea than citrate. The recovery was so clear that the patient could return to the job before his hospital admission. Cade observed the same results in nine other patients, obtaining the best responses in excited individuals. The effects of lithium were also studied in 6 patients with schizophrenia with agitation and in 3 patients with chronic melancholic depression. The results of these studies were published in 1949, in an article in *The Medical Journal of Australia*, entitled “*Lithium salts in the treatment of psychotic excitement*” (Figure 12) [61]. This publication is considered by many authors as the starting point of the so-called “psychiatric pharmacology revolution” [62,63]. The summaries of this work consisted of the following:

- Lithium salts showed great efficacy in the treatment of manic disorder and they did so in a short period of time within several days.
- Lithium was also relatively effective in treating manic manifestations in early dementia. Three of the six most agitated schizophrenic patients became eased and calm and were docile and treatable for the first time in years. All of them returned to their original state when lithium was stopped.
- The effectiveness of lithium in chronic depression was not shown.

- The recommended dosage regimen was 900 mg/day, to be divided in 300 mg 3 times a day until clinical improvement was observed and 300 mg/day during the maintenance period.
- The discontinuation of lithium treatment led to the reappearance of manic symptoms.
- The adverse effects of lithium therapy have two—digestive system (nausea, vomiting, diarrhoea, abdominal pain, etc.) and nervous system (tremors, dizziness, asthenia, depression, etc.)—categories of side effects, which were disappeared quickly in 2 to 4 days) after lithium discontinuation. To resume treatment, the patient needs to start receiving from a lower dose, or carbonate was to substitute for citrate, since carbonate salt is more soluble and more easily absorbed.



Figure 12. Medical Journal of Australia, Volume 3, September 1949, in which the results of the clinical experiments by John Cade about lithium salts and the handling of hectic manic and schizophrenic patients were published [61].

Nevertheless, in spite of the interesting perspectives that Cade's work posed, lithium salts did not become widely used in psychiatry until the mid-1960s, as a result of a series of

events that unfortunately coincided in time. This is the case of the clinical introduction and upsurge of neuroleptic drugs, which set aside the scientific interest in lithium. Also, many fatal poisonings that occurred in the late 1940s in the USA, when those lithium salts were marketed as a substitute for sodium salts in patients with heart disease [48,64,65]. Then, the media contributed to the discrediting of this drug. Additionally, Cade himself stated, “the discovery made by an unknown psychiatrist with no research training in a small chronic hospital with primitive techniques and negligible equipment was not likely to command attention” [66]. Cade abandoned his research with lithium and devoted himself to the study of psychotropic effects of other alkaline metals, such as rubidium and caesium. Cade further recalled that, “...in March 1949, lithium was effectively excommunicated as a therapeutic tool, at least in the United States” [67].

3.2. *From Discredit to Formal Recognition of the Antimanic Efficacy of Lithium*

For its part, Kline [68] lists another series of reasons that prevented the scientific recognition and clinical use of lithium, including the distrust of psychiatrists in such a simple substance, which was meant to treat a disease as complex as bipolar disorder. Also, their lack of understanding of how a single substance could show efficacy against both mania and depression. In addition, he points out the absence of commercial interest that the pharmaceutical industry could have in a natural substance that was cheap to obtain and not patentable. It is also worth noting that some clinical trials, poorly designed from the methodological point of view (in which lithium serum levels had to be monitored for safety reasons) and drew negative results. In any case, the loss of interest in lithium was such that even in the prestigious work Goodman and Gilman’s *The Pharmacological Basis of Therapeutics*, in its 1960 edition, stating “The lithium ion has no therapeutic applications. The only pharmacological interest in lithium lies in the fact that it is a toxic ion” [69].

Cade’s communication attracted the attention of other Australian researchers who delved into the contributions of this author [70,71]. The Danish psychiatrist, Mogens Schou (Figure 13), stood above all of them. In his family, some members had manic-depressive disorder. He and his team from Aarhus, Denmark—mainly his colleague Poul Christian Bastrup (Figure 13)—started the first randomized clinical trials using this drug in the history of psychiatry [72]. This phenomenon was defined by Cade [66] as the

“pharmacological rehabilitation of lithium.” The first of those clinical trials was a crossover study, placebo-controlled, alternating two weeks of treatment with lithium and two weeks of placebo, which verified Cade’s observations. Published in 1954, the study results confirmed that of the 30 patients with typical mania that had been included, 12 (40%) have shown clinical response to lithium and a worsening of symptoms with placebo. Additionally, another 15 patients have also shown improvement, although it was not possible to differentiate whether such improvement is from a natural remission [73].

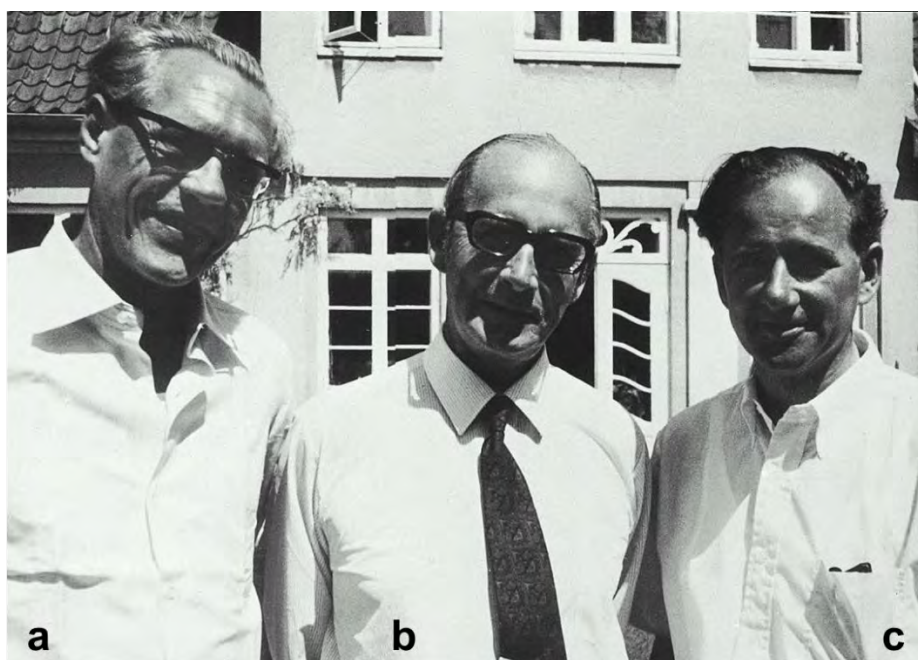


Figure 13. Three great pioneers of the clinical introduction of lithium: Poul Christia Baastrup (a), John Cade (b) and Mogens Schou (c).

Much of the success of the American “pharmacological rehabilitation of lithium” is directly credited to Samuel Gershon (University of Melbourne, Melbourne, Australia), who worked with John Cade before his emigrating to the USA. Gershon convinced many American psychiatrists of the therapeutic efficacy of lithium and published the first article on lithium and mania in the USA [74]. Later, in collaboration with Baron Shopsin, he published another one that, with time, would become the “bible” of pharmacological treatment with lithium salts, “Lithium: its role in psychiatric research and treatment”, in 1973 [75].

Steadily, the clinical efficacy of this ion was confirmed. Studies carried out by the group of Schou [76] and Ronald Maggs (Hellingly Hospital at Hailsham, Sussex, UK) [77],

under a placebo-controlled method, have demonstrated the superior efficacy of lithium in manic patients. The first American systematic study on the effectiveness of lithium was published in 1966 by Ralph Wharton and Ronald Fieve of New York State Psychiatric Institute. The investigators evaluated 19 patients who had been previously unsuccessfully treated with phenothiazines or electroconvulsive therapy [78]. Two years later, Gordon F. S. Johnson (University of Sydney, Sydney, Australia) and Gershon published the first study of a prospective, controlled double-blinded clinical trial. In their study, the investigators compared lithium and chlorpromazine, a standard treatment for mania, in a total sample of 41 patients. Those authors have obtained a complete or almost complete remission after eight days in 78% of the manic patients treated with 1.5–2 g/day of lithium, compared to only 36% of those who received chlorpromazine [79]. Subsequent studies would also confirm the superiority of lithium against chlorpromazine [80–82].

Finally, several highly relevant clinical trials were launched in the late 1960s with public funds from USA Veterans Administration and the National Institutes of Mental Health that dramatically changed the attitude of American physicians towards lithium [83]. In parallel, in the second half of the 1960s, there was a real conflict in the USA between the health authorities and some psychiatrists regarding the therapeutic use of lithium salts, a battle won by the latter. The great champion of this struggle, according to Ayd [84], was Paul H. Blachly, a Professor of Psychiatry at the University of Oregon, who requested that the FDA change its consideration of lithium carbonate, so that it could be given a clinical use. After many bureaucratic obstacles, he received a negative response, despite several appeals to the USA Congress and Senate. Blachly's final move was to write an aggressive article in the journal *Psychiatric Opinion*, entitled "FDA vs. physician: does the physician have a moral obligation to civil disobedience?" in which he concluded that physicians should have a moral obligation to rebel against health authorities that, as in the case of lithium, exceedingly restricted their prescription rights [85]. Popular pressure and the evidence from the afore-mentioned mentioned clinical trials, finally encouraged the FDA approval of this drug in 1970 (Table 2), 21 years after the publication of Cade's classic article [61].

Table 2. Drugs approved by the Food and Drug Administration of the United States (USA FDA) for treatment of patients with bipolar disorder.

Drug	Mania	Maintenance/Prevention	Bipolar Depression
Lithium	1970	1978	
Valproate	1995		
Carbamazepine	2004 ^a		
Lamotrigine		2003	
Chlorpromazine	1973		
Olanzapine	2000, 2003 ^b	2004	2003 ^c
Risperidone	2003, 2003 ^b	2009 ^{d,e}	
Quetiapine	2003, 2004 ^{a,b} , 2008 ^f	2007 ^g	2008 ^f
Ziprasidone	2004, 2004 ^b	2009 ^{e,g}	
Aripiprazole	2004 ^h , 2004 ^b	2005 ^e , 2017 ^d	
Asenapine	2009		
Cariprazine	2015		
Lurasidone			2013, 2018 ⁱ

^a Slow-release formulation; ^b Adding lithium or valproate increases antimanic efficacy; ^c Requiring combination with fluoxetine; ^d Long-active injectable form; ^e Efficacy mostly for preventing future manic episodes; ^f Sustained-release galenic form; ^g Requiring the addition of lithium or valproate; ^h Having data up to three months; ⁱ In paediatric patients 10 to 17 years old.

3.3. Lithium Salts in the Prevention of Manic Episodes' Recurrence

During the second half of the 1960s, prophylactic effects of lithium in preventing recurrence of manic episodes were also studied. Thus, several authors [22,86,87] found that lithium salts can reduce the number of manic episodes and their duration, as well as increase the duration of the period between episodes. They also found that the episodes have been less severe and that, in cases of relapse, hospitalization times have been shorter. All those facts were confirmed by Schou [88] in an uncontrolled study including 88 patients. The average time until relapse among patients who received a prolonged treatment has been 60 months, whereas before the treatment, the same patients relapsed at 8 months on average. On the other hand, the average annual time of relapse has been 13 weeks before lithium therapy was established, decreasing to 1.5 weeks after treatment. In addition, of the 25 patients who abandoned the treatment, 22 of them relapse in periods ranging from a few days to a year.

Despite many scientific papers supporting lithium prophylactic effect in manic-depressive disorder, the indication for lithium's antimanic effect, was highly disputed during the second half of the 1960s. Articles entitled "Prophylactic lithium, another therapeutic myth? an examination of the evidence to date" [89] and "A prophylactic myth" [90] illustrate this scenario. The first of them was published in the prestigious journal *The Lancet*, generating great controversy around this issue. This disagreement has been regarded to by some authors as the "Anglo-Danish polemic." Schou himself would definitively reaffirm his postulates in an article published in 1970 on a study carried out under a rigorous methodology. It was a randomized, placebo-controlled study with a sample of 84 manic-depressive disorder patients, either bipolar ($n = 50$) or depressive monopolar ($n = 34$). Patients were followed for five months, with no relapse in patients in the lithium group and 54% in the placebo group [91]. The relevance of these studies lies on both that they have demonstrated the effectiveness of lithium against manic-depressive episodes and that the study has a genuine innovative methodological design in psychiatric clinical trials, as pointed out by Noguera and Sáiz in 1996 [65].

The efficacy of lithium salts in the prophylaxis of bipolar disorders has definitively been proved in an interesting work by Prien et al. in 1984 [92]. These authors carried out a two-year comparative study in a sample of 117 patients with bipolar disorder, divided into three treatment groups—lithium, imipramine and lithium plus imipramine. The results showed that lithium is more effective in preventing the recurrence of manic episodes (26% in the lithium group, 28% in the lithium plus imipramine group and 53% in the imipramine group), while in the prevention efficacy for depressive episodes all groups are similar (28% of recurrences in the group treated with imipramine, 29% in the lithium group and 22% in the lithium plus imipramine group).

Schou in 1997 provided interesting data on a remarkable variation in the results of studies on the compliance of prophylactic lithium treatments through the last three decades [93]. In this sense, the frequency of therapeutic noncompliance, the main cause of recurrence in prophylactic lithium treatments, was notably higher in the late 1990s than in the 1970s. In addition, the data extracted from clinical trials have also showed a lower effectiveness of this therapy. Schou has attributed these facts to differences in the current profile of manic-depressive patients, whose pathology would be more severe, more atypical (being

higher in incidence of schizomanic symptoms) and with greater comorbidity (substance abuse or alcoholism, for example) [93].

3.4. Other Clinical Uses of Lithium in Psychiatric Therapeutics

Another clinical usage of lithium salts is associated with its effectiveness in cases of treatment-resistant depression, in combination with antidepressant drugs. This was already revealed in the 1981 classic work of De Montigny et al. [94], who observed that eight patients suffering from unipolar depression and who did not respond to a three-week treatment with tricyclic antidepressants (amitriptyline, imipramine, or doxepin), showed positive therapeutic effect 48 h after adding the administration of lithium. Subsequent studies, larger and better controlled, confirmed those results [94]. In a sample of 75 depressed patients treated for 29 months with antidepressant drugs, 48% of them have been observed to have an additional improvement after lithium salts were added to the existing treatment [95].

Lithium's potentiating effect of has also been studied more recently in conjunction with antidepressants from the selective serotonin reuptake inhibitors (SSRIs) family such as fluoxetine, yielding even better results than those obtained with tricyclic antidepressants. Ontiveros et al. [96] found that, in a group of 60 patients diagnosed with treatment-resistant depression, 60% have improved after a week when lithium carbonate was added to a regimen with fluoxetine, compared to 57% in patients treated with desipramine when lithium was added. The latter group of patients also shows slow responders.

Although the action mechanism underlying this synergistic effect has not been elucidated, a reinforcement of serotonergic neurotransmission has been hypothesized. In this sense, lithium causes a presynaptic increase in serotonergic function, due to an increase in the reuptake of tryptophan for its conversion into serotonin [46].

Finally, in the late 1970s, many articles assessing the effectiveness of lithium in various mental disorders were published. These covered schizophrenia, substance abuse (including alcoholism), aggressive or impulsive abnormal behaviours, premenstrual syndrome, and so forth. Results, unfortunately, were rather poor.

3.5. Conclusions from the “Cinderella of Psychopharmacology”

Despite all its drawbacks and adverse effects from hand tremors to renal toxicity, today, almost seventy years after Cade’s work, lithium salts are the first-choice treatment for the manic phases of bipolar affective disorders, as well as indispensable prophylactic tools in the prevention of cyclic episodes of bipolar disorder. In addition, thanks to the clinical introduction of lithium, the process that has come to be called “The Revolution of Psychopharmacology” was initiated. This means that, for the first time in history, the rational pharmacotherapeutic treatment of mental disorders took place, a process that would be completed with the clinical introduction of chlorpromazine, imipramine and benzodiazepines in the following years [24,97–100]. But despite these great contributions, lithium is a clear example how an effective drug was unable, in an unwelcoming environment, to find its therapeutic gap. Nathan Kline, one of the great pioneers in psychopharmacology, said in 1968, just when its properties began to be recognized by the scientific community: “Lithium the 20-year old Cinderella of psychopharmacology is at last receiving her sovereign due. Just plain old lithium—discredited by earlier abuse, briefly but dramatically misused as a substitute for precisely the type of patient in cardiac or renal failure for whom it should not be ordinarily used—the modest proclamation of its use for mania and other excitement states in a journal of limited circulation in a remote country that passed almost unnoted” [101].

4. Valproate as Mood Stabilizer

4.1. The Fortuitous Discovery of Valproate’s Anticonvulsant Activity

Beverly S. Burton in the USA was the first person who synthesized valproic acid in 1881 [102,103]. Valproic acid is 2-propylvaleric acid or *N*-dipropylacetic acid. It is a simple branched chain octacarbon aliphatic molecule [103,104]. It was not thought to be clinically useful because of its poor solubility in water but good solubility in fat [104]. It was only used as an organic solvent at that time.

During World War II, German scientists tried to find substitutes for butter [105] and rediscovered the synthesis of valproate. They did not know of Burton’s synthesis of valproate. After WWII, valproic acid became a popular organic solvent in various

industries in Western countries. It was commonly used as a diluent to solubilize other drugs [106].

In 1963, George Carraz and his colleagues working at the Laboratoire Berthier in Grenoble, France, studied the anticonvulsant activity [106] of various khellin compounds [103]. They used valproic acid as a diluent to dissolve the khellins. The results of their study showed that a correlation between anticonvulsant activity and different doses of the tested compound cannot be established but that the diluent has the anticonvulsant activity instead of the khellin derivatives using the pentylenetetrazol convulsion model [104,106]. The investigators realized that all of the solutions contain valproic acid [106–109]. Therefore, it has to be the effective anticonvulsant, describing an excellent story of pure serendipity [110].

4.2. Clinical Drug Trials for Valproate's Antiepileptic and Mood-Improving Properties

After Carraz and his team members knew that valproic acid had an antiepileptic effect, he synthesized valpromide (Depamide®), a derivative of valproic acid [106]. The investigators believed why the concentration of amine compounds such as imipramine or desipramine are higher in the brain because those drugs have an $-N-(CH_3)_2$ or $-NH-CH_3$ group, having an obvious lipid solubility. Those drugs can cross the blood-brain barrier easily, resulting in having higher concentration in the brain [106]. In Carraz' laboratory, the investigators showed that in animals, epileptic convulsions triggered by strychnine can be prevented by valpromide, not by valproate (Depakine®), another sodium-based derivative of valproic acid [106].

Carraz collaborated with Sergio Borselli, a psychiatric trainee under Pierre Lambert (Figure 14) at the Psychiatry Hospital of Brittany (Hôpital Psychiatrique de Bassens) in Rhône-Alpes, France [111]. They conducted a series of clinical drug trials in epileptic patients [111–113]. As often seen in large asylums in Europe at that time, 10% to 20% of patients were suffering from epilepsy [106]. Borselli and Lambert found that valpromide works as a sedative, particularly when used with other existing anticonvulsants such as phenobarbitone [106]. They also observed that valpromide and valproate have anticonvulsant [114] and psychotropic effects even when administered alone. Lambert described “patients felt more themselves, the mental stickiness, viscosity that had

sometimes been there on older agents, was less. We saw the disappearance of tendencies to depression, sometimes even a mild euphoria” [115]. The first report of mood-stabilizing effects of valproate in patients with bipolar disorders appeared in 1966 in the French literature [116]. Besides the French study on the psychotropic benefit of valpromide, Hinderk M. Emrich and associates at the Max Planck Institut für Psychiatrie in Munich, Germany also independently discovered that valpromide has antimanic efficacy [117].



Figure 14. Pierre A. Lambert, French psychiatrist, a pioneer in the field of psychopharmacology. He was a member and president of the prestigious Comité Lyonnais de Recherches Thérapeutiques en Psychiatrie. His role in the conceptualization of mood stabilizers gained great importance in the early stages of the psychopharmacological era.

4.3. Controlled Clinical Trials Leading to Valproate’s FDA Approval for an Antimanic Indication

Valproate was first introduced as an antiepileptic drug in France in 1967. It has been used in the Netherlands and Germany since 1968, as well as in the United Kingdom since 1973. It became available in the USA in 1983 [104]. There were four oral preparations—valproic acid (Convulex[®]); sodium valproate (Depakene[®]); divalproex sodium (Depokote[®]), an enteric coated compound containing equal proportions of valproic acid and sodium valproate; as well as diavalproex sodium sprinkle capsule (Depokote Sprinkle[®]). The manufacturer, Laboratoire Berthier, had long stopped producing and

promoting valpromide as sodium valproate. But it has been sold well in France and abroad [106].

Psychiatrists at the Abbot Pharmaceutical Company, Illinois, USA, owned the patent for divalproex sodium. They were interested in pursuing its antimanic effect. They supported a landmark multicentred, randomized, double-blind, placebo-controlled, parallel group drug trial [118]. This study included 179 acutely manic hospitalized patients meeting for the diagnosis of manic disorder of the Research Diagnostic Criteria [119]. Being considered as one of the most stringent clinical drug trials with the largest number of patients with bipolar disorders in history, the main results of the study showed that divalproex and lithium are more effective than placebo to reduce the symptoms of acute mania and that divalproex is as good as lithium as an antimanic treatment [118]. In 1995, the FDA approved divalproex sodium for its antimanic effects (Table 2) based on the results of this study and other studies [120,121]. The 1994 study by Bowden et al. [118] also proved that lithium is better than placebo in a high-quality placebo-controlled design for the first time with a respectable sample size in this industry-sponsored clinical drug trial, although lithium had already been approved by the FDA in 1970 (see Table 2).

4.4. Increased Popularity of Prescribing Divalproex Sodium by American Psychiatrists in the 1990's

USA FDA approval of divalproex sodium for an antimanic indication was received enthusiastically by psychiatrists in the USA. At that time, divalproex sodium was a major psychiatric product in the USA due to its extensive commercial promotion. Divalproex sodium was often featured besides the AADs (such as risperidone or olanzapine) in symposia sponsored by industry and in supplementary issues of professional journals. From 1994 to 1997, the number of divalproex sodium prescriptions was soared in the USA, whereas that of lithium was declined [122]. For example, 15.5% of adult inpatients received divalproex sodium in 1994 and 34.1% of patients among all public mental health facilities in the State of New York in 1996. Furthermore, 50% of patients with the diagnoses of bipolar disorder and schizoaffective disorder received divalproex in 1996 [122]. By contrast, the number of prescription of lithium was decreased year by year [123]. Both valproic acid and lithium have gained popularity in Latin-American countries. Heenren et al. [124] sent out a 14-item questionnaire to psychiatrists from eight

Latin-American countries—Argentina, Colombia, Costa Rica, Ecuador, Mexico, Peru and Venezuela—to study their treatment preferences for patients with bipolar disorder. The authors reported that lithium and valproic acid were by far the top choices among Latin-American psychiatrists when asked about the first mood stabilizer of choice for a patient with bipolar disorder and that with a manic episode, 50% and 41.6%, respectively [124].

The number of prescriptions of divalproex sodium in the USA reached a plateau in late 1990's and then declined due to the advent of AADs. Like lithium, valproate has been approved as an add-on to increase anti-manic efficacy with olanzapine and risperidone in 2003, quetiapine in 2004, as well as aripiprazole in 2008 (Table 2).

The popularity of valproate prescription was further decreased in the 2000's because the antimanic and maintenance efficacy of an AAD such as olanzapine are better than those of valproate [125]. At the same time, valproate has also been found to have problematic side effects such as gastrointestinal effects, tremor, sedation, pancreatitis, liver toxicity, weight gain and polycystic ovarian syndrome. Although some treatment guidelines for bipolar disorder suggest that valproate should be avoided during pregnancy due to its teratogenic risk (British Association for Psychopharmacology Guidelines), others, such as the World Federation of Societies of Biological Psychiatry Guidelines recommends close monitoring and risk evaluation in every case. However, in relation to teratogenicity, especially in unplanned pregnancy and with other adverse effects of valproate, such as the risk polycystic ovary syndrome, the benefits should be highlighted often outweigh the risks as patients may over-estimate the risk. Apart from more choice from AADs, valproate prescription has also been hurt by the findings that valproate has proven not to be as good as lithium in anti-suicidal efficacy [126] and maintenance therapy in preventing relapse [127]. Thus, the number of prescription was declined in the decades of 2000s and 2010s compared to 1990s in any country in the world where AADs were available.

5. The History of Carbamazepine as an Agent for Bipolar Disorders

5.1. Japanese Psychiatrists Discovered Carbamazepine's Antimanic Properties

Carbamazepine, a tricyclic anticonvulsant compound, was developed in the late 1950s in the laboratories of J. R. Geigy, in Basel, Switzerland [128]. In 1961, Walter Schindler described its synthesis. In 1963, W. Theobald and H. A. Kunz reported its antiepileptic properties. Its efficacy for patients with epilepsy and paroxysmal pain syndromes was demonstrated in Europe in the early 1960's [128].

In the early 1970's, lithium was not available in Japan [129]. This led to the use of other agents to treat manic-depressive disorders in Japan [129]. Japanese hospitals were also in the process of institutionalizing with large increasing hospital population following chlorpromazine's discovery [129,130]. This trend was opposite to what happened elsewhere in the world [130]. In addition, psychiatry was neuropsychiatrically oriented and psychiatrists instead of neurologists treated most patients in Japan [129,130]. As a result, carbamazepine was widely used in Japanese hospitals following its release as an anticonvulsant during the 1960's [129].

The sedative properties of carbamazepine (Figure 15) led to its use for manic patients instead of other sedatives such as the barbiturates. In the valpromide story for treating manic patients [114], carbamazepine was applied conditions by Japanese psychiatrists exclusively to patients with epileptic or manic [106]. Takezaki and Hanaoka [129] in Tottori, Japan reported their first clinical series of drug trials for manic-depressive patients with carbamazepine. They reported their results in a Japanese journal in 1971 [129]. After the report, many Japanese researchers, especially from the Teruo Okuma group, continued to demonstrate carbamazepine's advantage in treating patients with manic-depressive illness [131–134].



Figure 15. Carbamazepine (Tegretol®) advertisements in the Japanese medical press during the 1970s, which emphasized its anticonvulsant and sedative effects. Ads published in the journal *Psychiatria et Neurologia Japonica* in (A) 1970 and (B) 1978.

5.2. Information of Carbamazepine's Research Results Spread to the West from Japan

In a personal reflection, Okuma in 2000 stated that Western psychiatrists were not impressed when the Japanese reported about carbamazepine's psychotropic effectiveness was published in English [135]. It stated that carbamazepine has similar efficacy compared to chlorpromazine, which was discovered in 1952 [136,137]. The major criticism of the 1979 article [135] was that there was no real evidence of efficacy of carbamazepine at all. The chlorpromazine dose (250 mg/day) in their study was considered inadequate [134]. The reason this research report was not accepted was that a 250 mg dose of chlorpromazine was thought to be indistinguishable from placebo at a time when Western psychiatrists were using antipsychotic mega-doses [106,134]. The research protocol was similar to the one used to investigate lithium's efficacy but those outcomes were not contested [106]. The results of the antimanic efficacy of carbamazepine and lithium are comparable [138,139]. Even carbamazepine did not come into wide use in the West until 1878 when its antimanic effects were described by the American psychiatrists James Ballenger and Robert Post at the USA National Institute of

Mental Health [140]. By the time it became more widely used, it was clear that carbamazepine had imported psychotropic properties. Carbamazepine was used in Japan for a wide range of mental conditions (Figure 15). It was useful in stabilizing aggressive outbursts in young men [103]. Later, the use of carbamazepine for the management of episodic dyscontrol syndrome [103,141] was described in the Western literature [106].

5.3. Current Status of Carbamazepine for the Treatment of Bipolar Disorders in the USA

Carbamazepine has been observed to induce blood dyscrasias delayed its use in North America [106], even though this serious adverse side effect was rare. USA FDA approved carbamazepine as an antiepileptic agent for adults in 1974 and for children older than 6 years of age in 1978. The FDA allowed its use for all without any age limitations in 1987. In Latin-America, there is a high degree of polypharmacy in the treatment of bipolar disorder, with anticonvulsants being the most commonly prescribed medication. Among anticonvulsants, valproic acid was the most popular, followed by clonazepam and then carbamazepine [142]. As shown in Table 2, slow-release carbamazepine received FDA's approval for treating mania in 2004 but its use has never been expanded to other indications for other clinical phases of bipolar disorder.

Oxcarbazepine has a chemical structure with a keto group instead of a double-bond between two carbons in the central ring of carbamazepine. Those structures have also been shown to have antimanic efficacy in Europe [143]. Oxcarbazepine has a favourable side effect profile producing less blood dyscrasias and less drug-drug interactions. This drug was introduced as an antiepileptic to the USA from Europe under the trade name of Trileptal® in 2000. To date, the pharmaceutical industry is not interested in developing carbamazepine or oxcarbazepine for treating other phases of bipolar disorder.

6. New Antiepileptics in Bipolar Disorders

Despite the progress accomplished, treating bipolar disorder with lithium, valproate and carbamazepine involves four major loopholes:

- Many patients are resistant to conventional treatment.

- Good number of patients present themselves with tolerability problems, due to the frequent adverse effects of those drugs.
- The depressive phase still constitutes a serious problem, since lithium, carbamazepine and valproate are more effective in relieving symptoms in the manic than the depressive phase.
- Rapid cycling and mixed mania (dysphoric) respond poorly to treatment, etc. [144–146].

Although carbamazepine was already used in Europe as a substitute for lithium or in combination in resistant cases, the commercial success of valproate was the ultimate reason that stimulated the evaluation of the new anticonvulsant agents in treating bipolar disorders, particularly when it has been demonstrated in the field of epilepsy that they entailed better profile of side effects, interactions, toxicity and teratogenicity [147]. With those premises and significant financial support from the pharmaceutical industry, those new antiepileptics are aimed to displace lithium and second-generation anticonvulsants in treating bipolar disorder, a pathology at the entrance door to the emerging juicy market of psychiatric disorders.

In the individual analysis of the use of these new antiepileptic drugs in bipolar disorder, lamotrigine has been the most contrasted agent, both from the clinical and safety perspectives [148,149]. Lamotrigine has been licensed for the indication in preventing relapse of having future depressive episodes in patients with bipolar disorder.

6.1. Lamotrigine in the Prevention of Depressive Episodes in Bipolar Disorder

Lamotrigine was the third of the so-called new generation of antiepileptics to be marketed, after vigabatrin and felbamate. But those last two drugs were not studied as mood stabilizers because after their commercialization as antiepileptic drugs, significant idiosyncratic side effects were discovered, such as visual field loss or aplastic anaemia, limiting their use to special cases of epilepsy (Lennox-Gastaut syndrome, for example). In the case of lamotrigine, its side effects profile is more favourable in general than that of classic antiepileptic drugs, despite the feared of infrequent Stevens-Johnson syndrome.

Lamotrigine is a phenyltriazine that was synthesized in the early 1980s at Wellcome Research Laboratories (Beckenham, Kent, England) as part of a program to develop new antiepileptic agents that could be better tolerated than those available at that time [150]. This program was based on the mid-1960s hypothesis that folates had proconvulsant properties, so that antiepileptics were thought to exert folic acid antagonistic effects [151]. Taking pyrimethamine as a reference, a substance developed in 1950 as antimalarial (for the treatment and prevention of malaria), a series of structurally analogous phenyltriazines were synthesized to improve its anticonvulsant activity. One of these compounds, BW288U, presented a good anticonvulsant activity but a low antifolate activity, which they tried to optimize. As a result, lamotrigine was obtained, a compound with great anticonvulsant activity but weak dihydrofolate reductase inhibitory power [152]. Phase I clinical trials started soon, showing excellent pharmacological properties. Lamotrigine was finally approved in 1990 in Ireland for use in epilepsy. In 1994, USA FDA also approved its use in a combined treatment for this neurological disorder. Similarly, in those initial studies, Smith et al. [153] observed that this agent improves mood and communication skills in treated epileptic patients.

The first author who produced scientific data on the efficacy of lamotrigine in bipolar disorder was Richard H. Weisler (University of North Carolina Chapel Hill School of Medicine at Chapel Hill, North Carolina, USA). Having attended several international conferences, Weisler knew this molecule before it was approved in the USA and anticipated its possible use in psychiatry. After importing the drug from Europe and requesting authorization from the FDA for compassionate use in 1993, Weisler used lamotrigine to treat two long-term bipolar patients—a 43-year-old white male patient with bipolar II disorder and rapid cycling, as well as a 77-year-old female patient with bipolar I mood disorder with predominance of major depressive episodes and several suicide attempts. At that time, those two patients were refractory to all available pharmacological treatments—lithium, carbamazepine, clonazepam, valproate, 11 different antidepressants (including some of those only being available in Europe then), buspirone, levothyroxine and verapamil. The treatment regimen included, in addition to lamotrigine, other pharmacological agents such as lithium carbonate, bupropion and levothyroxine, in one case and only levothyroxine, in the other case. Both patients showed an evidence of clinical improvement after several weeks, a rapid normalization of social and family

relationships and one of them even resumed working activities. Weisler's group presented the results obtained with those two patients at the American Psychiatric Association's annual meeting held in 1994 in Philadelphia [154] and defended their use based on its action mechanisms (potent anti-kindling effect, sodium channel blockade and anti-glutamatergic activity). In the following two years, several more articles were published about diverse clinical cases, such as refractory bipolar patients, patients with overt depressive episodes, and/or rapid cycling [150].

In 1994, after the presentation of those clinical cases, the company marketing lamotrigine, Burroughs Wellcome, brought together in its research facilities in Beckenham (England) a series of international experts in bipolar disorder to address the possibility of developing of a research program on lamotrigine to treat this psychiatric disorder. Initially, they agreed to start an open, multi-centre clinical trial (five international centres) with a sample of 75 patients in any active phase of the disorder, either type I or type II and a follow-up of 12 months, treated with lamotrigine in monotherapy or in combination treatment. The results revealed that an 81% response rate and a 74% decrease in the Young Mania Rating Scale (YMRS) score are found in patients in the manic/hypomanic phase and that a 48% response rate and a 42% decrease in the Hamilton Depression Rating Scale (HDRS) score are also found in those in the depressive phase. Secondary analyses have shown additional benefits in other aspects related to the depressive episode and good tolerability with the most common adverse effects being dizziness, tremors, drowsiness, headaches, nausea and rash [155].

Given the positive results of this open study, GlaxoSmithKline launched between 1996 and 2001 an ambitious program of a controlled double-blind phase III trials and enrolled 2400 patients from four continents—5 trials in acute episode of bipolar depression, 2 in acute episode of mania, 2 in the prevention of manic or depressive episode and 2 in rapid cycling patients [150]. Unlike typical antipsychotics being more effective in the control of mania than depression, lamotrigine is especially effective in patients with a predominance of depressive phases. The results of the first double-blind, placebo-controlled clinical trial confirmed its effectiveness in bipolar depression at doses between 50 and 200 mg/day [156], although the improvement in the Hamilton 17-item Depression Scale, the main efficacy variable, is not significant. Similar results were obtained in the other four trials. These poor results might be due to the need to slowly increase the dose

of lamotrigine (up to 10 weeks to reach the final dose) to avoid the appearance of rash [157]. Subsequently, a meta-analysis considering all trials would confirm a significant, albeit small, efficacy of the treatment with lamotrigine [158]. By contrast, in double-blind clinical trials with patients in the manic phase, lamotrigine (50 mg) yielded negative results [159], presenting no statistical differences with placebo and lower efficacy than lithium. But in those studies, the risk of shift from mania to depression is not more than to placebo.

Yet, the best results with lamotrigine were obtained in studies of relapse prophylaxis in patients with bipolar disorder shown in two randomized double-blind trials which compared the efficacy of lamotrigine with that of lithium and placebo over 18 months. As a result, the USA FDA approved its use for this indication. Altogether ($n = 1300$ patients), both trials concluded that lithium is superior to lamotrigine and placebo in the prevention of manic phases and that lamotrigine is superior to lithium and placebo in the prevention of depressive phases [148,149]. The combination of data from both trials also showed that lamotrigine is effective in the prevention of mania, although the results is not as robust as that with lithium [160]. These findings confirmed the characteristically antidepressant profile of lamotrigine as a mood stabilizer, as opposed to other drugs available at the time and obtained its approval by USA FDA in 2003 (Table 2). In addition, they suggested the possibility to combine lamotrigine with lithium to obtain more symmetrical results in relapse prevention [161].

The effectiveness of lamotrigine in rapid cycling patients was also suggested, although data were based on a placebo-controlled clinical trial, is only positive in bipolar type 2 [162]. Finally, it was also confirmed that the combination of lithium and lamotrigine is safe and useful in refractory bipolar depression [163,164] and that the combination with valproate or carbamazepine is also possible, although implying more interaction risks [161].

6.2. Other Modern Antiepileptic Agents

Gabapentin was one of the first third-generation antiepileptic drugs to be studied for bipolar disorder and as almost all of them, it was initially evaluated for the treatment of mania. Although most open studies have positive outcomes [165] but the two controlled

clinical trials produce negative results [166,167] and raised considerable doubts about its efficacy. In the first one [166], lamotrigine shows better outcomes than gabapentin. In the second one, surprisingly, placebo is better than gabapentin in manic patients treated with lithium [167]. However, gabapentin could be an interesting drug as an enhancer of other mood stabilizers in cases in patient with a high anxiety component [168]. This is especially relevant at present, since many authors advocate combined treatment to prevent the natural disease progression towards a shortening of remission periods [169].

The history of topiramate shows paradigmatically how research on potentially anticonvulsant drugs is evolving. Topiramate was discovered in 1979 by Bruce E. Maryanoff and Joseph F. Gardocki through their research work at McNeil Pharmaceuticals (Fort Washington, PA, USA), a subsidiary of Johnson & Johnson Corporation. It was initially synthesized as a hypoglycaemic agent. In fact, topiramate is a sugar, a derivative from fructose. After having known its potential efficacy in diabetes being limited, the investigators studied topiramate in various animal models of different diseases, proving its anticonvulsant efficacy in rats. The preclinical research showed that the presumed antidiabetic was a potent antiepileptic. Some open studies suggested that it could be an effective drug as an add-on therapy in bipolar patients with partial response to other drugs [170] and a monotherapy [171]. But placebo-controlled clinical trials in manic patients cannot prove its efficacy [172], despite that several controlled trials of high methodological quality were carried out.

As for tiagabine, little relevant data exist to show its effect in bipolar disorder, although a study conducted in the Stanley Foundation Bipolar Network indicated that its mood stabilizing potential is scarce or null, together with a certain risk of seizure induction [173].

As mentioned before, oxcarbazepine, a 10-keta analogue of carbamazepine, was developed in the 1970s as an improved alternative to carbamazepine. In addition to the initial studies from the 1980s, recent data exist from experiments using oxcarbazepine to treat bipolar patients. Case series with positive results have been reported [174]. In addition, an open study with 12 patients receiving oxcarbazepine has been published, showing good results in participants with mild or moderate forms of mania, worsening in symptoms after discontinuing the drug and becoming improved again after resuming

treatment [175]. In any case, the APA advises the use of oxcarbazepine as a reasonable option in treating bipolar patients who do not respond to established treatments but more clinical trials are needed to confirm its potential as mood stabilizer in the maintenance treatment. Licarbazepine, an active metabolite of oxcarbazepine, was also evaluated in controlled clinical trials for manic episodes in bipolar disorder patients, with unsatisfactory results [176].

With respect to levetiracetam, pregabalin, retigabine, or zonisamide, the data published from patients with bipolar disorder are limited, although their properties are being assessed as mood stabilizers.

7. Atypical Antipsychotic Agents in Bipolar Disorders

The delay in the action onset of classical mood stabilizers in the treatment of symptomatic acute manic symptoms enabled the study with the use of antipsychotic drugs in this disorder [177]. Chlorpromazine was the only traditional antipsychotic drug (or first-generation antipsychotic drug, FGA) approved by USA FDA in 1973 for the treatment of manic episodes in bipolar disorder. Several clinical trials contrasted the efficacy of chlorpromazine in acute mania, both in monotherapy [83,178] and in combined treatment with lithium salts [179]. Nevertheless, its use in bipolar disorder was limited due to its poor tolerability, causing sedation and hypotension and the advent of new atypical antipsychotic drugs (AADs, or second-generation antipsychotic drugs, SGAs). The clinical introduction of risperidone on the USA market in 1993 to treat patients with schizophrenia heralds the advent of AADs and the clinical introduction of those agents reinvigorated the interest in therapeutic research on the different phases of bipolar disease [180]. In addition, its wide use in schizophrenia provided contrasted data regarding SGAs' superior safety over FGAs, especially with respect to extrapyramidal effects.

Besides, the unique biochemical properties of AADs (clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine and cariprazine), mainly their ability to antagonize dopamine receptors, together with other peculiarities of their pharmacological receptor profile and their effects on multiple neurotransmission systems [181] also fostered their study as potential antimanic agents [182]. In addition to dopamine D₂ antagonist effects, AADs block 5-HT₂ serotonergic receptors, basically 5-HT_{2A} and 5-

HT_{2C} and some of them, such as aripiprazole, ziprasidone and asenapine, are 5-HT_{1A} receptor partial agonists [181], which could result in an enhancement of noradrenergic and dopaminergic neurotransmission [183]. Although the exact mechanisms of AADs in the treatment of mania remain unclear, it seems obvious that this type of drugs have a specific antimanic effect regardless of the presence of comorbid psychosis or the degree of sedation induced by the agents [2].

Olanzapine was the first atypical antipsychotic drug to have been licensed for the indication of treating acute mania. Eli Lilly (Indianapolis, IN, USA) sponsored six double-blind studies published between 1999 and 2003, to evaluate olanzapine's efficacy for treating mania or mixed episodes compared to that of placebo, divalproex and haloperidol. The first of those was a placebo-controlled trial [184] with a three-week follow-up period. The study results showed a mean reduction in the YMRS score of 10.26 points in the olanzapine group versus 4.88 points in the placebo group and the percentage of patients being responders in olanzapine vs. placebo were 48.6% vs. 24.2%, respectively. The mean modal dose of olanzapine 14.9 mg/day, is superior to placebo in treating acute symptoms of mania in this trial. Subsequent studies confirmed the efficacy of olanzapine in acute mania, with an efficacy superior to valproate and lithium [185]. As a consequence, olanzapine was the first AAD approved by the USA FDA to treat manic episode of bipolar disorder in 2000 (Table 2).

In any case, the antimanic efficacy of AADs was later revealed by a series of randomized, placebo-controlled studies [12,186–190], suggesting that all AADs, as a pharmaceutical group, have a class-effect in treating mania. Almost all AADs got approval to treat mania one by one—risperidone in 2003; quetiapine, ziprasidone and aripiprazole in 2004; asenapine in 2009; as well as cariprazine in 2015 were approved by the USA FDA as monotherapeutic agents for the antimanic indication (Table 2). In addition, some of them were also approved for the prevention of relapse in patients with bipolar disorder who in a manic episode had already responded to the treatment with those antipsychotics (Table 2). At present, AADs are the first line of treatment for the manic phases of bipolar disorder [191].

Various AADs expanded their indications to treat all three clinical phases of bipolar disorder. Seemingly most AADs, if not all, can get the indication for relapse prevention

if they are combined with the use of lithium or valproate (Table 2). Finally, olanzapine (always in combination with fluoxetine) in 2003, quetiapine in 2008 and lurasidone in 2013 have been approved for the treatment of depressive episodes in bipolar disorder. This may be the reason why, recently, the number of scientific publications on bipolar disorder [9] and AADs have suddenly and exponentially increased in some countries of Asia and Europe and in Australia [192–196].

The treatment of bipolar depression is more complex than the treatment of manic episodes. It requires different therapeutic approaches from unipolar depression [197]. Also, the scientific evidence on the role of AADs is smaller and, in some cases, the results of meta-analyses have given rise to inconsistent conclusions [198]. The antidepressant properties of some AADs could be due to their ability to modulate three monoaminergic systems (noradrenergic, serotonergic and dopaminergic) involved in the pathophysiology of depression [199]. In the case of quetiapine, its active metabolite norquetiapine helps serotonergic transmission, acting as a partial agonist of 5-HT_{1A} receptors, in addition to working as a potent inhibitor of the noradrenaline transporter, which increases noradrenergic functionality [200,201].

Although olanzapine is approved by USA FDA in the treatment of bipolar depression, that is the case only in combination therapy with fluoxetine. The first AAD to obtain approval from USA FDA for the treatment of bipolar depression in monotherapy was quetiapine, based on a clinical trial program developed by AstraZeneca (London, UK) and known under the acronyms BOLDER (BipOLar DEpRession) and EMBOLDEN (Efficacy of Monotherapy Seroquel in BipOLAR DEpressionN). The BOLDER studies, placebo-controlled and 8 weeks long, confirmed that quetiapine at daily doses of 300–600 mg is superior to placebo in the total reduction of depressive symptoms according to the Montgomery-Asberg Depression Rating Scale. (MADRS) and that the improvement occurred from the first week in all the main symptoms of depression. Likewise, quality of life and anxiety are improved to a greater extent with quetiapine and this improvement was independent of the presence or absence of sedation [202,203]. The efficacy of quetiapine at a 300 mg/day dose is similar to that of 600 mg/day, so both doses have been approved for the treatment of bipolar depression. With respect to EMBOLDEN trials, an assessment was performed at week 8 and patients who met specific response criteria entered a 52-week treatment extension phase. In the EMBOLDEN I study, quetiapine at

600 mg/day (but not quetiapine at 300 mg/day) is superior to lithium in reducing the MADRS score at week 8 [204], while in the EMBOLDEN II study, quetiapine, at doses of 300 and 600 mg/day, reduces the total score of the MADRS scale more than the SSRI antidepressant paroxetine at dose of 20 mg/day. In addition, paroxetine does not differ from placebo [205]. In those studies, in acute episodes of bipolar depression, quetiapine achieves higher and earlier response and remission rates than placebo and it does so from the first or second week.

This decision to pursue clinical drug trial of lurasidone for patients with depressive episode in bipolar disorder was influenced by three relevant factors [206] because lurasidone has:

- special pharmacological profile [207] of receptor affinity (mainly as a 5-HT_{1A} receptor agonist and a 5-HT₇ receptor antagonist),
- efficacy in animal models of acute and chronic depression [208],
- shown favourable improvement in depressive mood in previous efficacy studies in schizophrenia [209].

Lurasidone is the first AAD whose efficacy in bipolar disorder was studied in the treatment of the depressive phase exclusively. The investigators observed that in patients treated with lurasidone for six weeks, the mean MADRS score is decreased more than those in the control group. Therefore, the pharmaceutical company Sunovion Pharmaceuticals, Inc. (Marlborough, MA, USA) launched in 2009 a clinical trial program called PREVAIL (Program to Evaluate the Antidepressant Impact of Lurasidone), with the aim to evaluate the efficacy and safety of this AAD both in monotherapy and in combination treatment with lithium or valproate, in adult patients diagnosed with bipolar depression according to clinical criteria of *DSM-IV-TR* [199,206]. The positive results of those trials and an open six-month long-term follow-up study allowed USA FDA approval of this agent in June 2013, for the treatment of depressive episodes of bipolar I patients.

8. Conclusions

The definition of a “mood stabilizer” is not clear. It means different things to different people (APA, 2002). According to one specific definition, it is a drug that has both antimanic and antidepressant effects on both mood states [210,211]. In conservative definition, it means a drug that has therapeutic efficacy in 2 of 3 different mental states, as shown in Table 2 [212]. But in a broader definition, it means a drug that: (A) is effective in 1 of any 3 phases as an antimanic, antidepressant, or for maintenance/prophylaxis; (B) does not worsen any mood state; and (C) does not have the potential of switching the patient from one to the other mood state [213,214]. According to this broad definition, tricyclic antidepressants do not belong to this category to treat patients with bipolar disorders. The results of meta-analysis data from clinical trials has shown that the rates of mania induced by tricyclics, SSRIs and placebo are 11.2%, 3.7% and 4.2%, respectively [215]. Venlafaxine and paroxetine have been found to have beneficial psychotropic properties. However, venlafaxine, instead of paroxetine, is noted to have a higher mood switch rate compared to paroxetine, 13% vs. 3% [216]. Valproic acid and carbamazepine have never been identified to switch the mood of bipolar patients from a depressive to a manic phase.

The American Psychiatric Association has discouraged the use of the term “mood stabilizer” [143]. It has never been officially used by USA FDA for a drug approved to treat patients with bipolar disorders (Table 2). Not to further invite confusion, we suggest that one should avoid the term “mood stabilizer” as much as possible even though no simple substitute term is available.

In this paper, we have used the USA FDA approval status as the milestone for describing drugs for the treatment of bipolar disorders. Approval by USA FDA frequently means a drug’s marketability not only in the USA but also all over the world. As shown in Table 2, only three AADs (olanzapine, quetiapine and lurasidone) have been approved by USA FDA for the treatment of the depressive phase of bipolar disorder and only two (olanzapine and quetiapine) for all three phases of “mood states.” But olanzapine needs to be combined with fluoxetine, an antidepressant, for the treatment of the depressive phase of bipolar disorder [217]. Lithium and valproate have been approved by USA FDA for antimanic indications in 1975 and 1995, respectively. Since 2000, olanzapine,

risperidone, quetiapine, ziprasidone, aripiprazole, asenapine and cariprazine have been approved for antimanic indication. Currently the AAD market is saturated with antimanic agents as listed in Table 2. No more motivation exists for a pharmaceutical company to invest money to develop oxcarbazepine or another antiepileptics for an antimanic indication. Hence, those drugs are most likely to remain off-label use for antimanic effects.

No shortage of available antimanic agents is shown on the market (Table 2). For other antiepileptic drugs, only lamotrigine has been approved by USA FDA for maintenance therapy. But lamotrigine or similar drugs, rather than valproic acid or carbamazepine, continues to draw attention in the treatment of patients with bipolar disorders. Their rare characteristic is their efficacy for both poles of bipolar depression.

Historical Implications at the Socio-Sanitary Level of the Clinical Introduction of the First Mood Stabilizers

The direct and delayed consequences of the introduction of the first psychotropic drugs in the 1950s have been multiple and lithium salts played a fundamental role [30,63,97,218,219]. At the purely scientific level, they favoured the postulate of the first biological hypotheses on the genesis of mental illnesses, giving birth to the so-called “biological psychiatry.” At the nosological level, the introduction of those drugs contributed to design new, much narrower diagnostic criteria, characterized, to a large extent, by a predictable and homogeneous response to treatment [220]. Clinical research methodology also benefited from the appearance of those drugs, specially lithium salts, with the rise of multicentre, double-blind, cross-over, randomized clinical trials, etc., as well as the development of a large number of generic and specific tests for the assessment of changes in psychopathological traits. Lithium played a decisive role in this whole process [62].

From the historical perspective, another relevant contribution of the clinical introduction of lithium and the FGAs lays at the health care level, giving rise to the progressive phenomenon of “deinstitutionalization” in psychiatry. This fact mitigated the stigma component that had accompanied psychiatric assistance. In this sense, the FGAs not only enabled patients to leave psychiatric hospitals but also helped their re-socialization. Some

data show the impact that the introduction of these agents had. During the first half of the 20th century, the number of patients admitted to psychiatric hospitals in the USA was alarmingly increased, from 150,000 to 500,000 patients. But from 1955, the year in which certain psychopharmaceuticals (FGAs and lithium salts, particularly) began to be used on a massive scale, the rate of hospitalizations was reversed and in 1975 the number of patients was dropped to 200,000 [221]. Another example comes from the economic benefits that lithium brought to the community, which have been estimated, in the USA, at USA \$145 billion dollars from its USA FDA approval in 1970 until 1994, mainly due to savings in hospitalization costs [222].

Even today, almost 70 years after Cade's work, lithium salts, applying the precautions associated with a drug of moderate toxic character (basically the control of lithium), constitute the first-choice treatment for the manic phases of affective bipolar disorders, as well as indispensable prophylactic tools in the prevention of cyclic episodes of manic-depressive illness. Even the "black history of lithium toxicity" should be revised, as proposed by Moncrieff [54], since, while the rate of deaths directly attributable to lithium stands at 14 per million prescriptions, this ratio rises to 50 in the case of dothiepin, 46.5 in the case of amitriptyline or 11.1 with clomipramine. In any case, the importance and transcendence of lithium in psychiatric therapeutics is reflected on the enormous amount of scientific publications on this agent, which reached 9500 in the 33 years after the classic work of Cade [223].

Currently, psychiatrists dispose of a therapeutic arsenal of 13 different drugs approved by regulatory agencies to address the different acute episodes of bipolar disorder and the prevention of relapse. Although the process was started 70 years ago by John Cade with the discovery of lithium salts antimanic effect has not yet concluded and there are broad aspects to be improved, the pharmacological treatment of bipolar disorder has established itself as a substantial part of the history of psychopharmacology. In any case, the scientific evidence accumulated over the last decade appears to confirm that there is no unitary biochemical mechanism to explain the effect of all the substances currently available for the treatment of bipolar disorder. In fact, research in this field is advancing in other directions, with the aim of finding new loci of drugs' action, such as the role of neurotrophic factors (neurotrophins and BDNF), corticotropin-releasing hormone (CRH) and glucocorticoids, excitatory amino acids and NMDA (*N*-methyl-d-aspartate) receptor,

as well as other possible targets (opioid system, interleukins, P substance, somatostatin, neuropeptide Y, melatonin, nitric oxide and so on). One of the most important objectives of the current neuroscience is the discovery of the molecular mechanisms responsible for intraneuronal communication. Detailed knowledge of these mechanisms could provide us, in the future, with much more specific and safer pharmacological tools for treating bipolar disorder. But this story continues to be written...

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Acknowledgments: This article contains clinical information of off-label use of drugs not approved by regulatory agencies. Physicians are advised to check package inserts of the mentioned drugs in this paper before prescribing them to their patients.

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Abbreviations

AAD	Atypical Antipsychotic Drug
APA	American Psychiatric Association
BDNF	Brain-Derived Neurotrophic Factor
BOLDER	BipOLar DEpReSSion
CRH	Corticotropin-Releasing Hormone
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECA	Epidemiological Catchment Area Study
EMBOLDEN	Efficacy of Monotherapy Seroquel in BipOLAR DEpression
FDA	Food and Drugs Administration
FGA	First-Generation Antipsychotic Drug
HDRS	Hamilton Depression Rating Scale
MADRS	Montgomery-Asberg Depression Rating Scale
NCS	National Comorbidity Survey
NMDA	N-Methyl-d-Aspartate
POW	Prisoner of War
PREVAIL	Program to Evaluate the Antidepressant Impact of Lurasidone
SGA	Second-Generation Antipsychotic Drug
SSRI	Selective Serotonin Reuptake Inhibitors

UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WWII	World War II
YMRS	Young Mania Rating Scale

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Research Article

Discovery Patterns of Drugs Approved for Treating Bipolar Disorder by Applying Operational Criteria of Serendipity: A Historical Analysis

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While the scientific community has long acknowledged the significant role of serendipity in shaping the field of contemporary psychopharmacology, its impact has not undergone a comprehensive analysis using operational methodologies. Serendipity, originally defined as discoveries stemming from a blend of luck and astuteness by Walpole, has been operationalized by our research group. Our definition builds upon Walpole's notion of fortuitous accidents and keen insight leading to the unexpected revelation of something unintended. We have discerned four unique serendipitous attributability patterns. In this paper, we delve into the historical aspect of how serendipity has played a role in the discovery and advancement of drugs approved for addressing different stages of bipolar disorder. The revelation of valproate's antimanic properties aligns with the pure serendipitous pattern (type I). Conversely, the discovery of lithium's antimanic effects corresponds to the mixed type II pattern, where the initial serendipitous observation of sedation in research animals, prompted by adding lithium salts to enhance uric acid solubility, led to the planned discovery of its calming impact on manic patients. On the contrary, the recognition of the mood-stabilizing attributes of lamotrigine aligns with the type III archetype. This particular pattern is defined by serendipity emerging as a consequence of a discovery that was initially nonserendipitous, as mood-stabilizing efficacy was incidentally observed during the treatment of epileptic patients for whom the drug was originally developed. Finally, carbamazepine and, notably, atypical antipsychotics fall within the type IV pattern. In this category, serendipity is entirely absent, as the antimanic use of carbamazepine was a straightforward extension of the use of other antiepileptic drugs. Atypical antipsychotics were introduced into bipolar disorder therapy through a deliberate and targeted design process, seeking drugs capable of acting on specific biological targets.

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ABSTRACT

While the scientific community has long acknowledged the significant role of serendipity in shaping the field of contemporary psychopharmacology, its impact has not undergone a comprehensive analysis using operational methodologies. Serendipity, originally defined as discoveries stemming from a blend of luck and astuteness by Walpole, has been operationalized by our research group. Our definition builds upon Walpole's notion of fortuitous accidents and keen insight leading to the unexpected revelation of something unintended. We have discerned four unique serendipitous attributability patterns. In this paper, we delve into the historical aspect of how serendipity has played a role in the discovery and advancement of drugs approved for addressing different stages of bipolar disorder. The revelation of valproate's anti-manic properties aligns with the pure serendipitous pattern (Type I). Conversely, the discovery of lithium's anti-manic effects corresponds to the mixed Type II pattern, where the initial serendipitous observation of sedation in research animals, prompted by adding lithium salts to enhance uric acid solubility, led to the planned discovery of its calming impact on manic patients. On the contrary, the recognition of the mood-stabilizing attributes of lamotrigine aligns with the Type III archetype. This particular pattern is defined by serendipity emerging as a consequence of a discovery that was initially non-serendipitous, as mood-stabilizing efficacy was incidentally observed during the treatment of epileptic patients for whom the drug was originally developed. Finally, carbamazepine and, notably, atypical antipsychotics fall within the Type IV pattern. In this

category, serendipity is entirely absent, as the anti-manic use of carbamazepine was a straightforward extension of the use of other antiepileptic drugs. Atypical antipsychotics were introduced into bipolar disorder therapy through a deliberate and targeted design process, seeking drugs capable of acting on specific biological targets.

Keywords: anticonvulsants; antipsychotics; bipolar disorder; history of neurosciences; lithium; mood stabilizer drugs; psychopharmacology; serendipity.

1. Introduction

Although bipolar disorder is a mental disorder known since Antiquity (“mania”, “manic-depressive psychosis”, “psychotic excitement”) [1], until recently it has not received adequate attention from science, and its etiopathogenesis is still largely unknown. Therefore, some authors contend that, in the context of current scientific research, bipolar disorder is regarded as a developing medical condition [2]. It is a severe, chronic affective disorder characterised by alternating episodes of mania or hypomania with euthymia and depressive episodes [3]. From an epidemiological point of view, this disorder has a high morbidity/mortality rate [4], with a lifetime prevalence estimated at 1-2% of the population over the age of 20 [5]. However, if we were to take the so-called “bipolar spectrum” into consideration, which includes the classic type I, type II and cyclothymic disorders, giving this pathology a much wider scope, we could estimate rates of prevalence at between 2.8 and 6.5 % of the population [4, 6-8].

Similarly, the history of the pharmacological approach to bipolar disorder is not a long one, as the only effective therapeutic tool for these patients was lithium salts, until the effectiveness of valproate in treating manic episodes was validated in the mid-1990s. The unearthing of lithium's effectiveness in treating mania, made by the Australian psychiatrist John F.K. Cade in the late 1940s, was a significant revelation [9] During the period known as the "modern psychopharmacology era," which became well-established in the 1950s with the clinical introduction of the extensive groups of pharmaceutical agents still employed today, including the conventional neuroleptics and antipsychotics, the traditional tricyclic antidepressants, and the benzodiazepine anxiolytics [10]. This is what is commonly referred to as the “psychopharmacology revolution”, as it not only provided the first specifically effective agents for managing psychiatric disorders, which drastically changed psychiatric care, but also allowed the neurobiological basis of mental illnesses to be understood.

In the specific case of bipolar disorder, until the antimanic effect of lithium was discovered, the therapeutic agents that had been used in clinical practice showed very low efficacy [10], with sedatives being the most commonly used drugs to manage manic patients. Opium and morphine were commonly used in the later part of the 19th century, along with alkaloids obtained from plants of the *Solanaceae* family, such as hyoscyamine

and hyoscine or scopolamine [1]. Later, chloral hydrate was used, which made it possible to treat manic patients at home [11], as were bromides [12], and then barbiturates in the 20th century. Barbital was the first drug in this family and was introduced into clinical practice in 1903. It had already been shown to be capable of calming manic patients, among other properties, although the most widely used in these conditions was phenobarbital, marketed in 1912, thanks to its more prolonged pharmacological action. Even highly excited manic patients were given so-called “sleep cures” based on barbiturates and other compounds, which induced an extended and profound state of sleep, lasting for at least 6-7 days [13].

The efficacy of lithium salts in managing manic episodes became apparent during the 1950s. Nonetheless, it wasn't until the latter part of the 1960s that it was confirmed that lithium also possessed effectiveness in averting manic-depressive episodes in individuals diagnosed with bipolar disorder [14, 15]. However, the drug's authorization for antimanic use by the US Food and Drugs Administration (FDA) was delayed until 1970 [16]. Valproic acid was approved in 1995 by the FDA for antimanic use and in 2004 carbamazepine was also approved, thereby giving classic anticonvulsants the status of established antimanic drugs. Finally, since 2000, the FDA and the European Medicines Agency (EMA) have authorised different atypical antipsychotic drugs (AADs) for antimanic use (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, cariprazine) or antidepressant use (quetiapine, olanzapine, lurasidone, lumateperone, cariprazine), and lamotrigine, which belongs to the class of contemporary antiepileptic drugs, is used for the prevention of depressive episodes in individuals with bipolar disorder (see Table 1; Figure 1). In any event, it should be noted that polypharmacy with drugs from different therapeutic groups is a prevalent approach in the treatment of individuals with bipolar disorder [17].

Certain researches have demonstrated that serendipity may have significantly contributed to the uncovering of mood-stabilizing properties in some of the medications presently employed in bipolar disorder treatment (basically lithium salts and classic antiepileptic drugs), as it did with other drugs discovered at the beginning of the “era of modern psychopharmacology” [18, 19]. Nevertheless, a significant degree of dispute exists within the scientific literature regarding this matter, perhaps stemming from the absence of agreement on the conceptual delineation of this phenomenon. This disparity is noticeable

even though there is a historical association between the 18th-century English writer, politician, and historian Horace Walpole and the British diplomat Sir Horace Mann. Their discussions revolved around the ancient Persian tale *The Three Princes of Serendip*, which initially referred to the two essential elements that would define "serendipity": accident and sagacity [18], it gradually evolved until it was considered a synonym for chance or random phenomenon and lost the component of sagacity.

Table 1. Drugs approved by the Food and Drug Administration of the United States (FDA) or European Medicines Agency (EMA) for treatment of patients with bipolar disorder.

Group / Family	Drug	ATC code	Mania (date approved)	Mixed Mania / Depression (date approved)	Maintenance / Prevention (date approved)	Bipolar depression (date approved)
Salts	Lithium	N05AN01	(1970)	No	(1978)	No
Classic antiepileptics	Carbamazepine	N03AF01	(2004)	(2004)	No	No
	Valproate / Divalproex sodium	N03AG01	(1995)	(2005)	No	No
New anticonvulsants	Lamotrigine	N03AX09	No	No	(2003)	No
Classic antipsychotics	Chlorpromazine	N05AA01	(1973)	No	No	No
Atypical antipsychotics	Aripiprazole	N05AX12	(2004)	(2004)	(2005)	No
	Asenapine	N05AH05	(2009)	(2015)	No	No
	Cariprazine ¹	N05AX15	(2015)	(2015)	No	(2019)
	Lumateperone ²	N05AD10	No	No	No	(2021)
	Lurasidone ³	N05AE05	No	No	No	(2013)
	Olanzapine	N05AH03	(2000)	(2000)	(2004)	(2003) ^a
	Quetiapine	N05AH04	(2003)	(2004)	(2008) ^b	(2006)
	Risperidone	N05AX08	(2003)	(2003)	(2009)	No
	Ziprasidone	N05AE04	(2004)	(2004)	(2009) ^b	No

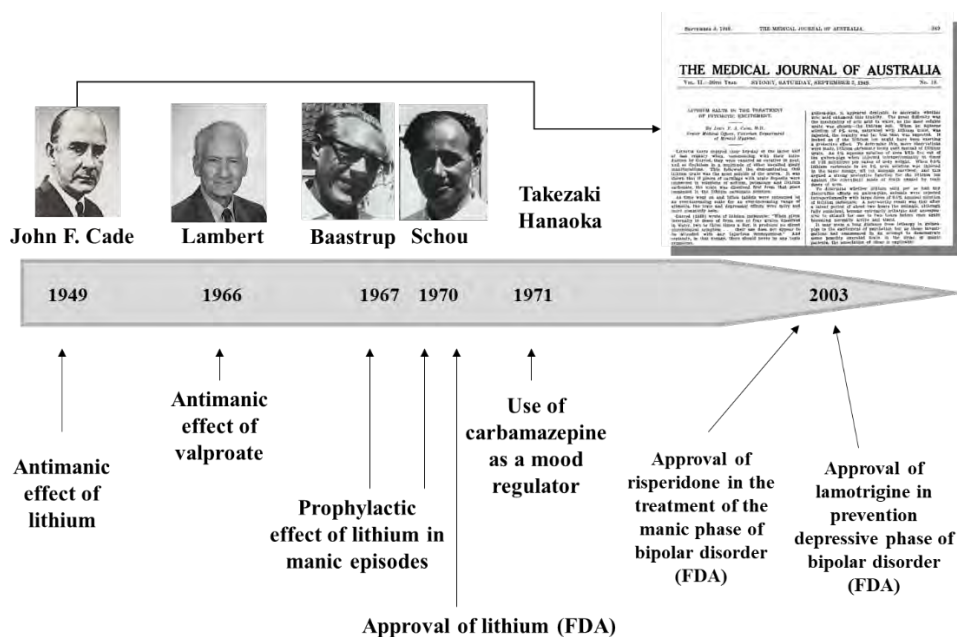
¹ Not authorized by the European Medicines Agency for the treatment of the bipolar disorder, only for the treatment of schizophrenia; ² Not approved by European Medicines Agency; ³ Not authorized by the European Medicines Agency for the treatment depressive phase of bipolar disorder, only for the treatment of schizophrenia; ^a Need to combine with fluoxetine; ^b Need to add lithium or divalproex.

Mood stabilizers were categorized using the Anatomical Therapeutic Chemical (ATC) classification system, overseen by the World Health Organization Collaborating Centre for Drugs Statistics Methodology (WHOC). This system groups the active ingredients of drugs based on their impact on specific organs or systems within the body https://www.whocc.no/atc_ddd_index/?code=N06AX&showdescription=no

Sagacity has now been recognised once again, along with unexpected observation, as a key element of serendipity. However, our group has argued that, when it comes to serendipitous discoveries, sagacity is subsequent to the accidental observation, i.e., We would be addressing the uncovering of something unintended, irrespective of the steps that led to the fortunate observation [18, 20]. Following this approach, the incorporation of numerous psychotropic drugs discovered during the 1950s into clinical practice would

be in line with the influence of serendipity. In this regard, Hargrave-Thomas et al. [21] postulate that a quarter of all existing drugs benefited from the phenomenon of serendipity at some point in their development, particularly psychotropic drugs.

Figure 1. Historical process of the discovery of mood stabilizer drugs.



Original figure created and designed by the authors.

Nevertheless, the extent of serendipity's involvement in these endeavors has traditionally been conveyed subjectively by the scientists who made these discoveries. To tackle this matter, we have formulated a precise characterization of serendipity based on four specific patterns of attributability [18, 22]. This framework enables us to objectively discern the actual contribution of serendipity to the drug discovery process. In this paper, we will use this methodology to analyse the influence of serendipity in the discovery of the mood-stabilizing characteristics of drugs authorized for managing bipolar disorder.

2. Materials and Methods

In earlier studies, we have introduced a functional characterization of serendipity [18, 22] which relies on identifying four distinct patterns of attributing serendipity within the process of discovering drugs (Figure 2):

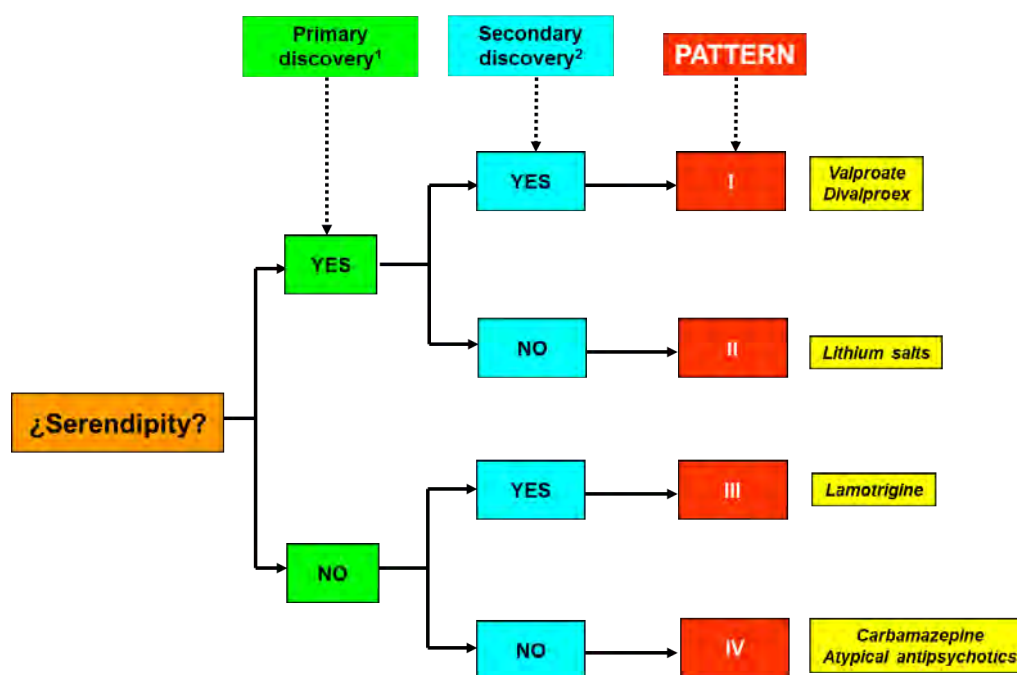
Pattern I, which includes purely serendipitous discoveries.

Pattern II, a modification of the preceding pattern, which outlines the initial chance findings leading to subsequent planned discoveries that lack serendipitous origins.

Pattern III, discoveries without serendipity that subsequently pave the way for serendipitous findings.

Pattern IV, which corresponds to purely non-serendipitous discoveries, outside the realm of chance or unintended accident. This last pattern includes all those discoveries of pharmacological drugs that fall within rational and systematic research programmes specifically designed to obtain agents with very specific effects on a given pathology.

Figure 2. Illustration depicting the four attributability patterns in the discovery of pharmaceutical agents and their application to mood stabilizer drugs.



Before applying the attributability criteria, we sourced the original manuscripts containing the initial pharmacological and clinical information on presently approved mood-stabilizing drugs from the subsequent website:

- 1) The primary databases in the biomedical field (Medline, Embase, Scopus).
- 2) The documentation resources provided by the pharmaceutical companies that distributed the mood-stabilizing medications.
- 3) The documentation accessible through the International Network for the History of Neuropsychopharmacology (INHn), under the guidance of Thomas A. Ban (Vanderbilt University).
- 4) David Healy's *The Psychopharmacologists* series of interviews (Arnold – Oxford University Press).
- 5) The History of Psychopharmacology collection of the International College of Neuropsychopharmacology (CINP) (Collegium Internationale Neuro-Psychopharmacologicum), coordinated by Thomas A. Ban, David Healy and Edward Shorter and published by Animula.
- 6) Prof. López-Muñoz's collection of documents on the history of psychopharmacology.

3. Results

3.1. The uncovering of lithium salts' antimanic characteristics

Lithium is an alkali metal that was first isolated by the Swedes Johann A. Arfwedson and Jöns J. Berzelius in 1817. In the mid-19th century, lithium was introduced therapeutically to treat gout, rheumatism and kidney stones, as a chance result of the so-called “uric acid diathesis” theory [23], according to which lithium salts were able to dissolve urate deposits. In this regard, it was also hypothesised that mental disorders could be related to high urate levels, referred to as “gout that affects the head” and “gouty mania” [24], for which lithium treatments were also recommended. However, excluding this anecdotal use, the actual introduction of lithium salts into psychiatric therapeutics took place in 1949, Due to the remarkable foresight of the Australian psychiatrist John F.K. Cade, Superintendent of the Bundoora Repatriation Mental Hospital (Victorian Department of Mental Hygiene of Australia) [1, 22, 25].

Cade's keen observational skills allowed him to observe how patients with thyroid pathologies showed a symptomatology very similar to that experienced by patients with manic-depressive disorder. Therefore, patients with hyperthyroidism manifested some symptoms very similar to those presented by patients in the manic phase; conversely, the symptoms of hypothyroid patients resembled those of patients in the depressive phase [26]. This astute observation led Cade to think that manic-depressive illness might be related to endocrine dysfunction and that there might be some sort of toxin in these patients that could be eliminated in the urine. To test this hypothesis, Cade designed an interesting and unusual experimental animal study: Several guinea pigs were subjected to intraperitoneal injections of varying concentrations of Urine collected from individuals experiencing manic and melancholic states, and individuals who were in a normal, healthy state. He noticed that those treated with high doses of urine, particularly from manic patients, exhibited convulsions, prolonged unconsciousness, and eventually succumbed. These outcomes prompted Cade to consider that urea in the urine of manic patients might be responsible for the observed toxic effects in guinea pigs. However, he soon realized that the levels of urea and creatinine in the urine of manic individuals were similar to those of other patients. Therefore, he shifted his focus to uric acid to validate his hypothesis. He administered a solution containing urea and various concentrations of uric acid to the laboratory animals. Nevertheless, due to the limited solubility of uric acid, he turned to lithium carbonate, a significantly more soluble compound. By chance, he noticed that the administration of this salt at a concentration of 0.5% in an 8% urea solution prevented the occurrence of the previously observed convulsive symptoms, and all the animals survived [27]. In light of these findings, Cade decided to assess the effects of exclusively administering lithium carbonate to guinea pigs, and observed that after 2 hours, the animals suffered a state of lethargy, which reverted 2 hours later [25, 28].

After analysing these experimental results, Cade considered the possible therapeutic effects of lithium salts on psychotically excited and manic patients, and opted to provide a 54-year-old individual with 1200 mg of lithium citrate, thrice daily. Patient diagnosed with manic excitement, who had a 5-year history of manic episodes. The patient started to improve 5 days after starting treatment and, 4 months later, upon his discharge from the hospital, he received an outpatient treatment consisting of 300 mg of lithium carbonate daily, administered in two doses. This choice was made due to the reduced likelihood of

nausea compared to citrate. The patient's remarkable improvement was such that he managed to resume his pre-hospitalization job. Cade achieved comparable outcomes with nine additional patients diagnosed with mania or psychosis, observing the most favorable responses in highly agitated individuals. These findings were subsequently published in 1949 in *The Medical Journal of Australia* [8], in an article that is considered to be the start of the so-called “revolution in psychiatric pharmacology” [1].

However, lithium salts were not officially approved to treat mania until 1970 (Table 1; Figure 1), due to a number of circumstances that adversely affected their clinical development. These include lithium's poor reputation due to the high number of fatal poisonings in the US in the late 1940s after lithium chloride was marketed as an alternative to sodium chloride or table salt for patients suffering from heart disease [29], and the subsequent rise of neuroleptic drugs from 1952 onwards, which led to scientific interest in lithium being abandoned [25].

The identification of the antimanic effects of lithium salts serves as a prime illustration of a serendipitous discovery (inducing a lethargic state in laboratory animals after adding these salts to improve the solubility of uric acid) Subsequently, this serendipitous discovery transformed into an intentional and non-accidental finding, particularly the calming effect observed in manic patients. In this way, the antimanic effect of lithium salts could be classified as fitting our Type II pattern of serendipitous attributability criteria, as outlined in Table 2. Nevertheless, this dual nature, a common feature in the discoveries of various psychotropic drugs in this period, has spurred debates concerning the actual influence of serendipity in these research and development procedures.

Table 2. Assigning serendipity's role in the finding of mood stabilizing drugs.

Group / Family	Drug	Date of discovery (psychiatric introduction)	Effect / primary properties ^a	Effect / secondary properties ^b	Pattern of discovery
Salts	Lithium	1817 (1949)	S	NS	II
Classic antiepileptics	Carbamazepine	1961 (1971)	NS	NS	IV
	Valproate / Divalproex sodium	1881 (1966)	S	S	I
New anticonvulsants	Lamotrigine	1981 (2002)	NS	S	III
Atypical antipsychotics	Aripiprazole	1988 (2002)	NS	NS	IV
	Asenapine	1990 (2009)	NS	NS	IV
	Cariprazine	2008 (2015)	NS	NS	IV
	Lumateperone	2007 (2019)	NS	NS	IV
	Lurasidone	2003 (2010)	NS	NS	IV
	Olanzapine	1991 (1996)	NS	NS	IV
	Quetiapine	1985 (1997)	NS	NS	IV
	Risperidone	1988 (1993)	NS	NS	IV
	Ziprasidone	1987 (2001)	NS	NS	IV

^a Usually, but not always, they correspond to discoveries in laboratory animals; ^b Discoveries related to clinical efficacy; NS (non-serendipitous discovery); S (serendipitous discovery).

3.2. Valproic acid and valproate as mood-stabilising drugs

Valproic acid was synthesised in 1881 by the American chemist Beverly S. Burton as an organic solvent analogue of valeric acid [30], becoming a very popular diluent in the mid-20th century, particularly in the pharmaceutical industry [31]. In 1963, Georg Carraz, a researcher at Laboratoire Berthier in Grenoble, conducted an assessment of the experimental anticonvulsant properties of several khellin compounds [32]. As was customary at that time, he employed valproic acid as a diluent. Employing the pentylenetetrazol convulsion model [33], Carraz serendipitously discovered that every solution containing valproic acid exhibited anticonvulsant properties, irrespective of the specific khellin compound being tested. He also determined that valproic acid was the substance responsible for this effect [34].

Following this breakthrough, Carraz synthesised valpromide, a derivative of valproic acid designed to have increased lipid solubility and improved permeability through the blood-brain barrier in theory [31]. To evaluate its potential for human use, Carraz collaborated with Sergio Borselli, a psychiatrist who had received training under Pierre A. Lambert at the Hôpital Psychiatrique de Bassens in Rhône-Alpes. This collaboration paved the way

for a series of clinical trials involving epilepsy patients [35, 36]. Initially, Borselli and Lambert observed that valpromide exhibited a sedative effect, especially when administered alongside other anticonvulsant drugs available at that time, such as phenobarbital. In any case, when valpromide and valproate were administered independently, these researches also appreciated, by chance, in 1966, that patients experienced a stabilisation of their mood, as well as an improvement in their neurological condition [36]. That same year, these researchers published, for the first time, in patients with bipolar disorder, the mood-stabilizing effects of valproate, such as an improvement in impulsivity, irritability and emotional lability [37] (Figure 1). Nevertheless, valproate would not be licensed as an antimanic drug in the US until 1995 (Table 1), after the publication of a series of clinical trials supported by Abbott Laboratories (Illinois, US), the company that owns the patent for the divalproex sodium. The studies showed that both divalproex and lithium were significantly more effective than placebo in reducing the symptoms of acute mania and that divalproex had antimanic efficacy similar to that of lithium [38].

Both the revelation of valproic acid's anticonvulsant properties and the discovery of valproate's mood-stabilizing effects serve as remarkable instances of unplanned scientific observations, exemplifying pure serendipity (Table 2).

3.3. The finding of the mood-stabilising effects of carbamazepine

Carbamazepine is a tricyclic anticonvulsant compound that was formulated in the laboratories of J.R. Geigy, situated in Basel, Switzerland, during the latter part of the 1950s [39]. The anticonvulsant characteristics of carbamazepine were elucidated in 1963 by Walter Theobald and H.A. Kunz [40]. However, its initial introduction to treat manic patients in Japan due to the concurrence of several factors, such as the lack of availability of lithium on the Japanese market in the early 1970s [41] and the preponderance of psychiatry over neurology in Japan [42], which resulted in the widespread use of this drug agent in Japanese hospitals after being marketed as an antiepileptic drug during the 1960s [41]. Furthermore, anticonvulsant drugs had been evaluated as mood stabilisers since the early 1970s, based on the hypothesis that epilepsy and bipolar disorder might share similar underlying properties, such as kindling [43].

In this setting, Japanese psychiatrists began to use carbamazepine on manic patients due to its sedative properties, rather than other less well-tolerated drugs such as barbiturates, particularly after learning that valpromide was being used for manic patients [31]. In 1971, Haruhiko Takezaki and Masanori Hanaoka, in Tottori, published the first clinical data on manic-depressive patients treated with carbamazepine [41] (Figure 1). It was an open study in which 20 patients were evaluated for periods between one and eleven months, with an improvement of “symptomatic manic-depressive” symptoms in 85% of them, although the authors did not mention whether the patients were treated previously with lithium. However, although controlled studies between carbamazepine and lithium showed similar efficacy [44], this input was not taken up in the West [45], where carbamazepine was not licensed by the FDA for this indication until 2004 (Table 1), with the introduction of an extended-release galenic formulation.

The identification of carbamazepine's anti-manic properties aligns with our Type IV attributability pattern, as serendipity played no part in its introduction into the management of bipolar disorder, which was merely an extrapolation concerning the application of different antiepileptic medications, like valproate (Table 2).

Although serendipity actively participated in the introduction of classical antiepileptic agents in terms of observing the clinical improvement of manic patients, the pharmacological actions that justified them took many more years to begin to be discovered. And also, coincidentally, it was found that many of them were shared with lithium, such as the enhancement of gabaergic neurotransmission, the decrease in dopamine turnover, the decrease in the release of noradrenaline or the increase in synaptic levels of serotonin, among others. However, despite the advances made in recent years, the mechanism of antimanic action of anticonvulsant drugs is not yet well determined and there is no evidence whether or not it coincides with their antiepileptic mechanism of action [1].

3.4. Lamotrigine and its efficacy in preventing depressive episodes in bipolar disorder

Lamotrigine, a phenyltriazine compound, was synthesized in the early 1980s at Wellcome Research Laboratories in Beckenham, Kent, England. This development was part of an

initiative to create novel antiepileptic drugs that offered improved tolerability compared to existing options during that period [46]. This initiative was founded based on the assumption developed in the mid-1960s concerning the potential pro-convulsant properties of folates whereby antiepileptic drugs would exert an antagonistic action on folic acid [47]. A number of phenyltriazines were synthesised taking pyrimethamine, a substance developed in 1950 as a malaria agent, as a reference, including BW288U, a compound exhibiting strong anticonvulsant efficacy while displaying limited antifolate properties. Attempts were made to optimise this compound, resulting in lamotrigine [48]. Phase I clinical trials were quickly initiated and it demonstrated excellent pharmacological properties. It was finally approved as an antiepileptic drug in Ireland in 1990 and by the FDA in 1994. In addition, it had an improved profile in terms of side effects compared to classical antiepileptic drugs, despite the problematic, but rare, Stevens-Johnson syndrome.

During the first clinical studies on epileptic patients with the new substance, Smith et al. [49] observed its positive impact on the emotional state and communication abilities of the individuals undergoing treatment with it, which made it possible to test it on bipolar patients in a psychiatric setting. The initial researcher to present scientific evidence regarding the effectiveness of lamotrigine in the context of bipolar disorder was Richard H. Weisler, affiliated with the University of North Carolina Chapel Hill School of Medicine in Chapel Hill, NC, US, who, as he himself acknowledged [46], knew about this molecule before it was authorised in the US, due to the fact that he had attended several international congresses. Following the importation of the medication from Europe and the submission of an application to the FDA for compassionate use authorization, in 1993, he employed this drug in combination with other treatments to manage two patients who had been grappling with bipolar disorders for an extended duration, who were resistant to all of the pharmacological treatments available at the time [1]. A marked clinical improvement was confirmed in both patients within several weeks. Weisler's group presented their results at the 1994 Annual Meeting of the American Psychiatric Association (APA) in Philadelphia [50] and defended its use based on the molecule's mechanism of action (a strong anti-kindling effect, inhibition of sodium channels, and suppression of glutamatergic activity).

Following the publication of several other clinical cases, GlaxoSmithKline launched an ambitious programme of clinical trials using lamotrigine on bipolar disorder between 1996 and 2001. A total of 2,400 patients from 4 continents enrolled in this phase III, controlled, double-blind trials [46]. Unlike classic antiepileptic drugs, which are more effective in controlling mania than depression, lamotrigine was shown to be particularly effective in patients with predominantly depressive phases. Lamotrigine yielded its most favorable outcomes in studies focused on preventing relapses in individuals with bipolar disorder, demonstrating its superiority over lithium and a placebo [51, 52], which led to its authorisation by the FDA for this indication in 2003 (Table 1; Figure 1). These findings corroborated lamotrigine's primarily antidepressant characteristics as a mood stabilizer, in comparison with the agents available up to that time.

The discovery of lamotrigine's mood-stabilizing attributes could align with the criteria for Type III serendipitous attributability in our framework, characterised by the presence of serendipity secondary to a non-serendipitous discovery (Table 2), as it was developed specifically as an antiepileptic agent, but the discovery of its mood-stabilising efficacy was serendipitous in the context of its use in the treatment of epileptic patients. However, at the time of this discovery, the antimanic effects of the classic anticonvulsant drugs, valproate and carbamazepine, were already known.

3.5. Atypical antipsychotics and their role in managing the bipolar spectrum

Chlorpromazine stands as the sole classic neuroleptic drug licensed by the FDA for the treatment of manic episodes in bipolar disorder, a designation granted in 1973. This authorisation was justified by the results of several clinical trials that confirmed their efficacy in acute mania [53] and their hypothetical faster action than classic mood regulators [54]. However, their use was very limited due to their high incidence of adverse effects and, above all, to the clinical introduction of the new, much better tolerated AADs.

Olanzapine was the first among the atypical antipsychotics to receive authorization for the treatment of acute mania. Eli Lilly (Indianapolis, US) initiated a series of clinical trials that were published from 1999 to 2003. These trials assessed the effectiveness of olanzapine in comparison to placebo, divalproex, and haloperidol in the treatment of acute mania or mixed episodes. Later, the efficacy of olanzapine in acute mania was confirmed,

with better results than valproate and lithium [55]. As a result, in the year 2000, olanzapine achieved the distinction of being the inaugural AAD to receive approval from the US FDA for the treatment of manic episodes in bipolar disorder (Table 1).

Subsequent to these developments, the effectiveness of AADs in the management of manic conditions was established through randomized, placebo-controlled studies [3, 56-60]. These studies indicated a class-wide efficacy among AADs in the treatment of mania. Consequently, one by one, nearly all AADs obtained approval for the treatment of mania: risperidone and quetiapine in 2003, ziprasidone and aripiprazole in 2004, asenapine in 2009, and cariprazine in 2015 were granted FDA approval as antimanic drugs for use in monotherapy (Table 1). In this sense, their indications were broadened to encompass the management of all three clinical phases of bipolar disorder. Certain medications were authorized for the purpose of averting the recurrence of manic episodes in patients with bipolar disorder who had previously exhibited a positive response to treatment with these antipsychotic drugs (Table 1), while others were sanctioned for the treatment of depressive episodes. This included olanzapine (in combination with fluoxetine) in 2003, quetiapine in 2006, lurasidone in 2013, cariprazine in 2019, and more recently, lumateperone in 2021. Currently, AADs constitute the frontline treatment for manic phases [61].

The particular neurochemical properties of AADs, notably their ability to inhibit dopamine receptors, as well as other elements of their drug receptor profiles and their influence on various neurotransmitter systems [62], prompted considerations of their potential efficacy in treating mania [63]. Neurobiological studies confirmed that AADs, in addition to antagonizing dopamine D₂ receptors, also exhibited antagonism toward serotonin 5-HT₂ receptors, particularly 5-HT_{2A} and 5-HT_{2C}. Additionally, some AADs, such as aripiprazole, ziprasidone, and asenapine, acted as partial agonists of the 5-HT_{1A} receptor [62]. These mechanisms collectively led to heightened noradrenergic and dopaminergic neurotransmission [64]. Nevertheless, the precise mechanisms by which AADs exert their influence on mania remain undisclosed. It's important to highlight that these substances exhibit a unique antimanic impact, regardless of the presence of concurrent psychosis or the degree of sedation induced by the medication [43].

Bipolar depression is more difficult to treat than manic episodes, and different pharmacologic approaches are required than for unipolar depression [65]. Quetiapine became the initial AAD to secure FDA authorization for standalone treatment of bipolar depression. This achievement was realized through a clinical trial initiative initiated by AstraZeneca (London, UK). In these studies, quetiapine demonstrated markedly superior and more rapid response and remission rates in cases of acute bipolar depression compared to placebos, with discernible benefits evident as early as the first or second week. [66, 67], and significantly better clinical improvement than lithium [68] and the antidepressant paroxetine [69]. From a neurobiological perspective, the active metabolite of quetiapine, norquetiapine, facilitates the transmission of serotonin by behaving as a partial agonist of 5-HT_{1A} receptors, and also strongly inhibits the noradrenaline transporter, leading to heightened functionality of the noradrenergic system [70, 71].

Meanwhile, lurasidone was the first AAD to be tested in bipolar disorder, although its efficacy was only analysed in the treatment of the depressive phase. This decision was influenced by three major factors [72]: its special pharmacological profile with receptor affinity (primarily its 5-HT_{1A} receptor and 5-HT₇ receptor agonist and antagonist activity respectively) [73], its efficacy in animal models of acute and chronic depression [74] and the results obtained in previous efficacy studies on schizophrenia [75], which found that patients treated with lurasidone showed a significantly greater reduction in scores on scales of depression than patients in the control group. Consequently, starting in 2009, Sunovion Pharmaceuticals, Inc. (Marlborough, Massachusetts, US) devised a series of clinical trials aimed at evaluating the effectiveness and safety of lurasidone. These trials encompassed both standalone use and combined treatment with lithium or valproate in adult patients grappling with bipolar depression [72, 76]. The favorable outcomes from these trials culminated in the FDA granting approval for this medication in June 2013 to treat depressive episodes in bipolar type I patients. The trail of lurasidone was followed by lumateperone, developed by Intra-Cellular Therapies (under licence from Bristol-Myers Squibb) and licensed only to treat the depressive phase of bipolar disorder, possibly due to its moderate selective serotonin transporter reuptake inhibition and simultaneous modulation of dopamine and glutamate [77].

The antidepressant effects of some AADs can be explained by their modulating properties of the three monoaminergic systems (noradrenergic, serotonergic and dopaminergic) related to the etiopathogenesis of depression [78].

The clinical introduction of AADs in bipolar disorder did not involve either chance or sagacity, implying that the uncovering of their anti-manic and antidepressant characteristics aligns with the Type IV pattern in our framework for serendipitous attributability criteria (Table 2). This family of drugs was introduced into the therapy of bipolar disorder following a rational and targeted design procedure, i.e., following a pre-planned strategy, in which drugs capable of acting on specific *loci* of action were sought.

4. Discussion

Many scientific contributions have tangentially commented that serendipity played a prominent part in the identification of the initial psychotropic drugs during the the mid-20th century's golden era. However, the true role of serendipity has not been studied sufficiently from the perspective of scientific methodology. This is partly because the very concept of serendipity has not been defined precisely [79], often assimilating it to the involvement of luck or chance ("happy discoveries"), without valuing the key role of the sagacity of researchers and clinicians. This led to our group developing operational criteria for serendipitous attributability in line with the original approach to the term, where sagacity shares preponderance with the accidental discovery of something not intentionally sought [22]. This is very much in line with Louis Pasteur's postulate: "In the field of scientific observation, chance favours only the prepared mind" [80].

Following our approach, and contrary to what many authors propose, we can affirm that purely serendipitous discoveries in the field of psychopharmacology do not occur very often, and that discoveries characterised by a mixed pattern are much more common. Other researchers have categorized these findings, denoted as type II and type III in our operational criteria, named "pseudo-serendipity" ("accidental discoveries of ways to achieve an end sought for") [81] or findings that can be likened to "serendipity analogs" [82]. In both cases, the discovery of the antibiotic effect of penicillin is always used as a characteristic example, in addition to many others outside of pharmacology and medicine, such as the process of vulcanization of rubber by Charles Goodyear, after many years of

hard work [81]. But even other authors only highlight the role of luck or chance in making these discoveries, deeming the end result of the process to be a formal continuity of previous serendipitous discoveries, rather than the occurrence of two clearly distinct events.

The most common pattern in these mixed serendipitous discoveries is usually an initial serendipitous observation that ends with a rational and intentional discovery that does not involve accident. This is what we have termed the type II pattern, which includes one of the most important contributions in the history of psychopharmacology in the field of mood-regulating agents: The identification of lithium salts' anti-manic properties, particularly the widely held belief that it was a result of pure serendipity, has been a subject of discussion among authors. However, Cade contended that his incidental observation of the sedative impact of lithium on guinea pigs was not inherently linked to the subsequent verification of the agent's anti-manic effectiveness in humans [27]. This Type II pattern, characterized by initial serendipitous findings, frequently in laboratory animals, that subsequently lead to planned and non-serendipitous findings, includes a multitude of additional revelations in the field of psychotropic medications throughout the 1950s. This includes the discovery of imipramine and iproniazid, which served as prototypes for the first two classes of antidepressant drugs, tricyclic antidepressants and monoamine oxidase inhibitors. It also involves the unearthing of the antipsychotic effects of chlorpromazine and clozapine, along with the accidental discovery of meprobamate's experimental tranquilizing properties and the subsequent confirmation of its distinct anxiolytic effects.

On the contrary, there are also, within the framework of our type III pattern, mixed discoveries that were initially non-serendipitous and that later caused serendipitous discoveries. In the case of current drugs approved to treat bipolar disorder, the only available example is lamotrigine, which was initially developed as an anti-epileptic agent. This subsequently led to the serendipitous discovery of its mood-stabilising and preventive effects on bipolar depressive episodes. Other historical examples of this pattern can be found in barbiturates [13].

Similarly, in the history of psychopharmacology there have also been instances of purely serendipitous discoveries, as exemplified by our Type I pattern. These include the chance

uncovering of the anticonvulsant effects of valproic acid, the anti-manic properties of valproate, and the psychotropic attributes of lysergic acid diethylamide (LSD). Conversely, during the initial years of the modern psychopharmacology era, there were discoveries where serendipity played no role whatsoever, aligning with our Type IV pattern. A notable example is the revelation of the anxiolytic effect of the first benzodiazepine, chlordiazepoxide [83], or the antipsychotic effect of haloperidol and reserpine [84, 85]. However, it should be noted that this pattern was consolidated from the 1970s onwards, as a consequence of the implementation of rational design processes for pharmacological drugs, particularly aimed at their interaction with specific biological targets, such as specific receptors, related to the aetiopathogenesis of mental disorders [86].

Tables 1 and 2 show all of the drugs approved by the FDA and the EMA to treat patients with bipolar disorder. While 11 drugs have been approved as antimanic drugs, only 5 have received approval to treat depressive episodes of bipolar disorder, including olanzapine, which has to be prescribed together with fluoxetine. Similarly, 7 drugs have been licensed for the maintenance treatment and prevention of any types of episodes of this disorder, including quetiapine and ziprasidone, which have to be administered together with lithium salts or divalproex. And only two drugs, olanzapine and quetiapine, include all three phases of bipolar disorder among their indications. Currently, including chlorpromazine, despite its anecdotal use, the therapeutic arsenal for treating bipolar disorder consists of 14 drugs, with only AADs having been added in the last 20 years. It is clear that the process that John Cade started with the discovery of the antimanic effect of lithium salts 73 years ago is still far from complete, not least because of the limited knowledge of the neurobiological basis underlying this pathology, and that we are a long way from having the ideal mood-stabilising agent.

We do not know what the role of serendipity will be in the future of research on mood-stabilising agents, although it is clear that, over recent decades, the influence of serendipity is decreasing in the progress of psychopharmacology [87], which has evolved, like other areas of pharmacology, towards much more planned and rational developments [85]. Some authors have claimed the role of serendipity in the scientific research process today. Klein [88] attributes, in part, the relative lack of innovation in the specific field of psychopharmacology during the last 40 years to the absence of serendipity and defends

its promotion through an adequate structuring of the environments of the processes of investigation. Our group has also identified various “anti-serendipity” factors [89] that could explain this phenomenon pointed out by Klein, such as the decrease in the time available to researchers to observe and follow up on their patients, the imposition of the “double-blind” methodology in the design of clinical trials, which limits the possibility of identifying individual markers of response to drugs, or the use, in mental health, of evaluation scales to measure the effects of drugs, instead of longitudinal clinical observation. Two other relevant factors would be the scientific turn of pharmacology towards a rational drug design based on translational research, which has put an end to specific observations of the effects of drugs on the behaviour of animals or humans, and the change in the structure of the pharmaceutical industry, which is closely linked to the phenomenon of lack of innovation in the field of psychopharmacology. The result of this change has been the continuous clinical introduction of multiple drugs that are practically equivalent in mechanism of action and effectiveness, the so-called “me too” drugs, whose final profitability would exceed the innovative and novel agents. The restriction on the diversity of compounds selected for clinical trials, which is inherent in this reductionist approach, minimizes the possible role of serendipity in this process and its importance in the discovery of new drugs.

In any case, there is no doubt that currently available psychopharmacological agents have many limitations and that current knowledge of the aetiology of psychiatric disorders is still quite limited. All this suggests that serendipitous discoveries can still take place in this new technical environment of the 21st century [19]. However, it is indisputable that serendipity played a significant role in the advancement of modern psychopharmacology throughout the latter half of the 20th century. In one of David Healy’s interviews with one of the pioneers of the “psychopharmacology revolution”, Jean Thuillier, this influence is clear: “Healy: How did it all start? / Thuillier: It was by chance” [90]. In any case, the outcomes of this research underscore the notion that serendipity ought to be regarded as a legitimate scientific concept rather than a mere literary curiosity.

Acronym list

5-HT: 5-Hydroxytryptamine or Serotonin

AAD: Atypical Antipsychotic Drug

APA: American Psychiatric Association

ATC: Anatomical Therapeutic Chemical

CINP: Collegium Internationale Neuro-Psychopharmacologicum - International College of Neuropsychopharmacology

EMA: European Medicines Agency

FDA: Food and Drugs Administration

INHN: International Network for the History of Neuropsychopharmacology

LSD: Lysergic Acid Diethylamide (from German *Lysergsäure-diethylamid*)

NS: Non-Serendipitous Discovery

S: Serendipitous Discovery

UK: United Kingdom

US: United States

WHOCC: World Health Organization Collaborating Centre for Drugs Statistics Methodology

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DISCUSIÓN GENERAL

Se puede afirmar que, si bien el fenómeno de la serendipia es ampliamente utilizado cuando se analizan y discuten los descubrimientos científicos, la adscripción de este fenómeno, al menos en el ámbito de la farmacología, es sumamente controvertida y en algunos casos bastante incoherente por parte de los investigadores que se han ocupado de este tema. Estos puntos de vista contrapuestos pueden deberse, como se ha resaltado en la presente tesis doctoral, a la indeterminación semántica del concepto “serendipia”, cuyo uso en la literatura científica se ha materializado en muy diversos sentidos y significados (Merton y Barber, 2004).

Así, y centrándonos en el área específica de la psicofarmacología, Blackwell indica que “... muchos descubrimientos importantes y la mayoría, si no todos, los relacionados con la psiquiatría biológica, surgieron de esta manera [gracias a la serendipia]” (Blackwell, 1970), mientras Klein opina que “todas estas grandes familias de agentes psicofarmacológicos se descubrieron de forma serendípica” (Klein, 2008), y Jeste y colaboradores apuntan que “en ningún caso puede afirmarse que el descubrimiento de los tratamientos biológicos más relevantes de la psiquiatría haya sido consecuencia de la serendipia” (Jeste et al., 1979). Como también se ha comentado anteriormente, estas aparentes diferencias de opinión podrían atribuirse a la relevancia otorgada a la sagacidad y al evento no previsto, pues es habitual que las posturas en torno a que los hallazgos más

trascendentales de la historia de la psicofarmacología fueron azarosos conllevan que la casualidad fue una circunstancia precisa y exclusiva en dichos episodios. No obstante, el azar, por sí mismo, no suele ser una circunstancia suficiente.

En el ámbito general de la psicofarmacología, y en particular en relación a los agentes utilizados en el tratamiento de los trastornos del humor, los hallazgos serendípicos puros son bastante excepcionales, al contrario de lo que se ha venido planteando. De hecho, en el ámbito de esta tesis doctoral, únicamente pueden catalogarse como tales los descubrimientos del efecto anticonvulsivante del ácido valproico, al emplearlo como agente diluyente, y el posterior efecto eutimizante del valproato, al constatar su actividad estabilizante del estado de ánimo en pacientes epilépticos (López-Muñoz et al., 2024). Al margen de los antidepresivos y normalizadores del humor, el hallazgo de los efectos psicotrópicos de la dietilamida del ácido lisérgico (LSD) constituiría un ejemplo paradigmático de descubrimiento serendípico puro (Hofmann, 1980). Por el contrario, la mayoría de ellos, durante las primeras fases de la moderna era psicofarmacológica, presentan un carácter mixto, en el que se mezclan hallazgos serendípicos y no serendípicos, y generalmente siguen un patrón consistente que parte de una observación inicial serendípica, nuestro patrón tipo II, tal como sucedió con las sales de litio, donde un hallazgo serendípico, la inducción de un estado letárgico en los animales de laboratorio tras la incorporación de estas sales para mejorar la solubilidad del ácido úrico, condujo a un descubrimiento planificado y no serendípico, como fue el efecto eutimizante en pacientes maníacos. Esto también sucedió con la imipramina, inicialmente pensada como un antipsicótico, y la iproniazida, desarrollada como un agente antituberculoso, y la observación posterior no fortuita de la eficacia antidepresiva de ambos agentes en pacientes esquizofrénicos y tuberculosos, respectivamente, y más tarde con la mianserina, investigada como un agente antihistamínico, y la moclobemida, estudiada por sus propiedades antihiperlipidémicas (López-Muñoz et al., 2022; 2025). Este es el caso también de la mayoría de los descubrimientos que tuvieron lugar en la década de 1950 con otras familias de agentes psicofarmacológicos, como sucedió con los efectos antipsicóticos de la clorpromazina y de la clozapina, las propiedades tranquilizantes experimentales del meprobamato y su acción clínica ansiolítica. Mucho menos frecuentes son los patrones mixtos que comienzan con una apreciación no serendípica que conduce secundariamente a descubrimientos de carácter serendípico. En este patrón tipo III de

imputación serendípica, dentro del conjunto de agentes antidepresivos y eutimizantes, sólo se pone de manifiesto en el caso de la lamotrigina, que fue desarrollada como un agente antiepiléptico, del que, posteriormente, se descubrieron, de forma serendípica, sus efectos eutimizantes y preventivos de los episodios depresivos en pacientes con trastorno bipolar (López-Muñoz et al., 2024), y de la ketamina, desarrollada inicialmente como un agente anestésico que condujo a una observación fortuita posterior, como fue el descubrimiento de su eficacia antidepresiva en individuos que la consumían ilícitamente (López-Muñoz et al., 2025). En otros ámbitos de la psicofarmacología se podría mencionar a los barbitúricos, cuyas propiedades hipnóticas fueron especialmente buscadas, lo que permitió el subsiguiente descubrimiento serendípico de sus acciones anticonvulsivas y su eficacia en pacientes epilépticos (López-Muñoz et al., 2005a).

Todos los hechos previamente comentados contribuyen a explicar los diferentes matices con que se aborda por parte de los investigadores la influencia de la serendipia en los descubrimientos científicos. Incluso algunos autores postulan que las consecuencias clínicas de los hallazgos serendípicos iniciales constituyen una mera extensión de los mismos y no un acontecimiento independiente y separado, glosándolo como una especie de *continuum* no diferencial. Para explicar mejor este punto, se puede recurrir al descubrimiento de los efectos antimaníacos del litio, evento considerado por muchos autores como ejemplo prototípico de un hallazgo serendípico puro. No obstante, su descubridor, John Cade, escribió que nunca fue evidente la conexión entre su inicial apreciación azarosa del efecto letárgico del litio en los cobayas y la posterior aportación clínica del efecto antimaníaco de este agente (Cade, 1970). En relación a este tipo de patrón, ciertos autores han acuñado los términos “pseudoserendipia” (Roberts, 1989) o descubrimientos “análogos de la serendipia” (Díaz de Chumaceiro y Yaber, 1995).

En cualquier caso, lo que sí parece evidente es que la serendipia, en mayor o menor medida, tuvo un papel fundamental en el proceso de construcción de la moderna psicofarmacología durante la dorada época de los años 50 del pasado siglo (López-Muñoz et al., 2014a; Wadhwa, 2023).

Como consecuencia de este proceso, la Salud Mental cambió radicalmente, y con ella numerosas áreas del entorno socio-sanitario. A título de ejemplo puede mencionarse el

paulatino fenómeno de “desinstitucionalización” de la asistencia psiquiátrica y la progresiva involucración de la Atención Primaria en la asistencia a los pacientes con trastornos mentales, lo que ha contribuido a reducir el estigma que siempre acompañó a este tipo de pacientes. Desde el punto de vista científico, esta “revolución” permitió plantear las primeras hipótesis biológicas en relación con el origen de las patologías mentales, incluidas las de los trastornos del humor (Pletscher, 1998; López-Muñoz y Álamo, 2012; 2014), que dieron lugar al nacimiento de la denominada “psiquiatría biológica”. En el plano nosológico, los nuevos fármacos contribuyeron, de una forma muy importante, al desarrollo de los nuevos criterios diagnósticos. Y finalmente, los agentes psicofarmacológicos posibilitaron un gran cambio en la metodología de investigación clínica, que, a su vez, redundó en la síntesis de nuevos fármacos introducidos en el manejo de las patologías psiquiátricas (López-Muñoz et al., 2014a).

Sin embargo, paulatinamente se fue imponiendo una mecánica de obtención de resultados basada en planteamientos racionales (Pieper y Baraban, 2017; Robinson, 2018), fenómeno inseparable de la propia investigación científica y que se fue consolidando desde la década de 1980 (Oh et al., 2021), básicamente con el desarrollo de la fluoxetina y del resto de ISRS y otros nuevos antidepresivos de diferentes familias (López-Muñoz et al., 2025), aunque este patrón tipo IV, o de ausencia de serendipidad, también se puede ver en el descubrimiento del efecto antimaníaco de los antipsicóticos atípicos (López-Muñoz et al., 2024). Incluso en las fases iniciales de la era psicofarmacológica ya existían hallazgos ajenos completamente a la influencia de la serendipia, como en el caso de la primera benzodiazepina, el clordiazepóxido (López-Muñoz et al., 2011), o el efecto antipsicótico del haloperidol y de la reserpina (Bhatara et al., 2004; López-Muñoz et al., 2004d; López-Muñoz y Álamo, 2009d).

El descubrimiento y la identificación de nuevas entidades químicas (*new chemical entities*, NCE) ha girado en las 4 últimas décadas, casi exclusivamente, en la tipificación de dianas moleculares sobre las que estos agentes puedan interactuar. Evidentemente, esta es una aproximación reduccionista, denominada por algunos autores como “targephilia”, y que pone el foco únicamente en las dianas de acción de los fármacos (Enna y Williams, 2009). Este paradigma es el que ha triunfado en el desarrollo de los nuevos fármacos antidepresivos y esto ha condicionado, como se pone de manifiesto en los resultados de

esta tesis doctoral, la práctica desaparición de la serendipia en dicho proceso.

Siguiendo este planteamiento, algunos autores han resaltado, reconocido y reivindicado el relevante papel que actualmente juega la serendipia en el proceso de investigación científica. Donald Klein, en su artículo titulado *The Loss of Serendipity in Psychopharmacology*, relaciona la escasa actividad innovadora actual en el ámbito específico de la psicofarmacología, que se arrastra desde hace 40 años, a la ausencia de serendipia, y propone el fomento de la misma a través de una correcta estructuración de los contextos de los procedimientos de investigación (Klein, 2008). En un trabajo más reciente de nuestro grupo, se han identificado diversos factores “anti-serendipia” que podrían explicar este fenómeno apuntado por Klein, como la disminución del tiempo disponible por parte de los investigadores para observar y seguir a los pacientes o la dependencia de la farmacología, y la exigencia por parte de las revistas científicas, de los ensayos clínicos bajo diseño doble-ciego, controlado con placebo, como herramienta indiscutible para demostrar la eficacia de los fármacos (Baumeister et al., 2013). Este tipo de diseño limita enormemente la posibilidad de identificar marcadores de respuesta individuales a los fármacos. Adicionalmente, los típicos ensayos clínicos de fase III en el ámbito de la Salud Mental, aunque pueden involucrar hasta miles de pacientes, sólo cubren un periodo de análisis de 6 a 8 semanas, un periodo relativamente corto para advertir “algo no buscado”, y suelen usar escalas de evaluación para medir los efectos de los fármacos, en vez de la observación clínica longitudinal, aspecto que también constituye un importante factor “anti-serendipia”. Finalmente, el factor más relevante podría ser el giro científico de la farmacología hacia un diseño racional de fármacos basado en la investigación traslacional. Previamente, la selección de fármacos para realizar los ensayos clínicos se basaba principalmente en observaciones concretas de los efectos de los fármacos en el comportamiento de animales o humanos, pero las modernas técnicas permiten, en la actualidad, el rápido desarrollo y detección de miles de compuestos diseñados para actuar sobre dianas moleculares o celulares específicas, lo que reduce tanto la variabilidad de los efectos biológicos de estos compuestos como la probabilidad de que suceda “algo no buscado” y sea reconocido (Oh et al., 2021). Otros autores apuntan factores mucho más concretos, como el desarrollo de las técnicas genéticas y de diagnóstico por imagen, como la resonancia magnética nuclear, de la química combinatoria y computacional, de la cristalografía por rayos X, etc. (Kubinyi,

1999).

El último factor “anti-serendipia” que ha podido jugar un destacado papel en las últimas décadas es la propia estructura de negocio a la que ha evolucionado la industria farmacéutica, lo que se vincula estrechamente con el fenómeno comentado de la falta de innovación en el ámbito de la psicofarmacología (Gribkoff y Kaczmarek, 2023). En la actualidad, el desarrollo de un nuevo medicamento y su puesta en el mercado supone una inversión de 80 a 100 millones de dólares y un tiempo medio de 10 años (Rivera y Gilman, 2011). Estos elevados costes de tiempo y dinero han ejercido una enorme presión sobre las compañías farmacéuticas para reducir el riesgo de que una molécula seleccionada para su desarrollo no sea finalmente aprobada. Para evitar este riesgo y mejorar el éxito en el desarrollo de fármacos, se ha recurrido básicamente a una estrategia generalizada consistente en desarrollar fármacos que sean similares a los que ya han sido aprobados y han mostrado éxito clínico. El resultado ha sido la continua introducción clínica de múltiples fármacos que son prácticamente equivalentes en mecanismo de acción y en eficacia, los llamados medicamentos “*me too*”, cuya rentabilidad final superaría a los agentes innovadores y novedosos (Gribkoff y Kaczmarek, 2023). La restricción en la diversidad de compuestos seleccionados para ensayos clínicos, que es inherente a este enfoque reduccionista, minimiza el posible papel de la serendipia en este proceso (Baumeister et al., 2013).

Todo ello se pone de manifiesto en los datos aportados por Hargrave-Thomas *et al.* (2012), quienes analizaron las pequeñas moléculas aprobadas como medicamentos por la FDA y posteriormente comercializadas hasta 2012, recogidas en el DrugBank. De los 1437 fármacos de estas características en uso clínico, sólo 84 fueron catalogados como descubrimientos serendípicos, lo que supone el 5,8% del total. Por tanto, la serendipia ha continuado ejerciendo su rol en este entorno adverso, que incluye a los medicamentos de imitación, ya que cuando las compañías farmacéuticas han observado un efecto inesperado, pero clínicamente útil y rentable en otra indicación terapéutica durante el desarrollo de un fármaco, no han dudado en variar el enfoque. Tal es el caso del sildenafil (Viagra®), un agente desarrollado como un inhibidor de la fosfodiesterasa para el tratamiento de la angina, pero que acabó comercializado para la disfunción eréctil tras observarse fortuitamente su efecto sobre la erección del pene (Osterloh, 2004). Otros

ejemplos son el minoxidilo, aprobado para el tratamiento de la hipertensión severa y autorizado posteriormente en el tratamiento de la alopecia, al notificarse numerosos casos de crecimiento del cabello en los pacientes hipertensos tratados con este fármaco (Bryan, 2011), o la flibanserina, desarrollada como agente antidepresivo, aunque la mejoría de la función sexual observada en mujeres tratadas derivó su autorización hacia el trastorno del deseo sexual hipoactivo en mujeres premenopáusicas (George et al., 2016).

Es evidente que el ritmo de descubrimiento de agentes farmacológicos eficaces para el tratamiento de las patologías mentales, incluyendo los trastornos del humor, se ha enlentecido en las últimas décadas y esto ha coincidido con una reducción del papel de la serendipia en este proceso. Como se ha comentado, la probabilidad de una observación fortuita está relacionada con la variabilidad de los compuestos probados, los puntos de medición establecidos y el tiempo asignado para observar los efectos. Por otro lado, desmarcarse del diseño racional de medicamentos representaría un retroceso hacia la irracionalidad científica, y potenciar el papel de la serendipia y del azar no constituye, en modo alguno, la solución para el estancamiento del desarrollo de nuevos fármacos. Más bien, la clave podría residir en apoyar la investigación promovida por instancias públicas para evitar el actual enfoque empresarial con excesivo ánimo de lucro y poder desarrollar compuestos novedosos sin la cruda espada de Damocles financiera. Y en este marco, posiblemente la serendipia, como herramienta científica contrastada, podría constituir un estímulo para la promoción de novedosas alternativas terapéuticas.

A modo de conclusión y aunque, como se ha comentado, no existe una definición “oficial” de serendipia, cada vez está calando más el enfoque original de Walpole. Prueba de ello es la edición en español, en 2004, del libro *Serendipia: Descubrimientos accidentales en la ciencia*, de Royston M. Roberts, en la que se traduce el término “*serendipity*” como “condición del descubrimiento que se realiza gracias a una combinación de accidente y sagacidad” (Roberts, 1989). El significado del término serendipia ha virado pues, en los últimos años, incluyendo no solamente los hallazgos científicos debidos al azar y que se alcanzan sin intención directa alguna, sino teniendo presente también el papel de los investigadores sagaces prestos a reconocer e identificar los eventos inesperados. Siguiendo este planteamiento, nosotros no consideramos sinónimas las acepciones “descubrimiento fortuito” y “serendipia”, pues este último

término hace referencia a aquellos descubrimientos en los que intervienen, como condiciones necesarias, tanto la casualidad y el accidente como la sagacidad y perspicacia del investigador. El filósofo y escritor alemán Johann Wolfgang von Goethe ya lo expuso claramente: “El descubrimiento necesita suerte, inventiva e intelecto: ninguno puede prescindir del otro” (cit. Kuhn, 1970).

Ateniéndonos, pues, a estos planteamientos, se debería entender la serendipia, según se ha postulado, más que como una curiosidad literaria, como una construcción básicamente científica. Aunque esto lo advirtió en su momento el gran científico Louis Pasteur: “En el reino de la observación científica, la suerte está reservada sólo para aquellos que están preparados para aprovecharla” (cit. Hofmann, 1980).

CONCLUSIONES

1. La serendipia es un fenómeno que requiere la convergencia de casualidad y sagacidad.
2. La serendipia, en mayor o menor medida, jugó un papel destacado en el descubrimiento y la introducción clínica de los primeros antidepresivos y eutimizantes en los albores de la psicofarmacología moderna durante la década de 1950, aunque su abordaje por la literatura científica ha sido controvertido.
3. En el ámbito de la psicofarmacología de los trastornos del estado de ánimo, los descubrimientos serendípicos puros (patrón de imputabilidad tipo I), en contra de lo que se ha venido postulando en la literatura científica, son más bien escasos. Únicamente se ha identificado el caso del ácido valproico, con el descubrimiento serendípico de su propiedad anticonvulsivante experimental, al emplearlo como agente diluyente, y el posterior descubrimiento, también serendípico, del efecto estabilizante del estado de ánimo en los pacientes epilépticos tratados con valproato.
4. La mayoría de los descubrimientos de agentes antidepresivos y eutimizantes durante las primeras décadas de la era psicofarmacológica presentan un carácter mixto, en el que se mezclan hallazgos serendípicos y no serendípicos, y generalmente siguen un patrón

consistente que parte de una observación inicial serendípica (patrón de imputabilidad tipo II). Tal es el caso de las sales de litio, donde un hallazgo serendípico, la inducción de un estado letárgico en los animales de laboratorio tras la incorporación de estas sales para mejorar la solubilidad del ácido úrico, conduce a un descubrimiento planificado y no serendípico, como fue el efecto eutimizante en pacientes maníacos. También se incluyen en esta categoría la imipramina, inicialmente pensada como un antipsicótico, y la iproniazida, desarrollada como un agente antituberculoso, y la observación posterior no fortuita de la eficacia antidepresiva de ambos agentes en pacientes esquizofrénicos y tuberculosos, respectivamente.

5. Dos agentes antidepresivos más modernos también se pueden encuadrar en este patrón mixto tipo II, en el que hallazgos fortuitos iniciales en el desarrollo de la mianserina, que se investigó como un agente antihistamínico, y la moclobemida, estudiada por sus propiedades hipolipemiantes y de la que se observó un efecto inhibidor de la MAO-A, condujeron, en segundo lugar, a los descubrimientos no fortuitos de sus efectos antidepresivos.

6. Más extraño es el patrón mixto tipo III, adjudicado únicamente a la ketamina, caracterizada por un desarrollo inicial como agente anestésico que conduce a una observación fortuita posterior (el descubrimiento de la eficacia antidepresiva en individuos que la consumían ilícitamente) y a la lamotrigina, desarrollada inicialmente como un agente antiepiléptico, que dio lugar posteriormente al descubrimiento serendípico de sus efectos eutimizantes y preventivos de episodios depresivos en pacientes con trastorno bipolar.

7. El resto de fármacos antidepresivos y reguladores del humor presentan un patrón tipo IV, donde no hay intervención de la serendipia en ningún momento. Tal es el caso de los antidepresivos tricíclicos que siguieron a la imipramina, los inhibidores de la monoaminoxidasa posteriores a la iproniazida, los antidepresivos heterocíclicos, «atípicos» o de «segunda generación», todos los nuevos antidepresivos, desde los inhibidores selectivos de la recaptación de serotonina hasta la actualidad, salvo la esketamina, y la introducción de los antipsicóticos atípicos en el tratamiento del trastorno bipolar (tanto por sus propiedades antimaníacas, como antidepresivas). Todos ellos

siguieron la estela de los primeros fármacos de cada familia y/o siguiendo un procedimiento de diseño racional y dirigido, es decir, una estrategia planificada con antelación, en la que se buscaron fármacos capaces de actuar sobre determinados locus de acción previamente caracterizados.

8. En las últimas décadas, la investigación en el ámbito general de la psicofarmacología y en el campo específico de los trastornos del humor se está alejando de la influencia de la serendipia hacia nuevos enfoques científicos planificados racionalmente, aunque se trata de un proceso gradual.

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ANEXO I



Review

A History of the Pharmacological Treatment of Bipolar Disorder

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Abstract: In this paper, the authors review the history of the pharmacological treatment of bipolar disorder, from the first nonspecific sedative agents introduced in the 19th and early 20th century, such as solanaceae alkaloids, bromides and barbiturates, to John Cade's experiments with lithium and the beginning of the so-called "Psychopharmacological Revolution" in the 1950s. We also describe the clinical studies and development processes, enabling the therapeutic introduction of pharmacological agents currently available for the treatment of bipolar disorder in its different phases and manifestations. Those drugs include lithium salts, valproic acid, carbamazepine, new antiepileptic drugs, basically lamotrigine and atypical antipsychotic agents (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, cariprazine and lurasidone). Finally, the socio-sanitary implications derived from the clinical introduction of these drugs are also discussed.

Keywords: bipolar disorder; pharmacological treatment; mood stabilizer drugs; lithium; antiepileptic drugs; antipsychotic drugs

1. Introduction

Bipolar disorder is a mental pathology that has been known since ancient times and has its origin in the concept of "mania," a term that comes from the Greek "*μανία*," meaning "madness" or "frenzy" [1]. The father of medicine, Hippocrates, already qualified mania as a subtype of mental illness. The term can even be found in the early Ancient Greece literature, as in Homer's *Iliad*, referring to the uncontrolled anger of Achilles against Agamemnon [2]. Philippe Pinel [3] established a series of categories of this type of madness (mania with delirious and non-delirious states) and throughout

the 19th century this entity was closely linked to psychosis. Halfway through the 19th century, with the rise of the anatomoclinic mentality, somatist movements began to emerge in the field of psychiatry. In this context, Jacques-Joseph Moreau de Tours and Wilhelm Griesinger postulated a structural alteration of the brain as the etiological basis of “madness” [4]. Finally, in this anatomoclinical atmosphere, Emil Kraepelin, at the end of the 19th century coined the concept of manic-depressive psychosis and dissociates this disorder from the so-called dementia praecox (schizophrenia) [5]. In the 1950s, Karl Leonhard first introduced the concept of polarity in understanding affective disorders [6], which would later be included among the DSM diagnostic criteria in *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (APA). Accordingly, there would be unipolar patients, who only experience depressive episodes and bipolar patients, presenting a manic or hypomanic episode [7].

Until relatively recent dates, bipolar disorder had not received properly deserved scientific and social recognition as it enjoys today [8]. Due to “scientific negligence,” compared to other psychiatric disorders—for example, major depression or schizophrenia—the lack of knowledge about its etiopathogenesis, the erroneous underestimation of its prevalence and the status of therapeutic pseudo-orphanage had not been amended until almost two decades ago [9]. In fact, until the mid-1990s, before valproate’s anti-manic efficacy was demonstrated, the only drug available for treating those patients was lithium salts.

From a current scientific research perspective, bipolar disorder is an emerging pathology [9]. From a clinical perspective, it presents an important morbidity/mortality [10]. The well-known epidemiological studies Epidemiological Catchment Area Study (ECA) in 1981 and National Comorbidity Survey (NCS) in 1991 estimated the prevalence of bipolar disorder in about 1% of the population and it is currently estimated that its prevalence throughout the lifespan is between 1% and 2% of the population over 20 years of age [11]. It is a serious mood disorder of a chronic nature, characterized by the constant or irregular appearance of alternative episodes of mania/hypomania with euthymia/depressive episodes [12]. Traditionally, a difference has been made between bipolar disorder type I, which is characterized by the presence of, at least, a manic or mixed episode in combination with depression; and bipolar disorder type II, characterized by one or more depressive episodes, with at least one episode of hypomania lasting longer than four days, with bipolar disorder type II being more frequent than type I. Cyclothymic disorder has a recurrent and chronic course, with greater symptomatic oscillation but of less severity than that observed in bipolar disorder types I and II. Between 15–50% of cyclothymic patients usually progress to either bipolar disorder type I or, mainly, to type II [13]. Nevertheless, nowadays a tendency exists to consider this pathology from a broader context, including all those cases with less obvious and apparent clinical manifestations. This way of approaching the disease, called “bipolar spectrum,” implies prevalence ranging from 2.8% to 6.5% of the population [10,14–16].

Bipolar disorder, largely due to its chronic and recurrent course, poses an important burden for the patient, the family and the society and its treatment is essential to avoid the main complications of the disease. In developed countries, bipolar disorder is ranked among the top 10 causes of disability [17]. According to the World Health Organization (WHO), bipolar disorder is the fourth cause of neuropsychiatric disability in people aging 15–44 years. Additionally, the use of health resources that bipolar patients make is greater than that of patients with depressive or chronic medical conditions [18]. One should also bear in mind that the most serious complication of bipolar disorder is suicide. Between 25–50% of patients with bipolar disorder attempt suicide, with prevalence of 32.4% and 36.3% for bipolar disorder type I and type II, respectively [19]. It is in the depressive phase that most attempts and completed suicides occur. Other important burdens associated with bipolar disorder are increased mortality from medical causes, substance abuse (mainly alcoholism), comorbidity with other psychiatric disorders such as anxiety, behaviour and eating disorders and chronic affective symptoms. To note, bipolar disorder patients have enormous economic burden of this disorder, estimated in the USA to be about \$31 billion in direct costs and \$120 billion in indirect costs [20].

Until the discovery of lithium's antimanic effect, the pharmacological tools used in clinical practice had limited efficacy, not only in this type of patient but in the entire field of mental pathology [21]. This was in part a result of the inheritance and influence of Benedict Agustin Morel, a degenerationist who considered that the cause of mental disorders was hereditary transmission, implying their incurability [4]. Yet, during the first half of the 20th century, the first drugs used systematically in the treatment of manic patients were introduced, with barbiturates standing out among them. The antimanic efficacy of lithium salts was confirmed during the 1950s and in the late 1960s it was finally demonstrated in Europe that lithium was effective in the prophylaxis of manic-depressive episodes in bipolar disorder [22]. But the Food and Drugs Administration (FDA) of the United States resisted to authorize this drug for its antimanic indication until 1970 [23] and for its indication as maintenance/prophylactic treatment of manic-depressive episodes until 1978. Twenty-eight years later, in 1995, valproic acid, an anticonvulsant agent, was approved by the FDA for its antimanic indication. In parallel to valproic acid, carbamazepine, another antiepileptic drug, was developed for the treatment of patients with bipolar disorder. This drug has been authorized by numerous regulatory agencies in multiple countries and enjoys a good acceptance by psychiatrists worldwide. Finally, since 2000, different atypical antipsychotic drugs (AADs) have been authorized by the FDA for their antimanic (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, etc.) or antidepressant indication (quetiapine, lurasidone). Lamotrigine, a modern antiepileptic agent, has been authorized for the prevention of depressive episodes in bipolar disorder. Table 1 shows the most important historical milestones in the pharmacological treatment of bipolar disorder. Overall, the pharmacological treatment of bipolar disorder is complex and treatment guidelines exist for its different phases—manic episodes, depressive episodes and maintenance (or prophylaxis) periods. In this sense, polypharmacy combining drugs from different therapeutic groups and different mechanisms of action is the norm rather than the exception.

Table 1. Key milestones in the history of the pharmacological treatment of bipolar disorder.

Year	Important Events
1817	Isolation of lithium (Arwedson and Berzelius)
1832	Synthesis of chloral hydrate (von Liebig)
1857	Introduction of bromides as hypnotic-sedatives (Locock)
1863	Synthesis of barbiturates (von Baeyer)
1868	Description of the sedative-hypnotic properties of <i>Solanaceae</i> alkaloids (Schroff)
1869	Use of chloral hydrate as a hypnotic (Liebreich)
1870	Use of chloral hydrate in manic patients (Elstun)
1880	Isolation of hyoscine or scopolamine (Ladenburg)
1881	Synthesis of valproic acid (Burton)
1903	Introduction of barbitol in medicine (Fisher and von Mehring)
1912	Marketing of phenobarbital
1915	Introduction of barbiturate sleep cures (Epifanio)
1920	Application of morphine and scopolamine "sleep cures" (Klaesi)
1943	Introduction of promethazine in psychiatry, for the treatment of manic symptoms (Daumézou)
1949	Introduction of lithium in the management of manic and schizophrenic disorders (Cade)
1954	First controlled clinical trial with lithium in manic patients (Schou)
1957	II World Congress of Psychiatry (Zurich): first classification of psychotropic drugs (Delay) International Symposium on Psychotropic Drugs (Milan): first specific scientific meeting on psychotropic drugs
1958	Foundation of the Collegium Internationale Neuropsychopharmacologicum
1960	Confirmation of the prophylactic effect of lithium salts in manic episodes (Schou)
1961	Synthesis of carbamazepine (Schindler) Foundation of the American College of Neuropsychopharmacology
1963	Discovery of the anticonvulsant effect of valproic acid (Carraz)
1966	First data on the antimanic effect of valproic acid (Lambert) First systematic study on the effectiveness of lithium in the USA (Wharton and Fieve)
1970	Demonstration of the prophylactic properties of lithium in manic-depressive psychosis (Schou) Approval of the clinical use of lithium (USA FDA)
1971	Use of carbamazepine as mood regulator (Takezaki and Hanaoka)

Table 1. Cont.

Year	Important Events
1973	Approval of chlorpromazine in the treatment of manic episodes (USA FDA) Publication of the book <i>Lithium: its role in psychiatric research and treatment</i> (Gershon and Yuwiler)
1978	Approval of lithium salts for the prevention of manic/depressive episodes (USA FDA) First study about the antimanic effects of carbamazepine in the West (Ballenger and Post)
1994	First controlled trial with divalproex in mania (Bowden) First publication on the efficacy of lamotrigine in bipolar disorder (Weisler)
1995	Approval of valproic acid as an antimanic drug (USA FDA)
1999	First controlled trial with olanzapine in manic episodes (Tohen)
2000	Approval of olanzapine in bipolar disorder (USA FDA)
2003	Approval of risperidone in bipolar disorder (USA FDA) Approval of the combination olanzapine-fluoxetine in depressive episodes of bipolar disorder (USA FDA) First controlled trials of lamotrigine on relapse prophylaxis in bipolar disorder (Bowden and Calabrese)
	Approval of lamotrigine for the prevention of depressive episodes of bipolar disorder (USA FDA)
2004	Approval of quetiapine, zipresidone and aripiprazole in bipolar disorder (USA FDA) Approval of olanzapine for the prevention of new episodes of bipolar disorder (USA FDA)
2005	Approval of aripiprazole for the prevention of new episodes of bipolar disorder (USA FDA)
2007	Approval quetiapine for the prevention of new episodes of bipolar disorder (USA FDA)
2008	Approval of quetiapine in depressive episodes of bipolar disorder (USA FDA)
2009	Approval of asenapine in bipolar disorder (USA FDA) Approval of risperidone and ziprasidone for the prevention of new episodes of bipolar disorder (USA FDA)
2013	Approval of lurasidone in depressive episodes of bipolar disorder (USA FDA)
2015	Approval of cariprazine in bipolar disorder (USA FDA)

2. The Therapeutic Precedents of the Psychopharmacological Era

Until the clinical introduction of lithium salts, sedatives [24] were the main axis of pharmacological treatment of manic symptoms. During the second half of the 19th century, a time referred to by some authors as the “alkaloid period” [25], those agents were the most used sedatives. They were introduced into psychiatric care thanks to the isolation of morphine from opium in 1805 by Friedrich Wilhelm Sertürner [26]. In the book *Traité des Maladies Mentales*, published in 1865, Griesinger noted that anxious and agitated patients improve after receiving opium [27]. Hashish was also used as a sedative and its effects were studied in depth by Moreau de Tours [28]. But the most successful alkaloids in psychiatry were isolated essential chemicals of various components of the *Solanaceae* family (Figure 1), the plants known for their hallucinogenic effects. One of them was hyoscyamus, which was isolated in 1839 by chemists from the company E. Merck (Darmstadt, Germany) to show their sedative and hypnotic properties as described in 1868 by the Viennese pharmacologist Karl Schroff. Hyoscyamine was another alkaloid that became a popular ingredient in many cocktails in the latest years of the 19th century. Finally, in 1880, another hyoscyamine alkaloid—hyoscine—isolated by Albert Ladenburg in Germany. Hyoscine (called scopolamine in North America) was then also a widely used ingredient in psychiatric cocktails (such as the famous Hyoscine CoA, containing hyoscine, morphine and atropine), was often used in controlling highly excited and aggressive manic patients [29,30].

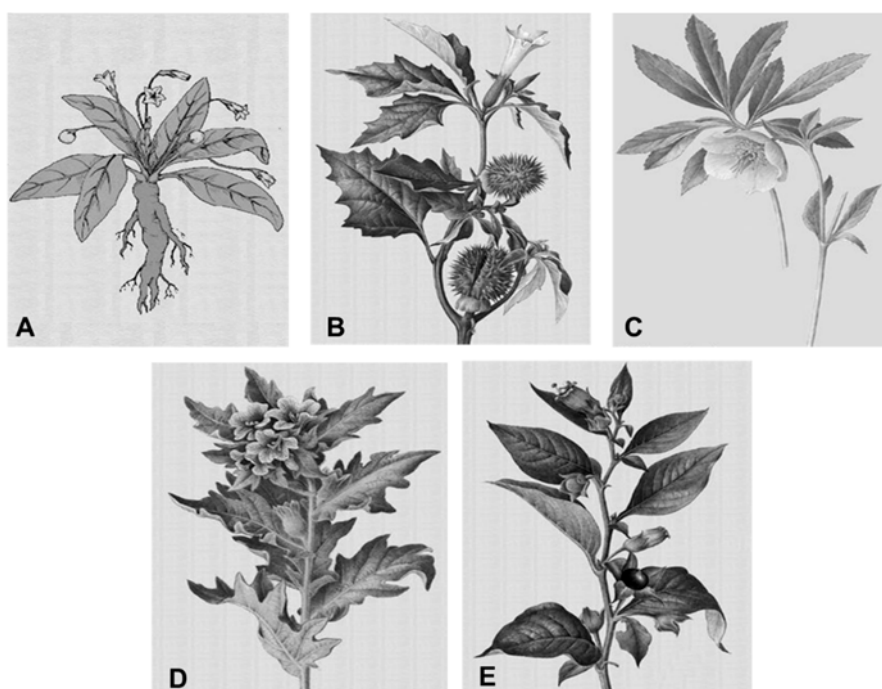


Figure 1. Illustrations of the most relevant plants in the *Solanaceae* family, from which several alkaloids were obtained to be used in psychiatric practice as sedatives prior to modern psychopharmacology: (A) Mandrake (*Mandragora officinalis*); (B) Stramonium (*Datura estramonio*); (C) Eleboro (*Helleborus niger*); (D) Hellebore (*Hyoscyamus niger*); (E) Belladonna (*Atropa belladonna*).

The advent of synthetic chemistry was another of the great milestones in pharmacology in the 19th century, because for the first time in history, synthesized substances instead of existing nature plants with biological activity were produced [31]. Chloral hydrate was first produced synthetically [32]. Synthesized in 1832 by a chemist from Giessen, Justus von Liebig, it was not assessed as a hypnotic until 1869, by the pharmacologist Mathias Otto Liebreich. The following year, the American psychiatrist William J. Elstun reported that 5 patients (3 manic and 2 melancholic) from Indiana Hospital for the Insane improve after receiving chloral hydrate [33]. Soon chloral hydrate was replacing both morphine and solanaceous alkaloids because it could be conveniently given orally. Among its great contributions to the history of psychopharmacology, chloral hydrate was the first drug to make home treatment possible, without the need to have a patient admitted to a psychiatric institution [25].

Bromides were another therapeutic contribution in the 19th century [32]. Isolated in 1826 by the pharmacist from Montpellier, Antoine Balard, bromine was used as an iodine substitute as a food additive. It became popular in France, where they could already observe that bromine salt-induced sedation (*"inveresse bromurique"*). Although first used as antiepileptics, bromides in the second half of the 19th century were widely used as sedatives for this indication in 1857 by the London internist and Queen Victoria's obstetrician, Sir Charles Locock (Figure 2). Similarly, they were also used as one of the best remedies for controlling agitation in psychotic manic and melancholic patients, as well as those affected by different phobias, which were favourably used in European asylums and mental hospitals. The use of bromides had extended until the early years of the 20th century [34].

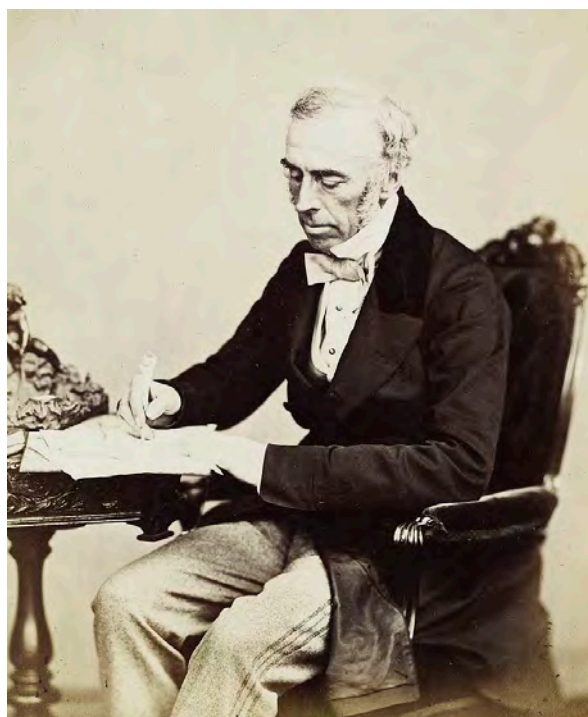


Figure 2. Portrait of Sir Charles Locock (1799–1875) dated 1862. Locock was an obstetrician, First Physician Accoucheur to the Queen Victoria and a member of the St. Albans Medical Club.

By the end of the century, new drugs with sedative activity were added to this therapeutic arsenal. Those drugs—ecodine, papaverine, chloroform, chloral syrup, paraldehyde, carbamide acid, or hydrocyanic acid—were isolated in pharmacology laboratories. Even a treatment with adrenal cortex extracts was suggested, following the observation that serum cholesterol levels were increased in bipolar patients [35,36]. Subsequently, the introduction of some nonspecific chemical preparations included succinic dinitrile, malonic nitrite, or lactic acid, although delivering unsatisfactory results [37]. Another commonly used drug was sodium diphenylhydantoin (Dilantin®), tested by Kalinowsky and Putnam [38] but producing only limited success in cases of manic excitement.

Without a doubt, barbiturates had been the most widely used agents in treating manic patients during the first half of the 20th century and until the mid-1950s [39,40]. Chemically, those uranium compounds have a six-element ring structure, with a central nucleus of malonylurea. They were synthesized in 1863 by Adolf von Baeyer (Figure 3). Barbitol (diethyl-barbituric acid) was the first agent of this family introduced clinically as a hypnotic in Germany. It was marketed in 1903 by the company Bayer & Comp. (Elberfeld, Germany) under the name Veronal® (Emil Fischer and Joseph von Mehring), although it had been synthesized long before (1882) by Max Konrad and Max Guthzeit. This drug was presented itself as an anticonvulsant, then a sedative and, eventually a hypnotic. Veronal® was found to calm manic patients, restore sleep in melancholic patients and induce sleep in patients with insomnia [39,40]. Due to changes in chemical structure of the barbituric acid molecule, more than 2500 different barbiturates were synthesized but only about 50 of them have ever been on the market. One of the first such drugs and perhaps the most used later, was phenobarbital, marketed in 1912 by the company Bayer under the name of Luminal®. This long-acting drug, was widely used as an antimanic, anxiolytic and anticonvulsant; other barbiturates with short and intermediate action (such as secobarbital, amobarbital, pentobarbital, etc.) were initially used as hypnotics [39].

Figure 3. Adolf von Baeyer (1835–1917), discoverer of barbituric acid, in the centre, with a hat in his hands, together with his team from the Chemistry Laboratory of the Munich Academy of Sciences in 1893.

The hypnotic properties of some barbiturates were quickly used in treating psychotic and manic patients, as they induced a deep and prolonged sleep state [41]. The pioneer in the use of these techniques was the Italian psychiatrist Giuseppe Epifanio, assistant at the University Psychiatric Clinic of Turin. Published in 1915 in an Italian journal in the middle of World War I, this article did not get proper attention from the international scientific community [42]. The clinical introduction of those techniques is attributed historically to Jakob Klaesi, a psychiatrist at the University Clinic of Zurich (Figure 4A). Klaesi enjoyed great prestige at the time right after he proposed his sleep cures in 1920 [43]. These techniques consisted of premedication with morphine and scopolamine, as well as the use of the so-called Cloetta or Cloetta mixture [44,45] containing barbiturates rectally, namely hyalhydrate, alcohol, chloral hydrate, digitaline, paraldehyde, and ephedrine. The main clinical indications of “sleep cures” were manic excitations and agitated depressions, although they were also tested in schizophrenia with less satisfactory results [41]. Another preparation of these characteristics was the so-called Cloetta or Cloetta mixture [44,45], using barbiturates rectally, amyl hydrate, alcohol, chloral hydrate, digitaline, paraldehyde, and ephedrine. The main clinical indications of “sleep cures” were manic excitations and agitated depressions, although they were also tested in schizophrenia with less satisfactory results [41].

Figure 4. Jakob Klaesi (right) (1883–1980) with the Burghölzli Hospital psychiatric staff, including its director, Eugen Bleuler (centre), in a photograph taken around 1910 (A) and a container of Somnifen drops of the first third of the century 20th century, commercialized in Spain by F. Hoffmann-La Roche & Cie, Paris (B).



A



B

Figure 4. Jakob Klaesi (right) (1883–1980) with the Burghölzli Hospital psychiatric staff, including its director, Eugen Bleuler (centre), in a photograph taken around 1910 (A) and a container of Somnifen drops of the first third of the century 20th century, commercialized in Spain by F. Hoffmann-La Roche & Cie, Paris (B).

3. Lithium as an Antimanic Agent

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Lithium is coined from the Greek “lithos,” meaning stone. Chemically, lithium is the simplest drug among those used in psychiatric therapy, as it is the lightest metal in nature. The distribution of this metal in small quantities is wide, being detected in seawater, the water of rivers and springs, the organs of different animals, the remains of many plants and even in meteorites [46].

Lithium and mental disorders enjoy a long story. Although the great Greek, Roman and Arab classical authors did not specifically mention lithium in their medical works, the use of alkaline waters for the treatment of the mental illness known as “mania” dates from the time of Gaius Aulianus, in the fifth century, in the fifth section, dedicated to the treatment of mania of this author, who wrote: *quoque naturalibus aquis, ut in nitrosæ (natural (waters) such as those of alkaline springs must be used)*. In 1817, this alkaline metal was isolated from a mineral known as petalite by the Swedes Johann August Arfwedson (Figure 5A) and Jöns Jakob Berzelius (Figure 5B) and they originally named it lithium. Since lithium has been incorporated into therapeutics, being used in treating different pathologies, both organic (gout and cancer, for example) and neurological (epilepsy) [47,48].



Figure 5. Mid-nineteenth century lithographs of the two Swedish chemists responsible for the discovery of lithium: Johann August Arfwedson (1792–1841) (A) and Jöns Jakob Berzelius (1779–1848) (B), Professor of Chemistry and Pharmacy at the Karolinska Institute. Both were members of the Royal Swedish Academy of Sciences.

In addition, one should consider the great popularity that, around the years of the turn of the century, the intake of water gained, mainly in the USA. In that series of the years of the turn of the century, the intake of water was commercialized in the USA. Thus, a series of products that supposedly contained lithium water were commercialized, using aggressive advertising stunts. Such is the case of Buffalo Lithia Water (“the best natural remedy for excess uric acid in blood”), Tedyffrin Water (“cures dyspepsia, rheumatism, Bright’s disease and dissolves bladder stones”), or Manadnock Lithia Spring Water (“the most wonderful spring water known in the world”). Even a beer manufactured with lithium water (Lithia Beer), was marketed in Wisconsin and it was highly appreciated in those decades (Figure 6). All of those stated in their instructions that they were harmless and effective remedies for treating all kinds of nervous disorders [47]. But the decline in consuming lithium waters and, therefore, the popularity of lithium, took place at the end of the first decade of the 20th century, as the public came to know that these products only contained spectroscopically traces of lithium and, above all, due to the first cases of intoxication of cardiac patients, as a consequence of chronic use [49]. In *The Practitioner*, several cases of “cardiac depression and even dilation as a result of an excessive and continued consumption of lithium tablets” were reported in 1907 [50]. In spite of all this, in 1929, Charles Leiper Grigg (Howdy Corporation, St. Louis, MO, USA) invented the 7-UP Lithiated Lemon Soda, with the advertising claim of “an abundance of energy, enthusiasm, clear complexion

complexion and shining eyes,” referred to simply as 7-UP since 1936, although lithium was part of its composition until the 1940s, coinciding with the North American cases of toxicity discussed above [51].

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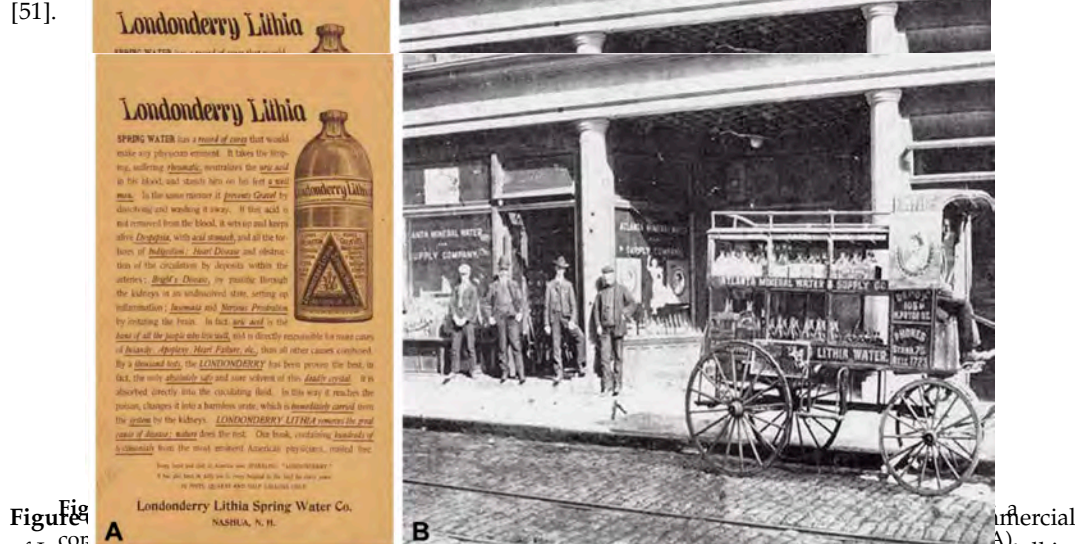


Figure 6. Londonderry Lithia Spring Water Co. (A) and a photograph of the late 19th century of the head office and distribution system of Atlanta Mineral Water and Supply Co. (Atlanta, GA, USA) (B), advertising its Lithia Water.

In the mid-nineteenth century, the rise of the “uric acid diathesis” theory, proposed by Sir Alfred B. Garrod, advertising its Lithia Water, played an important role in the introduction of lithium into pharmacological therapy [52]. In 1859, Alexander Ure, a surgeon at the Western Ophthalmic Institution (London), could dissolve bladder stones in a lithium carbonate solution [47]. Almost at the same time, Garrod could verify, in the corpses of patients with gout, that when phalanges with deposits of uric acid were introduced in lithium, potassium or sodium carbonate solutions, the quickest dissolution of such deposits occurred in lithium carbonate. This theory was based on the observation that, in test tubes, lithium salts could dissolve urate deposits from cartilage. Hence, lithium was becoming widely used in treating kidney stones, rheumatism and gout [53]. In fact, in the United Kingdom, lithium was sporadically and unofficially used in treating gout until the 1970s [54].

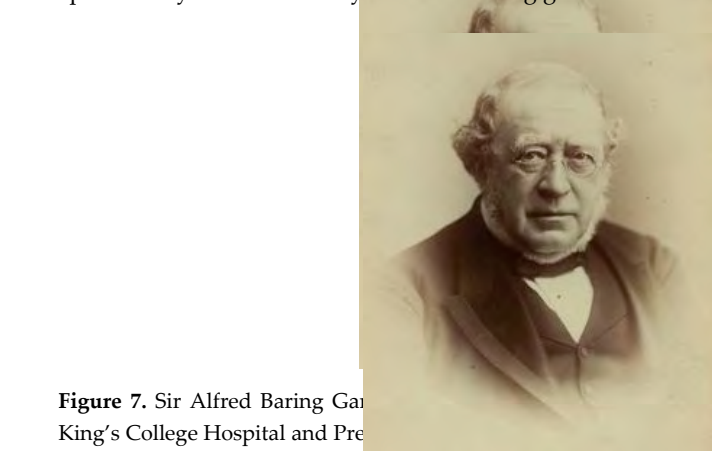


Figure 7. Sir Alfred Baring Garrod (1819–1907), professor of Materia Medica and Therapeutics at King’s College Hospital and President of the Medical Society of London in 1860. He was knighted as “Sir Alfred Baring Garrod” and in 1890 was appointed “Physician Extraordinary” to Queen Victoria.

Similarly, some of mental disorders were hypothesized to be related to having high levels of urates, being referred to as “gout that affects the head” and “gouty mania”. Lithium treatments were also recommended in those patients [47]. It even came to be occasionally used in treating other psychiatric disorders. For example, the American general surgeon William Hammond (Bellevue Hospital in New York) (Figure 8A) used lithium bromide in treating acute mania, although he could not discern whether the effects observed were (Figure 8A) used lithium bromide [55], and the Danish internist Carl G. Lange (University of Copenhagen) (Figure 8B) stated in 1886 that the use of a mixture containing lithium was capable of preventing the so-called “periodic depression” [56]. On the other hand, in the British Isles, as Henderson and Gillespie [57] recalled that lithium waters were believed to have important virtues for treating mental illness. Even much earlier, Sir John Floyer, in his book *History of Cold Bathing* (1722), described that the success achieved in a case of mania with a lithium-based treatment. Still, all these events went completely unnoticed for many years.



Figure 8. Pioneers in the use of lithium in the treatment of mental disorders: William Alexander Hammond (1828–1900) (A), Surgeon General of the United States Army, professor of anatomy and physiology at the University of Maryland School of Medicine, professor of Nervous and Mental Diseases at Bellevue Hospital and at the New York University; and Carl Georg Lange (1854–1900) (B), Danish physician who made contributions to the fields of neurology, psychiatry and psychology.

The interest in lithium came back in 1927, when the use of lithium bromide in the treatment of epilepsy was postulated. The key contribution was from David M. R. Culbreth, who observed that lithium bromide was the most sedative and hypnotic of all bromides [47]. Yet, it would not be until the end of the 1940s when lithium salts finally became part of the therapy of mental illnesses.

As in many other events in biomedical research, chance played an important role in the introduction of lithium into the psychopharmacological arsenal [58,59]. Thanks to the careful observation of Australian psychiatrist John F. Cade (Figure 9), who in 1949 was Senior Medical Officer, in the Victorian Department of Mental Hygiene of Australia (Superintendent in the Repatriation Mental Hospital of Bundora, Victoria, Australia), he noted how patients with thyroid endocrine diseases presented themselves symptoms that were similar to the clinical manifestations of manic-depressive disorder, so that individuals with hyperthyroidism experienced symptoms similar to those seen in individuals in the manic phase, while the traits of thyroid hypofunction were resembling those of the depressive phase [60].

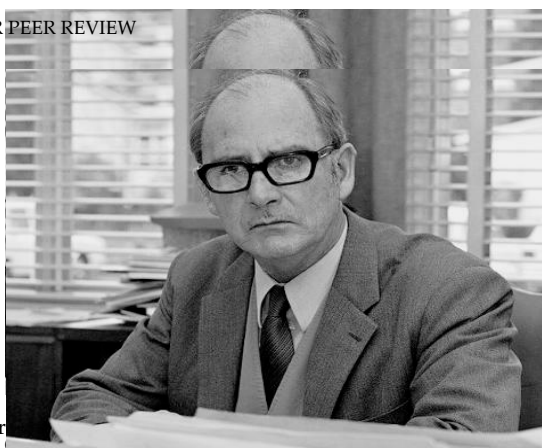


Figure 9. John Frederick Cade (1912–1980), authentic pioneer of modern psychopharmacology with his experiments on lithium.

Given this similarity, the Australian psychiatrist questioned whether at the origin of manic-depressive illness is a hormonal dysfunction of some toxin that was being excreted in the urine and so he designed a series of interesting animal research studies (Figure 10). Initially, he collected urine samples from manic and melancholic patients, as well as from healthy controls and after a process of concentration, he injected them intraperitoneally to guinea pigs, at different doses. Some animals which had been treated with high doses of urine suffered convulsive movements, prolonged unconsciousness and even died, which reaffirmed Cade's idea that the urine of these patients could have contained some sort of toxic substance. At first, he believed that this substance could be urea, but he observed that the urine of manic patients was markedly more toxic than the rest, even when the amount of urea or creatinine was similar between manic and non-manic patients. This study finding made Cade to think that another substance should exist to increase the toxicity of urea, such as uric acid.



Figure 10. The kitchen at Bundoora Repatriation Mental Hospital where John Cade conducted some of his lithium experiments.

Figure 10. The kitchen at Bundoora Repatriation Mental Hospital where John Cade conducted some of his lithium experiments. To demonstrate this theory, Cade designed a study based on giving laboratory animals of a solution with urea and different concentrations of uric acid (Figure 11). Due to the poor solubility of this substance, Cade turned to lithium urate, a much more soluble salt and surprisingly found that the injection of this salt at 0.5% in the 8% urea solution protected the animals from the previously observed convulsive phenomenon. In addition, the animals did not respond to stimuli, not even painful ones and their mobility and appetite for food considerably have been decreased. These observations led Cade to investigate the effects in guinea pigs of the exclusive

administration of lithium carbonate. Two hours after having received test drug, animals showed a state of lethargy, which was reversed another two hours later [47,48].

10/10/49

1. Tan 9 white ♂, white l. bear paw. 1003.
 2. Grey tan w. ♂, 3 paw pink, R.R. paw black. 1503.
 3. White ♂, black paw & ears. 1303.
 4. B.T. ♀, R.R. quarter tan, L. rear quarter black. 703.
 5. Grey ♀ tan belly. 1303.

G.P. ① = 1003. 7.5 cc 8% urea aa { 16% urea
 at 12:19 PM reduced ppt from shake.
 N.H.D. at 12:09 PM 0.75 cc / 03 body wt.

G.P. ② = 1303. 16 1/2 cc at 12:54 PM 1.25 cc / 03 body wt.
 N.H.D. at 2:10 PM

G.P. ③ = 703. 12 1/2 cc at 2:17 PM 1.5 cc / 03 body wt.

G.P. ④ = 1503. 20 cc of 8% urea aa { 16% urea
 at 2:47 PM supersaturated lemon coloured
 fluid removed from ppt.
 1.3 cc / 03. 3:20 PM - nothing noteworthy. This contains approx. 5% NaCl.
 3:30 - translucent & acidic, myoglobin - for spec! Mrs. N.H.D. following 4 PM

Figure 11. Laboratory notes by Cade regarding the effects of the injection of different compounds and lithium salts to guinea pigs.

The results of these studies made Cade to think of the possible benefit that certain manic patients could experience after the giving those lithium salts. But before taking this step and following the great experience of the previous century and under the Hippocratic principle of *primum non nocere*, he had lithium citrate self-administered to assess its safety. Immediately after testing the absence of toxicity on himself—which is not illustrative, given his high level of tolerance to suffering after his having spent three years as a prisoner-of-war in the Japanese POW camp of Changi, Singapore, during World War II—he administered, on 29 March 1948, 1200 mg/day of lithium citrate, three times a day in divided dose, to a 54-year-old man, Mr. W. B. in manic excitement of five years of evolution. After a five-days treatment, the patient was eventually improved. He left the hospital four months later, with a daily ambulatory treatment of 300 mg of lithium carbonate, twice a day, because this salt caused less nausea than citrate. The recovery was so clear that the patient could be also studied by Cade before his admission. Cade observed the same results in nine other patients, obtaining the best responses in excited individuals. The effects of lithium were also studied in 6 patients with schizophrenia with agitation and in 3 patients with chronic melancholic depression. The results of these studies were published in 1949, in an article in *The Medical Journal of Australia*, entitled “Lithium salts in the treatment of psychotic excitement” (Figure 12) [61]. This publication is considered by many authors as the starting point of the so-called “psychiatric pharmacology revolution” [62,63]. The summaries of this work consisted of the following:

- Lithium salts showed great efficacy in the treatment of manic disorder and they did so in a short period of time for the first time in years. All of them returned to their original state when lithium was stopped.
- The effectiveness of lithium in chronic depression was not shown.
- The recommended dosage regimen was 900 mg/day, to be divided in 300 mg 3 times a day until clinical improvement was observed and 300 mg/day during the maintenance period.
- The discontinuation of lithium treatment led to the reappearance of manic symptoms.
- The recommended dosage regimen was 900 mg/day to be divided in 300 mg 3 times a day, until clinical improvement was observed and 300 mg/day during the maintenance period (etc.)—
- The discontinuation of lithium treatment led to the reappearance of manic symptoms.
- The adverse effects of lithium therapy have two—digestive system (nausea, vomiting, diarrhoea, abdominal pain, etc.) and nervous system (tremors, dizziness, asthenia, depression,

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etc.)—categories of side effects, which were disappeared quickly in 2 to 4 days) after lithium discontinuation. To resume treatment, the patient needs to start receiving from a lower dose, or discontinue. To substitute for citrate, since carbonate salt is more soluble and more easily absorbed, as to substitute for citrate, since carbonate salt is more soluble and more easily absorbed.



Figure 12. Medical Journal of Australia, Volume 3, September 1949, in which the results of the clinical experiments by John Cade about lithium salts and the handling of hectic manic and schizophrenic patients were published [61].

Nevertheless, in spite of the interesting perspectives that Cade's work posed, lithium salts did not become widely used in psychiatry until the mid-1960s, as a result of a series of events that unfortunately coincided in time. This is the case of the clinical introduction and upsurge of neuroleptic drugs, which set aside the scientific interest in lithium. Also, many fatal poisonings that occurred in the late 1940s in the USA, when those lithium salts were marketed as a substitute for sodium salts in patients with heart disease [48,64,65]. Then, the media contributed to the discrediting of this drug. Additionally, Cade himself stated, "The discovery made by an [66] Cade psychiatrist, who was not really maintaining in a small provincial hospital with primitive psychotropic effects and other alkali metals such as rubidium and caesium. Cade further recalled that, "in March 1949, lithium was effectively excommunicated as a therapeutic tool, at least in the United States" [67].

For its part, Kline [68] lists another series of reasons that prevented the scientific recognition and clinical use of lithium in the treatment of bipolar disorder. Also, their lack of understanding of how a single substance could show efficacy against both mania and depression. In addition, he points out the absence of commercial interest that the pharmaceutical industry could have in a natural substance that was cheap to obtain and not patentable. It is also worth noting that some clinical trials, poorly designed from the methodological point of view (in which lithium serum levels had to be monitored

for safety reasons) and drew negative results. In any case, the loss of interest in lithium was such that even in the prestigious work Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, in its 1960 edition, stating "The lithium ion has no therapeutic applications. The only pharmacological interest in lithium lies in the fact that it is a toxic ion" [69].

even in the prestigious work Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, in its 1960 edition, stating "The lithium ion has no therapeutic applications. The only pharmacological interest in lithium lies in the fact that it is a toxic ion" [69].

Cade's communication attracted the attention of other Australian researchers who delved into the contributions of this author [70,71]. The Danish psychiatrist, Mogens Schou (Figure 13) stood above all of them. In his family, some members had manic-depressive disorder. He and his team from Aarhus, Denmark—mainly his colleague Poul Christia Bastrup (Figure 13)—started the first randomized clinical trials using this drug in the history of psychiatry [72]. This phenomenon was defined by Cade [66] as the "pharmacological rehabilitation of lithium". [The first of those clinical trials was a crossover study, placebo-controlled, alternating weeks of lithium or placebo treatment with lithium and two weeks of placebo, which verified Cade's observations. Published in 1954, the study results confirmed that of the 30 patients with typical mania that had been included, 12 (40%) have shown clinical response to lithium and a worsening of symptoms with placebo. Additionally, another 15 patients have also shown clinical improvement, although it was not possible to differentiate whether such improvement is from a natural remission [73].]



Figure 13. Three great pioneers of the clinical introduction of lithium: Poul Christia Bastrup (a), John Cade (b) and Mogens Schou (c).

Much of the success of the American "pharmacological rehabilitation of lithium" is directly credited to Samuel Gershon (University of Melbourne, Melbourne, Australia), who worked with John Cade before his emigrating to the USA. Gershon convinced many American psychiatrists of the therapeutic efficacy of lithium and published the first article on lithium and mania in the USA [74]. Later, in collaboration with Baron Shopsin, he published another one that, with time, would become the "bible" of pharmacological treatment with lithium salts—"Lithium: its role in psychiatric research and treatment" in 1973 [75].

Steadily, the clinical efficacy of this ion was confirmed. Studies carried out by the group of Schou and Ronald Mags (Hellingly Hospital at Hailsham, Sussex, UK) [77], under a placebo-controlled study, have demonstrated the superior efficacy of lithium in manic patients. The first American study, carried out by the group of Schou and Ronald Mags (Hellingly Hospital at Hailsham, Sussex, UK) [77], under a placebo-controlled study, have demonstrated the superior efficacy of lithium in manic patients. The first American study carried out with the effectiveness of lithium was published in 1966 by Ralph Wharton and Ronald Freve of New York State Psychiatric Institute. The investigators evaluated 19 patients who had been previously unsuccessfully treated with phenothiazines or electroconvulsive

therapy [78]. Two years later, Gordon F. S. Johnson (University of Sydney, Sydney, Australia) and Gershon published the first study of a prospective, controlled double-blinded clinical trial. In their study, the investigators compared lithium and chlorpromazine, a standard treatment for mania, in a total sample of 41 patients. Those authors have obtained a complete or almost complete remission after eight days in 78% of the manic patients treated with 1.5–2 g/day of lithium, compared to only 36% of those who received chlorpromazine [79]. Subsequent studies would also confirm the superiority of lithium against chlorpromazine [80–82].

Finally, several highly relevant clinical trials were launched in the late 1960s with public funds from USA Veterans Administration and the National Institutes of Mental Health that dramatically changed the attitude of American physicians towards lithium [83]. In parallel, in the second half of the 1960s, there was a real conflict in the USA between the health authorities and some psychiatrists regarding the therapeutic use of lithium salts, a battle won by the latter. The great champion of this struggle, according to Ayd [84], was Paul H. Blachly, a Professor of Psychiatry at the University of Oregon, who requested that the FDA change its consideration of lithium carbonate, so that it could be given a clinical use. After many bureaucratic obstacles, he received a negative response, despite several appeals to the USA Congress and Senate. Blachly's final move was to write an aggressive article in the journal *Psychiatric Opinion*, entitled “FDA vs. physician: does the physician have a moral obligation to civil disobedience?” in which he concluded that physicians should have a moral obligation to rebel against health authorities that, as in the case of lithium, exceedingly restricted their prescription rights [85]. Popular pressure and the evidence from the afore-mentioned mentioned clinical trials, finally encouraged the FDA approval of this drug in 1970 (Table 2), 21 years after the publication of Cade's classic article [61].

Table 2. Drugs approved by the Food and Drug Administration of the United States (USA FDA) for treatment of patients with bipolar disorder.

Drug	Mania	Maintenance/Prevention	Bipolar Depression
Lithium	1970	1978	
Valproate	1995		
Carbamazepine	2004 ^a		
Lamotrigine		2003	
Chlorpromazine	1973		
Olanzapine	2000, 2003 ^b	2004	2003 ^c
Risperidone	2003, 2003 ^b	2009 ^{d,e}	
Quetiapine	2003, 2004 ^{a,b} , 2008 ^f	2007 ^g	2008 ^f
Ziprasidone	2004, 2004 ^b	2009 ^{e,g}	
Aripiprazole	2004 ^h , 2004 ^b	2005 ^e , 2017 ^d	
Asenapine	2009		
Cariprazine	2015		
Lurasidone			2013, 2018 ⁱ

^a Slow-release formulation; ^b Adding lithium or valproate increases antimanic efficacy; ^c Requiring combination with fluoxetine; ^d Long-active injectable form; ^e Efficacy mostly for preventing future manic episodes; ^f Sustained-release galenic form; ^g Requiring the addition of lithium or valproate; ^h Having data up to three months; ⁱ In paediatric patients 10 to 17 years old.

3.3. Lithium Salts in the Prevention of Manic Episodes' Recurrence

During the second half of the 1960s, prophylactic effects of lithium in preventing recurrence of manic episodes were also studied. Thus, several authors [22,86,87] found that lithium salts can reduce the number of manic episodes and their duration, as well as increase the duration of the period between episodes. They also found that the episodes have been less severe and that, in cases of relapse, hospitalization times have been shorter. All those facts were confirmed by Schou [88] in an uncontrolled study including 88 patients. The average time until relapse among patients who received a prolonged treatment has been 60 months, whereas before the treatment, the same patients relapsed at

8 months on average. On the other hand, the average annual time of relapse has been 13 weeks before lithium therapy was established, decreasing to 1.5 weeks after treatment. In addition, of the 25 patients who abandoned the treatment, 22 of them relapse in periods ranging from a few days to a year.

Despite many scientific papers supporting lithium prophylactic effect in manic-depressive disorder, the indication for lithium's antimanic effect, was highly disputed during the second half of the 1960s. Articles entitled "Prophylactic lithium, another therapeutic myth? an examination of the evidence to date" [89] and "A prophylactic myth" [90] illustrate this scenario. The first of them was published in the prestigious journal *The Lancet*, generating great controversy around this issue. This disagreement has been regarded to by some authors as the "Anglo-Danish polemic." Schou himself would definitively reaffirm his postulates in an article published in 1970 on a study carried out under a rigorous methodology. It was a randomized, placebo-controlled study with a sample of 84 manic-depressive disorder patients, either bipolar ($n = 50$) or depressive monopolar ($n = 34$). Patients were followed for five months, with no relapse in patients in the lithium group and 54% in the placebo group [91]. The relevance of these studies lies on both that they have demonstrated the effectiveness of lithium against manic-depressive episodes and that the study has a genuine innovative methodological design in psychiatric clinical trials, as pointed out by Noguera and Sáiz in 1996 [65].

The efficacy of lithium salts in the prophylaxis of bipolar disorders has definitively been proved in an interesting work by Prien et al. in 1984 [92]. These authors carried out a two-year comparative study in a sample of 117 patients with bipolar disorder, divided into three treatment groups—lithium, imipramine and lithium plus imipramine. The results showed that lithium is more effective in preventing the recurrence of manic episodes (26% in the lithium group, 28% in the lithium plus imipramine group and 53% in the imipramine group), while in the prevention efficacy for depressive episodes all groups are similar (28% of recurrences in the group treated with imipramine, 29% in the lithium group and 22% in the lithium plus imipramine group).

Schou in 1997 provided interesting data on a remarkable variation in the results of studies on the compliance of prophylactic lithium treatments through the last three decades [93]. In this sense, the frequency of therapeutic noncompliance, the main cause of recurrence in prophylactic lithium treatments, was notably higher in the late 1990s than in the 1970s. In addition, the data extracted from clinical trials have also showed a lower effectiveness of this therapy. Schou has attributed these facts to differences in the current profile of manic-depressive patients, whose pathology would be more severe, more atypical (being higher in incidence of schizomanic symptoms) and with greater comorbidity (substance abuse or alcoholism, for example) [93].

3.4. Other Clinical Uses of Lithium in Psychiatric Therapeutics

Another clinical usage of lithium salts is associated with its effectiveness in cases of treatment-resistant depression, in combination with antidepressant drugs. This was already revealed in the 1981 classic work of De Montigny et al. [94], who observed that eight patients suffering from unipolar depression and who did not respond to a three-week treatment with tricyclic antidepressants (amitriptyline, imipramine, or doxepin), showed positive therapeutic effect 48 h after adding the administration of lithium. Subsequent studies, larger and better controlled, confirmed those results [94]. In a sample of 75 depressed patients treated for 29 months with antidepressant drugs, 48% of them have been observed to have an additional improvement after lithium salts were added to the existing treatment [95].

Lithium's potentiating effect of has also been studied more recently in conjunction with antidepressants from the selective serotonin reuptake inhibitors (SSRIs) family such as fluoxetine, yielding even better results than those obtained with tricyclic antidepressants. Ontiveros et al. [96] found that, in a group of 60 patients diagnosed with treatment-resistant depression, 60% have improved after a week when lithium carbonate was added to a regimen with fluoxetine, compared to 57% in patients treated with desipramine when lithium was added. The latter group of patients also shows slow responders.

Although the action mechanism underlying this synergistic effect has not been elucidated, a reinforcement of serotonergic neurotransmission has been hypothesized. In this sense, lithium causes a presynaptic increase in serotonergic function, due to an increase in the reuptake of tryptophan for its conversion into serotonin [46].

Finally, in the late 1970s, many articles assessing the effectiveness of lithium in various mental disorders were published. These covered schizophrenia, substance abuse (including alcoholism), aggressive or impulsive abnormal behaviours, premenstrual syndrome, and so forth. Results, unfortunately, were rather poor.

3.5. Conclusions from the “Cinderella of Psychopharmacology”

Despite all its drawbacks and adverse effects from hand tremors to renal toxicity, today, almost seventy years after Cade’s work, lithium salts are the first-choice treatment for the manic phases of bipolar affective disorders, as well as indispensable prophylactic tools in the prevention of cyclic episodes of bipolar disorder. In addition, thanks to the clinical introduction of lithium, the process that has come to be called “The Revolution of Psychopharmacology” was initiated. This means that, for the first time in history, the rational pharmacotherapeutic treatment of mental disorders took place, a process that would be completed with the clinical introduction of chlorpromazine, imipramine and benzodiazepines in the following years [24,97–100]. But despite these great contributions, lithium is a clear example how an effective drug was unable, in an unwelcoming environment, to find its therapeutic gap. Nathan Kline, one of the great pioneers in psychopharmacology, said in 1968, just when its properties began to be recognized by the scientific community: “Lithium the 20-year old Cinderella of psychopharmacology is at last receiving her sovereign due. Just plain old lithium—discredited by earlier abuse, briefly but dramatically misused as a substitute for precisely the type of patient in cardiac or renal failure for whom it should not be ordinarily used—the modest proclamation of its use for mania and other excitement states in a journal of limited circulation in a remote country that passed almost unnoted” [101].

4. Valproate as Mood Stabilizer

4.1. The Fortuitous Discovery of Valproate’s Anticonvulsant Activity

Beverly S. Burton in the USA was the first person who synthesized valproic acid in 1881 [102,103]. Valproic acid is 2-propylvaleric acid or *N*-dipropylacetic acid. It is a simple branched chain octacarbon aliphatic molecule [103,104]. It was not thought to be clinically useful because of its poor solubility in water but good solubility in fat [104]. It was only used as an organic solvent at that time.

During World War II, German scientists tried to find substitutes for butter [105] and rediscovered the synthesis of valproate. They did not know of Burton’s synthesis of valproate. After WWII, valproic acid became a popular organic solvent in various industries in Western countries. It was commonly used as a diluent to solubilize other drugs [106].

In 1963, George Carraz and his colleagues working at the Laboratoire Berthier in Grenoble, France, studied the anticonvulsant activity [106] of various khellin compounds [103]. They used valproic acid as a diluent to dissolve the khellins. The results of their study showed that a correlation between anticonvulsant activity and different doses of the tested compound cannot be established but that the diluent has the anticonvulsant activity instead of the khellin derivatives using the pentylenetetrazol convulsion model [104,106]. The investigators realized that all of the solutions contain valproic acid [106–109]. Therefore, it has to be the effective anticonvulsant, describing an excellent story of pure serendipity [110].

4.2. Clinical Drug Trials for Valproate’s Antiepileptic and Mood-Improving Properties

After Carraz and his team members knew that valproic acid had an antiepileptic effect, he synthesized valpromide (Depamide®), a derivative of valproic acid [106]. The investigators believed

why the concentration of amine compounds such as imipramine or desipramine are higher in the brain because those drugs have an $-N-(CH_3)_2$ or $-NH-CH_3$ group, having an obvious lipid solubility. Those drugs can cross the blood-brain barrier easily, resulting in having higher concentration in the brain [106]. In Garraz' laboratory, the investigators showed that in animals, epileptic convulsions

triggered by strychnine can be prevented by valpromide, not by valproate (Depakine®), another sodium-based derivative of valproic acid [106].

Carraz collaborated with Sergio Borselli, a psychiatric trainee under Pierre Lambert (Figure 14) at the Psychiatric Hospital of Brittany (Hôpital Psychiatrique de Bassens) in Rhone-Alpes, France [111].

They conducted a series of clinical drug trials in epileptic patients [111–113]. As often seen in large asylums in Europe at that time, 10% to 20% of patients were suffering from epilepsy [106]. Borselli

and Lambert found that valpromide works as a sedative, particularly when used with other anticonvulsants such as phenobarbitone [106]. They also observed that valpromide and valproate

have with pain management [11] and psychological effects of the intervention when administered to described “patients felt more like themselves, the mental slides in less, and a society that had so many times been in there

older agents was less. We saw the disappearance of tendencies, sometimes even a mild euphoria" [115]. The first report of mood-stabilizing effects of valproate in patients with bipolar disorders appeared in 1966 in the French literature [116]. Besides the French

disorders appeared in 1966 in the French literature [16]. Besides the French study on the psychotropic benefit of valpromide, Hinderk M. Emrich and associates at the Max Planck Institut für Psychiatrie in Munich, Germany also independently discovered that valpromide

in Munich, Germany also independently discovered that valpromide has antimanic efficacy [117].

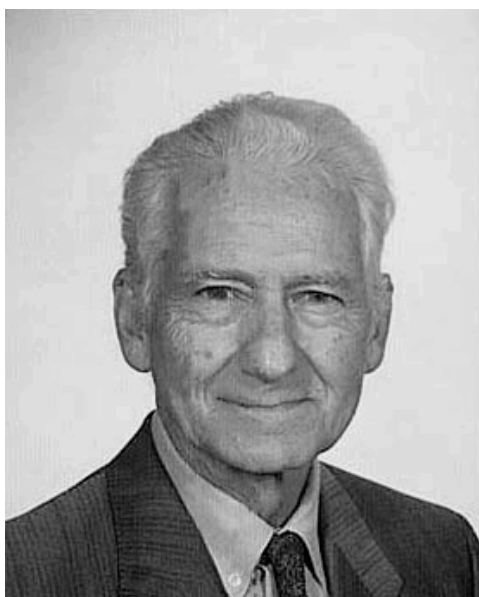


Figure 14. Pierre A. Lambert, French psychiatrist, a pioneer in the field of psychopharmacology. He was a member and president of the prestigious Comité Lyonnais de Recherches Thérapeutiques en Psychiatrie. His pioneering concept of the pathophysiology of mood stabilizers gained great importance in the early stages of the psychopharmacological era.

4.3. Controlled Clinical Trials Leading to Valproate's FDA Approval for an Antimanic Indication

4.3. Controlled Clinical Trials Leading to Valproate's FDA Approval for an Antimanic Indication

Netherlands and Germany, since 1968, as well as in the United Kingdom since 1973. It became available in the USA in 1983 [104]. There were four oral preparations – valproic acid (Convulex®), sodium valproate (Depakene®), divalproex sodium (Depokote®), an enteric coated compound in the USA in 1983 [104]. There were four oral preparations – valproic acid (Convulex®), sodium valproate (Depakene®), divalproex sodium (Depokote®), an enteric coated compound containing equal proportions of valproic acid and sodium valproate, as well as divalproex sodium valproate (Depakene®), divalproex sodium (Depokote®), an enteric coated compound containing equal proportions of valproic acid and sodium valproate, as well as divalproex sodium sprinkle capsule (Depokote Sprinkle®). The manufacturer, Laboratoire Berthier, had long stopped producing and promoting valproate in the Abbot pharmaceutical company, which sold VPA in France and abroad [106].

Psychiatrists at the Abbot Pharmaceutical Company, Illinois, USA, owned the patent for divalproex sodium. They were interested in pursuing its antimanic effect. They supported a landmark multicentred, randomized, double-blind, placebo-controlled, parallel group drug trial [118]. This study included 179 acutely manic hospitalized patients meeting for the diagnosis of manic disorder of the Research Diagnostic Criteria [119]. Being considered as one of the most stringent clinical drug trials with the largest number of patients with bipolar disorders in history, the main results of the study showed that divalproex and lithium are more effective than placebo to reduce the symptoms of acute mania and that divalproex is as good as lithium as an antimanic treatment [118]. In 1995, the FDA approved divalproex sodium for its antimanic effects (Table 2) based on the results of this study and other studies [120,121]. The 1994 study by Bowden et al. [118] also proved that lithium is better than placebo in a high-quality placebo-controlled design for the first time with a respectable sample size in this industry-sponsored clinical drug trial, although lithium had already been approved by the FDA in 1970 (see Table 2).

4.4. Increased Popularity of Prescribing Divalproex Sodium by American Psychiatrists in the 1990's

USA FDA approval of divalproex sodium for an antimanic indication was received enthusiastically by psychiatrists in the USA. At that time, divalproex sodium was a major psychiatric product in the USA due to its extensive commercial promotion. Divalproex sodium was often featured besides the AADs (such as risperidone or olanzapine) in symposia sponsored by industry and in supplementary issues of professional journals. From 1994 to 1997, the number of divalproex sodium prescriptions was soared in the USA, whereas that of lithium was declined [122]. For example, 15.5% of adult inpatients received divalproex sodium in 1994 and 34.1% of patients among all public mental health facilities in the State of New York in 1996. Furthermore, 50% of patients with the diagnoses of bipolar disorder and schizoaffective disorder received divalproex in 1996 [122]. By contrast, the number of prescription of lithium was decreased year by year [123]. Both valproic acid and lithium have gained popularity in Latin-American countries. Heenren et al. [124] sent out a 14-item questionnaire to psychiatrists from eight Latin-American countries—Argentina, Colombia, Costa Rica, Ecuador, Mexico, Peru and Venezuela—to study their treatment preferences for patients with bipolar disorder. The authors reported that lithium and valproic acid were by far the top choices among Latin-American psychiatrists when asked about the first mood stabilizer of choice for a patient with bipolar disorder and that with a manic episode, 50% and 41.6%, respectively [124].

The number of prescriptions of divalproex sodium in the USA reached a plateau in late 1990's and then declined due to the advent of AADs. Like lithium, valproate has been approved as an add-on to increase anti-manic efficacy with olanzapine and risperidone in 2003, quetiapine in 2004, as well as aripiprazole in 2008 (Table 2).

The popularity of valproate prescription was further decreased in the 2000's because the antimanic and maintenance efficacy of an AAD such as olanzapine are better than those of valproate [125]. At the same time, valproate has also been found to have problematic side effects such as gastrointestinal effects, tremor, sedation, pancreatitis, liver toxicity, weight gain and polycystic ovarian syndrome. Although some treatment guidelines for bipolar disorder suggest that valproate should be avoided during pregnancy due to its teratogenic risk (British Association for Psychopharmacology Guidelines), others, such as the World Federation of Societies of Biological Psychiatry Guidelines recommends close monitoring and risk evaluation in every case. However, in relation to teratogenicity, especially in unplanned pregnancy and with other adverse effects of valproate, such as the risk polycystic ovary syndrome, the benefits should be highlighted often outweigh the risks as patients may over-estimate the risk. Apart from more choice from AADs, valproate prescription has also been hurt by the findings that valproate has proven not to be as good as lithium in anti-suicidal efficacy [126] and maintenance therapy in preventing relapse [127]. Thus, the number of prescription was declined in the decades of 2000s and 2010s compared to 1990s in any country in the world where AADs were available.

5. The History of Carbamazepine as an Agent for Bipolar Disorders

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5.1. Japanese Psychiatrists Discovered Carbamazepine's Antimanic Properties

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Carbamazepine, a tricyclic anticonvulsant compound, was developed in the late 1950s in the laboratories of J. R. Geigy, in Basel, Switzerland [128]. In 1961, Walter Schindler described its synthesis. In 1963, W. Theobald and H. A. Kunz reported its antiepileptic properties. Its efficacy for patients with epilepsy and paroxysmal pain syndromes was demonstrated in Europe in the early 1960s [128].

In the early 1970's, lithium was not available in Japan [129]. This led to the use of other agents to treat manic-depressive disorders in Japan [129]. Japanese hospitals were also in the process of institutionalizing with large increasing hospital population following chlorpromazine's discovery [129,130]. This trend was opposite to what happened elsewhere in the world [130]. In addition, psychiatry was neuropsychiatrically oriented and psychiatrists instead of neurologists treated most patients in Japan [129,130]. As a result, carbamazepine was widely used in Japanese hospitals following its release as an anticonvulsant during the 1960's [129].

The sedative properties of carbamazepine (Figure 15) led to its use for manic patients instead of other sedatives such as the barbiturates. In the valpromide story for treating manic patients [114], carbamazepine was applied conditions by Japanese psychiatrists exclusively to patients with epileptic or manic [106]. Takezaki and Hanaoka [129], in Tottori, Japan, reported their first clinical series of drug trials for manic-depressive patients with carbamazepine. They reported their results in a Japanese journal in 1971 [129]. After the report, many Japanese researchers, especially from the Teruo Okuma group, continued to demonstrate carbamazepine's advantage in treating patients with manic-depressive illness [131–134].



Figure 15. Carbamazepine (Tegretol®) advertisements in the Japanese medical press during the 1970s, which emphasized its anticonvulsant and sedative effects. Ads published in the journal *Psychiatria et Neurologia Japonica* in (A) 1970 and (B) 1978.

5.2. Information of Carbamazepine's Research Results Spread to the West from Japan

In a personal reflection, Okuma in 2000 stated that Western psychiatrists were not impressed when the Japanese reported about carbamazepine's psychotropic effectiveness was published in English [135]. It stated that carbamazepine has similar efficacy compared to chlorpromazine, which was discovered in 1952 [136,137]. The major criticism of the 1979 article [135] was that there was no real evidence of efficacy of carbamazepine at all. The chlorpromazine dose (250 mg/day) in their study was considered inadequate [134]. The reason this research report was not accepted was that a 250 mg dose of chlorpromazine was thought to be indistinguishable from placebo at a time when Western psychiatrists were using antipsychotic mega-doses [106,134]. The research protocol was similar to the one used to investigate lithium's efficacy but those outcomes were not contested [106]. The results of the antimanic efficacy of carbamazepine and lithium are comparable [138,139]. Even carbamazepine did not come into wide use in the West until 1878 when its antimanic effects were described by the American psychiatrists James Ballenger and Robert Post at the USA National Institute of Mental Health [140]. By the time it became more widely used, it was clear that carbamazepine had imported psychotropic properties. Carbamazepine was used in Japan for a wide range of mental conditions (Figure 15). It was useful in stabilizing aggressive outbursts in young men [103]. Later, the use of carbamazepine for the management of episodic dyscontrol syndrome [103,141] was described in the Western literature [106].

5.3. Current Status of Carbamazepine for the Treatment of Bipolar Disorders in the USA

Carbamazepine has been observed to induce blood dyscrasias delayed its use in North America [106], even though this serious adverse side effect was rare. USA FDA approved carbamazepine as an antiepileptic agent for adults in 1974 and for children older than 6 years of age in 1978. The FDA allowed its use for all without any age limitations in 1987. In Latin-America, there is a high degree of polypharmacy in the treatment of bipolar disorder, with anticonvulsants being the most commonly prescribed medication. Among anticonvulsants, valproic acid was the most popular, followed by clonazepam and then carbamazepine [142]. As shown in Table 2, slow-release carbamazepine received FDA's approval for treating mania in 2004 but its use has never been expanded to other indications for other clinical phases of bipolar disorder.

Oxcarbazepine has a chemical structure with a keto group instead of a double-bond between two carbons in the central ring of carbamazepine. Those structures have also been shown to have antimanic efficacy in Europe [143]. Oxcarbazepine has a favourable side effect profile producing less blood dyscrasias and less drug-drug interactions. This drug was introduced as an antiepileptic to the USA from Europe under the trade name of Trileptal® in 2000. To date, the pharmaceutical industry is not interested in developing carbamazepine or oxcarbazepine for treating other phases of bipolar disorder.

6. New Antiepileptics in Bipolar Disorders

Despite the progress accomplished, treating bipolar disorder with lithium, valproate and carbamazepine involves four major loopholes:

- Many patients are resistant to conventional treatment.
- Good number of patients present themselves with tolerability problems, due to the frequent adverse effects of those drugs.
- The depressive phase still constitutes a serious problem, since lithium, carbamazepine and valproate are more effective in relieving symptoms in the manic than the depressive phase.
- Rapid cycling and mixed mania (dysphoric) respond poorly to treatment, etc. [144–146].

Although carbamazepine was already used in Europe as a substitute for lithium or in combination in resistant cases, the commercial success of valproate was the ultimate reason that stimulated the evaluation of the new anticonvulsant agents in treating bipolar disorders, particularly when it has

been demonstrated in the field of epilepsy that they entailed better profile of side effects, interactions, toxicity and teratogenicity [147]. With those premises and significant financial support from the pharmaceutical industry, those new antiepileptics are aimed to displace lithium and second-generation anticonvulsants in treating bipolar disorder, a pathology at the entrance door to the emerging juicy market of psychiatric disorders.

In the individual analysis of the use of these new antiepileptic drugs in bipolar disorder, lamotrigine has been the most contrasted agent, both from the clinical and safety perspectives [148,149]. Lamotrigine has been licensed for the indication in preventing relapse of having future depressive episodes in patients with bipolar disorder.

6.1. *Lamotrigine in the Prevention of Depressive Episodes in Bipolar Disorder*

Lamotrigine was the third of the so-called new generation of antiepileptics to be marketed, after vigabatrin and felbamate. But those last two drugs were not studied as mood stabilizers because after their commercialization as antiepileptic drugs, significant idiosyncratic side effects were discovered, such as visual field loss or aplastic anaemia, limiting their use to special cases of epilepsy (Lennox-Gastaut syndrome, for example). In the case of lamotrigine, its side effects profile is more favourable in general than that of classic antiepileptic drugs, despite the feared of infrequent Stevens-Johnson syndrome.

Lamotrigine is a phenyltriazine that was synthesized in the early 1980s at Wellcome Research Laboratories (Beckenham, Kent, England) as part of a program to develop new antiepileptic agents that could be better tolerated than those available at that time [150]. This program was based on the mid-1960s hypothesis that folates had proconvulsant properties, so that antiepileptics were thought to exert folic acid antagonistic effects [151]. Taking pyrimethamine as a reference, a substance developed in 1950 as antimalarial (for the treatment and prevention of malaria), a series of structurally analogous phenyltriazines were synthesized to improve its anticonvulsant activity. One of these compounds, BW288U, presented a good anticonvulsant activity but a low antifolate activity, which they tried to optimize. As a result, lamotrigine was obtained, a compound with great anticonvulsant activity but weak dihydrofolate reductase inhibitory power [152]. Phase I clinical trials started soon, showing excellent pharmacological properties. Lamotrigine was finally approved in 1990 in Ireland for use in epilepsy. In 1994, USA FDA also approved its use in a combined treatment for this neurological disorder. Similarly, in those initial studies, Smith et al. [153] observed that this agent improves mood and communication skills in treated epileptic patients.

The first author who produced scientific data on the efficacy of lamotrigine in bipolar disorder was Richard H. Weisler (University of North Carolina Chapel Hill School of Medicine at Chapel Hill, North Carolina, USA). Having attended several international conferences, Weisler knew this molecule before it was approved in the USA and anticipated its possible use in psychiatry. After importing the drug from Europe and requesting authorization from the FDA for compassionate use in 1993, Weisler used lamotrigine to treat two long-term bipolar patients—a 43-year-old white male patient with bipolar II disorder and rapid cycling, as well as a 77-year-old female patient with bipolar I mood disorder with predominance of major depressive episodes and several suicide attempts. At that time, those two patients were refractory to all available pharmacological treatments—lithium, carbamazepine, clonazepam, valproate, 11 different antidepressants (including some of those only being available in Europe then), buspirone, levothyroxine and verapamil. The treatment regimen included, in addition to lamotrigine, other pharmacological agents such as lithium carbonate, bupropion and levothyroxine, in one case and only levothyroxine, in the other case. Both patients showed an evidence of clinical improvement after several weeks, a rapid normalization of social and family relationships and one of them even resumed working activities. Weisler's group presented the results obtained with those two patients at the American Psychiatric Association's annual meeting held in 1994 in Philadelphia [154] and defended their use based on its action mechanisms (potent anti-kindling effect, sodium channel blockade and anti-glutamatergic activity). In the following two years, several more articles were

published about diverse clinical cases, such as refractory bipolar patients, patients with overt depressive episodes, and/or rapid cycling [150].

In 1994, after the presentation of those clinical cases, the company marketing lamotrigine, Burroughs Wellcome, brought together in its research facilities in Beckenham (England) a series of international experts in bipolar disorder to address the possibility of developing a research program on lamotrigine to treat this psychiatric disorder. Initially, they agreed to start an open, multi-centre clinical trial (five international centres) with a sample of 75 patients in any active phase of the disorder, either type I or type II and a follow-up of 12 months, treated with lamotrigine in monotherapy or in combination treatment. The results revealed that an 81% response rate and a 74% decrease in the Young Mania Rating Scale (YMRS) score are found in patients in the manic/hypomanic phase and that a 48% response rate and a 42% decrease in the Hamilton Depression Rating Scale (HDRS) score are also found in those in the depressive phase. Secondary analyses have shown additional benefits in other aspects related to the depressive episode and good tolerability with the most common adverse effects being dizziness, tremors, drowsiness, headaches, nausea and rash [155].

Given the positive results of this open study, GlaxoSmithKline launched between 1996 and 2001 an ambitious program of a controlled double-blind phase III trials and enrolled 2400 patients from four continents—5 trials in acute episode of bipolar depression, 2 in acute episode of mania, 2 in the prevention of manic or depressive episode and 2 in rapid cycling patients [150]. Unlike typical antipsychotics being more effective in the control of mania than depression, lamotrigine is especially effective in patients with a predominance of depressive phases. The results of the first double-blind, placebo-controlled clinical trial confirmed its effectiveness in bipolar depression at doses between 50 and 200 mg/day [156], although the improvement in the Hamilton 17-item Depression Scale, the main efficacy variable, is not significant. Similar results were obtained in the other four trials. These poor results might be due to the need to slowly increase the dose of lamotrigine (up to 10 weeks to reach the final dose) to avoid the appearance of rash [157]. Subsequently, a meta-analysis considering all trials would confirm a significant, albeit small, efficacy of the treatment with lamotrigine [158]. By contrast, in double-blind clinical trials with patients in the manic phase, lamotrigine (50 mg) yielded negative results [159], presenting no statistical differences with placebo and lower efficacy than lithium. But in those studies, the risk of shift from mania to depression is not more than to placebo.

Yet, the best results with lamotrigine were obtained in studies of relapse prophylaxis in patients with bipolar disorder shown in two randomized double-blind trials which compared the efficacy of lamotrigine with that of lithium and placebo over 18 months. As a result, the USA FDA approved its use for this indication. Altogether ($n = 1300$ patients), both trials concluded that lithium is superior to lamotrigine and placebo in the prevention of manic phases and that lamotrigine is superior to lithium and placebo in the prevention of depressive phases [148,149]. The combination of data from both trials also showed that lamotrigine is effective in the prevention of mania, although the results is not as robust as that with lithium [160]. These findings confirmed the characteristically antidepressant profile of lamotrigine as a mood stabilizer, as opposed to other drugs available at the time and obtained its approval by USA FDA in 2003 (Table 2). In addition, they suggested the possibility to combine lamotrigine with lithium to obtain more symmetrical results in relapse prevention [161].

The effectiveness of lamotrigine in rapid cycling patients was also suggested, although data were based on a placebo-controlled clinical trial, is only positive in bipolar type 2 [162]. Finally, it was also confirmed that the combination of lithium and lamotrigine is safe and useful in refractory bipolar depression [163,164] and that the combination with valproate or carbamazepine is also possible, although implying more interaction risks [161].

6.2. Other Modern Antiepileptic Agents

Gabapentin was one of the first third-generation antiepileptic drugs to be studied for bipolar disorder and as almost all of them, it was initially evaluated for the treatment of mania. Although most open studies have positive outcomes [165] but the two controlled clinical trials produce negative

results [166,167] and raised considerable doubts about its efficacy. In the first one [166], lamotrigine shows better outcomes than gabapentin. In the second one, surprisingly, placebo is better than gabapentin in manic patients treated with lithium [167]. However, gabapentin could be an interesting drug as an enhancer of other mood stabilizers in cases in patient with a high anxiety component [168]. This is especially relevant at present, since many authors advocate combined treatment to prevent the natural disease progression towards a shortening of remission periods [169].

The history of topiramate shows paradigmatically how research on potentially anticonvulsant drugs is evolving. Topiramate was discovered in 1979 by Bruce E. Maryanoff and Joseph F. Gardocki through their research work at McNeil Pharmaceuticals (Fort Washington, PA, USA), a subsidiary of Johnson & Johnson Corporation. It was initially synthesized as a hypoglycaemic agent. In fact, topiramate is a sugar, a derivative from fructose. After having known its potential efficacy in diabetes being limited, the investigators studied topiramate in various animal models of different diseases, proving its anticonvulsant efficacy in rats. The preclinical research showed that the presumed antidiabetic was a potent antiepileptic. Some open studies suggested that it could be an effective drug as an add-on therapy in bipolar patients with partial response to other drugs [170] and a monotherapy [171]. But placebo-controlled clinical trials in manic patients cannot prove its efficacy [172], despite that several controlled trials of high methodological quality were carried out.

As for tiagabine, little relevant data exist to show its effect in bipolar disorder, although a study conducted in the Stanley Foundation Bipolar Network indicated that its mood stabilizing potential is scarce or null, together with a certain risk of seizure induction [173].

As mentioned before, oxcarbazepine, a 10-keta analogue of carbamazepine, was developed in the 1970s as an improved alternative to carbamazepine. In addition to the initial studies from the 1980s, recent data exist from experiments using oxcarbazepine to treat bipolar patients. Case series with positive results have been reported [174]. In addition, an open study with 12 patients receiving oxcarbazepine has been published, showing good results in participants with mild or moderate forms of mania, worsening in symptoms after discontinuing the drug and becoming improved again after resuming treatment [175]. In any case, the APA advises the use of oxcarbazepine as a reasonable option in treating bipolar patients who do not respond to established treatments but more clinical trials are needed to confirm its potential as mood stabilizer in the maintenance treatment. Licarbazepine, an active metabolite of oxcarbazepine, was also evaluated in controlled clinical trials for manic episodes in bipolar disorder patients, with unsatisfactory results [176].

With respect to levetiracetam, pregabalin, retigabine, or zonisamide, the data published from patients with bipolar disorder are limited, although their properties are being assessed as mood stabilizers.

7. Atypical Antipsychotic Agents in Bipolar Disorders

The delay in the action onset of classical mood stabilizers in the treatment of symptomatic acute manic symptoms enabled the study with the use of antipsychotic drugs in this disorder [177]. Chlorpromazine was the only traditional antipsychotic drug (or first-generation antipsychotic drug, FGA) approved by USA FDA in 1973 for the treatment of manic episodes in bipolar disorder. Several clinical trials contrasted the efficacy of chlorpromazine in acute mania, both in monotherapy [83,178] and in combined treatment with lithium salts [179]. Nevertheless, its use in bipolar disorder was limited due to its poor tolerability, causing sedation and hypotension and the advent of new atypical antipsychotic drugs (AADs, or second-generation antipsychotic drugs, SGAs). The clinical introduction of risperidone on the USA market in 1993 to treat patients with schizophrenia heralds the advent of AADs and the clinical introduction of those agents reinvigorated the interest in therapeutic research on the different phases of bipolar disease [180]. In addition, its wide use in schizophrenia provided contrasted data regarding SGAs' superior safety over FGAs, especially with respect to extrapyramidal effects.

Besides, the unique biochemical properties of AADs (clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine and cariprazine), mainly their ability to antagonize dopamine receptors, together with other peculiarities of their pharmacological receptor profile and their effects on multiple neurotransmission systems [181] also fostered their study as potential antimanic agents [182]. In addition to dopamine D₂ antagonist effects, AADs block 5-HT₂ serotonergic receptors, basically 5-HT_{2A} and 5-HT_{2C} and some of them, such as aripiprazole, ziprasidone and asenapine, are 5-HT_{1A} receptor partial agonists [181], which could result in an enhancement of noradrenergic and dopaminergic neurotransmission [183]. Although the exact mechanisms of AADs in the treatment of mania remain unclear, it seems obvious that this type of drugs have a specific antimanic effect regardless of the presence of comorbid psychosis or the degree of sedation induced by the agents [2].

Olanzapine was the first atypical antipsychotic drug to have been licensed for the indication of treating acute mania. Eli Lilly (Indianapolis, IN, USA) sponsored six double-blind studies published between 1999 and 2003, to evaluate olanzapine's efficacy for treating mania or mixed episodes compared to that of placebo, divalproex and haloperidol. The first of those was a placebo-controlled trial [184] with a three-week follow-up period. The study results showed a mean reduction in the YMRS score of 10.26 points in the olanzapine group versus 4.88 points in the placebo group and the percentage of patients being responders in olanzapine vs. placebo were 48.6% vs. 24.2%, respectively. The mean modal dose of olanzapine 14.9 mg/day, is superior to placebo in treating acute symptoms of mania in this trial. Subsequent studies confirmed the efficacy of olanzapine in acute mania, with an efficacy superior to valproate and lithium [185]. As a consequence, olanzapine was the first AAD approved by the USA FDA to treat manic episode of bipolar disorder in 2000 (Table 2).

In any case, the antimanic efficacy of AADs was later revealed by a series of randomized, placebo-controlled studies [12,186–190], suggesting that all AADs, as a pharmacologic group, have a class-effect in treating mania. Almost all AADs got approval to treat mania one by one—risperidone in 2003; quetiapine, ziprasidone and aripiprazole in 2004; asenapine in 2009; as well as cariprazine in 2015 were approved by the USA FDA as monotherapeutic agents for the antimanic indication (Table 2). In addition, some of them were also approved for the prevention of relapse in patients with bipolar disorder who in a manic episode had already responded to the treatment with those antipsychotics (Table 2). At present, AADs are the first line of treatment for the manic phases of bipolar disorder [191].

Various AADs expanded their indications to treat all three clinical phases of bipolar disorder. Seemingly most AADs, if not all, can get the indication for relapse prevention if they are combined with the use of lithium or valproate (Table 2). Finally, olanzapine (always in combination with fluoxetine) in 2003, quetiapine in 2008 and lurasidone in 2013 have been approved for the treatment of depressive episodes in bipolar disorder. This may be the reason why, recently, the number of scientific publications on bipolar disorder [9] and AADs have suddenly and exponentially increased in some countries of Asia and Europe and in Australia [192–196].

The treatment of bipolar depression is more complex than the treatment of manic episodes. It requires different therapeutic approaches from unipolar depression [197]. Also, the scientific evidence on the role of AADs is smaller and, in some cases, the results of meta-analyses have given rise to inconsistent conclusions [198]. The antidepressant properties of some AADs could be due to their ability to modulate three monoaminergic systems (noradrenergic, serotonergic and dopaminergic) involved in the pathophysiology of depression [199]. In the case of quetiapine, its active metabolite norquetiapine helps serotonergic transmission, acting as a partial agonist of 5-HT_{1A} receptors, in addition to working as a potent inhibitor of the noradrenaline transporter, which increases noradrenergic functionality [200,201].

Although olanzapine is approved by USA FDA in the treatment of bipolar depression, that is the case only in combination therapy with fluoxetine. The first AAD to obtain approval from USA FDA for the treatment of bipolar depression in monotherapy was quetiapine, based on a clinical trial program developed by AstraZeneca (London, UK) and known under the acronym BOLDER

(BipOLar DEpRession) and EMBOLDEN (Efficacy of Monotherapy Seroquel in BipOLAR DEpressionN). The BOLDER studies, placebo-controlled and 8 weeks long, confirmed that quetiapine at daily doses of 300–600 mg is superior to placebo in the total reduction of depressive symptoms according to the Montgomery-Asberg Depression Rating Scale. (MADRS) and that the improvement occurred from the first week in all the main symptoms of depression. Likewise, quality of life and anxiety are improved to a greater extent with quetiapine and this improvement was independent of the presence or absence of sedation [202,203]. The efficacy of quetiapine at a 300 mg/day dose is similar to that of 600 mg/day, so both doses have been approved for the treatment of bipolar depression. With respect to EMBOLDEN trials, an assessment was performed at week 8 and patients who met specific response criteria entered a 52-week treatment extension phase. In the EMBOLDEN I study, quetiapine at 600 mg/day (but not quetiapine at 300 mg/day) is superior to lithium in reducing the MADRS score at week 8 [204], while in the EMBOLDEN II study, quetiapine, at doses of 300 and 600 mg/day, reduces the total score of the MADRS scale more than the SSRI antidepressant paroxetine at dose of 20 mg/day. In addition, paroxetine does not differ from placebo [205]. In those studies, in acute episodes of bipolar depression, quetiapine achieves higher and earlier response and remission rates than placebo and it does so from the first or second week.

This decision to pursue clinical drug trial of lurasidone for patients with depressive episode in bipolar disorder was influenced by three relevant factors [206] because lurasidone has:

- special pharmacological profile [207] of receptor affinity (mainly as a 5-HT_{1A} receptor agonist and a 5-HT₇ receptor antagonist),
- efficacy in animal models of acute and chronic depression [208],
- shown favourable improvement in depressive mood in previous efficacy studies in schizophrenia [209].

Lurasidone is the first AAD whose efficacy in bipolar disorder was studied in the treatment of the depressive phase exclusively. The investigators observed that in patients treated with lurasidone for six weeks, the mean MADRS score is decreased more than those in the control group. Therefore, the pharmaceutical company Sunovion Pharmaceuticals, Inc. (Marlborough, MA, USA) launched in 2009 a clinical trial program called PREVAIL (Program to Evaluate the Antidepressant Impact of Lurasidone), with the aim to evaluate the efficacy and safety of this AAD both in monotherapy and in combination treatment with lithium or valproate, in adult patients diagnosed with bipolar depression according to clinical criteria of *DSM-IV-TR* [199,206]. The positive results of those trials and an open six-month long-term follow-up study allowed USA FDA approval of this agent in June 2013, for the treatment of depressive episodes of bipolar I patients.

8. Conclusions

The definition of a “mood stabilizer” is not clear. It means different things to different people (APA, 2002). According to one specific definition, it is a drug that has both antimanic and antidepressant effects on both mood states [210,211]. In conservative definition, it means a drug that has therapeutic efficacy in 2 of 3 different mental states, as shown in Table 2 [212]. But in a broader definition, it means a drug that: (A) is effective in 1 of any 3 phases as an antimanic, antidepressant, or for maintenance/prophylaxis; (B) does not worsen any mood state; and (C) does not have the potential of switching the patient from one to the other mood state [213,214]. According to this broad definition, tricyclic antidepressants do not belong to this category to treat patients with bipolar disorders. The results of meta-analysis data from clinical trials has shown that the rates of mania induced by tricyclics, SSRIs and placebo are 11.2%, 3.7% and 4.2%, respectively [215]. Venlafaxine and paroxetine have been found to have beneficial psychotropic properties. However, venlafaxine, instead of paroxetine, is noted to have a higher mood switch rate compared to paroxetine, 13% vs. 3% [216]. Valproic acid and carbamazepine have never been identified to switch the mood of bipolar patients from a depressive to a manic phase.

The American Psychiatric Association has discouraged the use of the term “mood stabilizer” [143]. It has never been officially used by USA FDA for a drug approved to treat patients with bipolar disorders (Table 2). Not to further invite confusion, we suggest that one should avoid the term “mood stabilizer” as much as possible even though no simple substitute term is available.

In this paper, we have used the USA FDA approval status as the milestone for describing drugs for the treatment of bipolar disorders. Approval by USA FDA frequently means a drug’s marketability not only in the USA but also all over the world. As shown in Table 2, only three AADs (olanzapine, quetiapine and lurasidone) have been approved by USA FDA for the treatment of the depressive phase of bipolar disorder and only two (olanzapine and quetiapine) for all three phases of “mood states.” But olanzapine needs to be combined with fluoxetine, an antidepressant, for the treatment of the depressive phase of bipolar disorder [217]. Lithium and valproate have been approved by USA FDA for antimanic indications in 1975 and 1995, respectively. Since 2000, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine and cariprazine have been approved for antimanic indication. Currently the AAD market is saturated with antimanic agents as listed in Table 2. No more motivation exists for a pharmaceutical company to invest money to develop oxcarbazepine or another antiepileptics for an antimanic indication. Hence, those drugs are most likely to remain off-label use for antimanic effects.

No shortage of available antimanic agents is shown on the market (Table 2). For other antiepileptic drugs, only lamotrigine has been approved by USA FDA for maintenance therapy. But lamotrigine or similar drugs, rather than valproic acid or carbamazepine, continues to draw attention in the treatment of patients with bipolar disorders. Their rare characteristic is their efficacy for both poles of bipolar depression.

Historical Implications at the Socio-Sanitary Level of the Clinical Introduction of the First Mood Stabilizers

The direct and delayed consequences of the introduction of the first psychotropic drugs in the 1950s have been multiple and lithium salts played a fundamental role [30,63,97,218,219]. At the purely scientific level, they favoured the postulate of the first biological hypotheses on the genesis of mental illnesses, giving birth to the so-called “biological psychiatry.” At the nosological level, the introduction of those drugs contributed to design new, much narrower diagnostic criteria, characterized, to a large extent, by a predictable and homogeneous response to treatment [220]. Clinical research methodology also benefited from the appearance of those drugs, specially lithium salts, with the rise of multicentre, double-blind, cross-over, randomized clinical trials, etc., as well as the development of a large number of generic and specific tests for the assessment of changes in psychopathological traits. Lithium played a decisive role in this whole process [62].

From the historical perspective, another relevant contribution of the clinical introduction of lithium and the FGAs lays at the health care level, giving rise to the progressive phenomenon of “deinstitutionalization” in psychiatry. This fact mitigated the stigma component that had accompanied psychiatric assistance. In this sense, the FGAs not only enabled patients to leave psychiatric hospitals but also helped their re-socialization. Some data show the impact that the introduction of these agents had. During the first half of the 20th century, the number of patients admitted to psychiatric hospitals in the USA was alarmingly increased, from 150,000 to 500,000 patients. But from 1955, the year in which certain psychopharmaceuticals (FGAs and lithium salts, particularly) began to be used on a massive scale, the rate of hospitalizations was reversed and in 1975 the number of patients was dropped to 200,000 [221]. Another example comes from the economic benefits that lithium brought to the community, which have been estimated, in the USA, at USA \$145 billion dollars from its USA FDA approval in 1970 until 1994, mainly due to savings in hospitalization costs [222].

Even today, almost 70 years after Cade’s work, lithium salts, applying the precautions associated with a drug of moderate toxic character (basically the control of lithium), constitute the first-choice treatment for the manic phases of affective bipolar disorders, as well as indispensable prophylactic tools in the prevention of cyclic episodes of manic-depressive illness. Even the “black history of

lithium toxicity” should be revised, as proposed by Moncrieff [54], since, while the rate of deaths directly attributable to lithium stands at 14 per million prescriptions, this ratio rises to 50 in the case of dothiepin, 46.5 in the case of amitriptyline or 11.1 with clomipramine. In any case, the importance and transcendence of lithium in psychiatric therapeutics is reflected on the enormous amount of scientific publications on this agent, which reached 9500 in the 33 years after the classic work of Cade [223].

Currently, psychiatrists dispose of a therapeutic arsenal of 13 different drugs approved by regulatory agencies to address the different acute episodes of bipolar disorder and the prevention of relapse. Although the process was started 70 years ago by John Cade with the discovery of lithium salts antimanic effect has not yet concluded and there are broad aspects to be improved, the pharmacological treatment of bipolar disorder has established itself as a substantial part of the history of psychopharmacology. In any case, the scientific evidence accumulated over the last decade appears to confirm that there is no unitary biochemical mechanism to explain the effect of all the substances currently available for the treatment of bipolar disorder. In fact, research in this field is advancing in other directions, with the aim of finding new loci of drugs’ action, such as the role of neurotrophic factors (neurotrophins and BDNF), corticotropin-releasing hormone (CRH) and glucocorticoids, excitatory amino acids and NMDA (N-methyl-D-aspartate) receptor, as well as other possible targets (opioid system, interleukins, P substance, somatostatin, neuropeptide Y, melatonin, nitric oxide and so on). One of the most important objectives of the current neuroscience is the discovery of the molecular mechanisms responsible for intraneuronal communication. Detailed knowledge of these mechanisms could provide us, in the future, with much more specific and safer pharmacological tools for treating bipolar disorder. But this story continues to be written...

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Abbreviations

AAD	Atypical Antipsychotic Drug
APA	American Psychiatric Association
BOLDER	BipOLAR DEpRession
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECA	Epidemiological Catchment Area Study
EMBOLDEN	Efficacy of Monotherapy Seroquel in BipOLAR DEpressionN
FDA	Food and Drugs Administration
FGA	First-Generation Antipsychotic Drug
HDRS	Hamilton Depression Rating Scale
MADRS	Montgomery-Asberg Depression Rating Scale
NCS	National Comorbidity Survey
POW	Prisoner of War
PREVAIL	Program to Evaluate the Antidepressant Impact of Lurasidone
SGA	Second-Generation Antipsychotic Drug
SSRI	Selective Serotonin Reuptake Inhibitors
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WWII	World War II
YMRS	Young Mania Rating Scale

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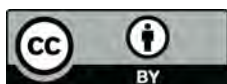
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Role of serendipity in the discovery of classical antidepressant drugs: Applying operational criteria and patterns of discovery

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Abstract

The role played by serendipity in the origin of modern psychopharmacology has proven to be controversial in scientific literature. In its original meaning (Walpole), serendipity refers to discoveries made through a combination of accidents and sagacity. We have implemented an operational definition of serendipity based on finding something unexpected or unintended, regardless of the systematic process that led to the accidental observation, and we have established four different patterns of serendipitous attributability. In this paper, we have analyzed the role of serendipity in the discovery and development of classical antidepressant drugs, tricyclic antidepressants and monoamine oxidase inhibitors as well as heterocyclic, “atypical” or “second generation” antidepressants. The discovery of the antidepressant properties of imipramine and iproniazid, the prototypes of tricyclic antidepressants and monoamine oxidase inhibitors, respectively, fits the mixed type II pattern; initial serendipitous discoveries (imipramine was an antipsychotic and iproniazid was an anti-tuberculosis agent) led secondarily to non-serendipitous discoveries. But the other

components of these two families of drugs were developed specifically as antidepressants, modifying the chemical structure of the series leaders, thereby allowing all of them to be included in the type IV pattern, characterized by the complete absence of serendipity. Among the heterocyclic drugs, mianserin (originally developed as an antihistamine) also falls into the type II pattern.

Key Words: Serendipity; Antidepressants; Imipramine; Iproniazid; Psychopharmacology; History of neurosciences

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Core Tip: In this paper, we have analyzed, for the first time, the role of serendipity in the discovery and development of classical antidepressant drugs through our operational definition of serendipity. We have assigned each of the classic antidepressants its corresponding pattern of serendipitous attributability according to four different patterns.

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INTRODUCTION

The era of modern psychopharmacology began in the late 1940s, with the publication of the antimanic effects of lithium by Australian psychiatrist Cade[1]. However, it was in the 1950s that what has come to be known as the “psychopharmacological revolution”[2] came into being, with the introduction of the large families of pharmacological agents that are still in use today: typical neuroleptics or antipsychotics, benzodiazepine anxiolytics and the two large groups of classic antidepressants, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)[3]. All of these psychotropic drugs drastically changed the state of psychiatric care, starting from a fundamentally empirical therapeutic approach, which nevertheless allowed for a gradual understanding of some of the neurobiological bases of mental illnesses and how to treat them.

The year 1957 should be regarded as a key date in modern psychiatry, as this was the year when the first two specific antidepressant drugs in history were introduced into clinical practice, belonging to two completely different pharmacological families and two completely different geographical areas of research. Iproniazid, an MAOI agent, was the result of a research process developed in the United States, and imipramine, the prototypical representative of the TCA family, was developed and studied in Europe[4]. Prior to the clinical introduction of these antidepressant agents, the therapeutic tools used to manage affective disorders were extremely limited[5]. At the beginning of the 20th century, chloral hydrate, barbiturates, amphetamines and opiate derivatives were used in agitated melancholic patients. During the first half of the century, excluding biological treatments (insulin comas, chemical, electrical shock therapies, and “sleep cures”), there were only a few nonspecific chemical preparations available to doctors, such as dinitrile succinate, malonic nitrite and lactic acid, all of which had rather unsatisfactory antidepressant results[6,7] confirmed in the few clinical studies carried out. However, this was also due in part to Freudian ideas prevalent until the 1950s that depressive syndromes had only psychodynamic, not biological, causes, meaning that these patients could not benefit from treatment with pharmacological agents[8,9].

In the specific field of antidepressant drugs, TCA agents that ushered in a new era in the treatment of depression are still the benchmarks today, especially in clinical research, and have the same efficacy rates as other antidepressants that have appeared since then. However, unlike TCAs, which continue to be used in clinical practice though not as a first-line treatment, the use of MAOIs has largely fallen off, due primarily to their adverse effects and problems of interactions with other psychostimulant drugs and tyramine-rich foods, which can lead to tragic hypertensive crises. However, atypical depressions are still candidates for treatment with these drugs. During the 1970s, new heterocyclic antidepressants appeared, known at the time as “atypical” or “second generation” antidepressants (maprotiline, mianserin, trazodone, viloxazine, nomifensine). The main characteristic of which was that they were more selective in their action on monoaminergic transmission systems. All of these drugs can be categorized as traditional antidepressants (Table 1).

Table 1 Classification of classical monoaminergic antidepressants according to action mechanism and historical perspective on their clinical introduction

Family	Mechanisms of action	Acronym	Prototype substance	Period
Tricyclic antidepressants	5-HT and NA reuptake inhibitors with blocking action of diverse receptors	TCA	Imipramine	1957-1980
Monoamine oxidase inhibitors	Irreversible MAO inhibitors	MAOI	Phenelzine	1958-1965
Heterocyclic or “second generation” antidepressants	NA reuptake inhibitors with blocking action of diverse receptors		Maprotiline	1967-1980
	Antagonists of α_2 auto-receptors		Mianserin	1970-1980
	DA and NA reuptake inhibitors		Nomifensine	1970-1980
	5-HT reuptake inhibitor and antagonist of 5-HT ₂ receptors		Trazodone	1970-1980

5-HT: Serotonin; NA: Norepinephrine; DA: Dopamine; TCAs: Tricyclic antidepressants; MAOIs: Monoamine oxidase inhibitors.

Finally, in the late 1980s, a new series of drug families were introduced into clinical practice, including selective serotonin reuptake inhibitors, which were widely used and accepted. These drugs offered considerable advantages over their predecessors, particularly in terms of safety and tolerability, and opened up the field of antidepressant therapy to non-psychiatrists. The first selective serotonin reuptake inhibitor was zimelidine, which was withdrawn from the market, but we can say that the period of “modern” antidepressants began with the successful clinical introduction of fluoxetine[10].

Serendipity may have played a crucial role in the process of discovering classic psychotropic drugs during the 1950s[11,12], although opinions in scientific literature in recent decades are rather contradictory possibly due to a lack of consensus on what is meant by serendipity. In the specific field of science, this concept has traditionally been associated with those discoveries or findings of a fortunate and unexpected nature, fortuitous events or accidental encounters (“happy accident,” “pleasant surprise,” *etc.*), although its meaning has also been linked to the very concept of chance, randomness or coincidence.

The differences in opinion about the role of serendipity or chance discoveries in science may lie in the semantic ambiguity of the term “serendipity.” The origin of which can be traced to correspondence between the English writer, politician and historian Horace Walpole, 4th Earl of Oxford and the British diplomat Sir Horace Mann. One epistle in this fluid correspondence, which refers to the classic Persian tale *The Three Princes of Serendip*, contains the two components that should make up the concept of serendipity: accidents and sagacity[13]. Therefore, it is sagacity that marks the difference between serendipitous discovery and the absence of discovery in the presence of relevant accidental information. But is not sagacity a basic and indispensable component of the scientific mentality itself? If the answer is yes, this element must be present irrespective of whether the phenomena observed in the scientific discovery were foreseen or not. However, we have postulated that there is a structural difference in this approach. Sagacity always precedes and leads observation in non-serendipitous discoveries, but in serendipitous discoveries, sagacity manifests itself after the unexpected observation has been made. However, even this assessment leads to interpretative problems as once scientists have made their discovery, they tend to explain them as a consequence of perfectly planned working hypotheses even when they take place in a completely random way.

Thus, from a conceptual point of view, we can conclude that serendipitous discovery is the discovery of something unsought, regardless of the systematic process that led to the accidental observation. Viewed in this light, serendipity is undoubtedly a key factor in the creative process in the arts and humanities[14,15]. However, it can also be seen as an integral part of the development of social sciences and of course of biomedical sciences in general and psychopharmacology in particular.

Kubinyi[16] briefly analyzed the discoveries of different pharmacological agents in which serendipity was somehow involved, and Hargrave-Thomas *et al*[17] confirmed that 24% of all commercially available drugs were positively influenced by serendipity during their development, particularly psychopharmaceuticals. In this sense, the discovery of most of the psychopharmacological agents that revolutionized the care of mental illnesses during the 1950s has not escaped this conceptualization either[13]. However, although the researchers responsible for these discoveries have themselves reported that chance was a key factor in their findings, the role of serendipity in the early days of psychopharmacology is still far from being established.

To address this point further, we have established an operational definition of serendipity based on four different patterns of attributability[13,18], which allows us to reflect on the actual role that serendipity played in the findings that shaped the origins of modern psychopharmacology. In this paper following this approach, we will look at the role played by serendipity in the discovery of the classic antidepressant drugs.

PATTERNS OF SERENDIPITOUS ATTRIBUTABILITY

In previous papers[13,18], we have proposed a standardized definition for the term serendipity in the field of science, given the semantic ambiguity of this concept. This “operational” definition would establish that serendipity is the discovery of something not sought. Moreover, we have proposed a working definition of serendipity[13,18] based on four different patterns of serendipitous imputation in the drug discovery process (Figure 1): (1) The first pattern, which would encompass pure serendipitous discoveries, was more frequent in the first half of the 20th century; (2) The second pattern, which is a variant of the previous one, would correspond to those initial serendipitous discoveries that secondarily lead to non-serendipitous discoveries; (3) The third pattern would include non-serendipitous discoveries that are secondarily partnered with serendipitous discoveries; and (4) The fourth pattern of non-serendipitous discoveries, in line with our operational definition of finding something unsought, has become more and more frequent since the second half of the last century. In the latter pattern, beyond serendipity, drugs evolved out of systematic research programs specifically designed to develop effective drugs for different pathological conditions.

Mixed discoveries (patterns 2 and 3) were very common towards the middle of the 20th century (coinciding with the so-called “golden decade” of psychopharmacology in the 1950s) and were characterized by initial serendipitous discoveries (in some cases in laboratory animals) leading secondarily to non-serendipitous discoveries and vice versa.

Prior to applying the attributability criteria, a detailed historical study of the development process of each of the antidepressant drugs analyzed was carried out, using the original articles in which the first pharmacological and clinical data on these drugs were published. This was done using most important databases in this field (Medline, Embase, Scopus), the documentation services of the pharmaceutical companies that have marketed these drugs and the documentation available in the Network for the History of Neuropsychopharmacology, coordinated by Thomas A. Ban (Vanderbilt University), the series of interviews entitled *The Psychopharmacologists*, by David Healy (Arnold-Oxford University Press), the *History of Psychopharmacology* collection of the Collegium Internationale Neuro-Psychopharmacologicum, coordinated by Thomas A. Ban, David Healy and Edward Shorter and edited by Animula and the documentary background on the history of psychopharmacology by Prof. López-Muñoz.

SERENDIPITY IN THE PROCESS OF DISCOVERY OF CLASSICAL ANTIDEPRESSANT DRUGS

Discovery of the antidepressant properties of imipramine and TCAs

The history of the clinical introduction of the first antidepressant drug (from the family of TCA), imipramine, was part of a search for antipsychotic drugs[19,20], following the therapeutic success reported with the clinical introduction of chlorpromazine[21] and reserpine, an alkaloid from *Rauwolfia serpentina*[22] in 1952 (Figure 2). See López-Muñoz *et al*[23-25] for details. These developments intensified the search for substances with similar properties by pharmaceutical companies. Accordingly, the pharmaceutical company J.R. Geigy (Basel) dusted off some phenothiazine substances that it had initially tried to develop unsuccessfully as dyes[8] and later on as antihistamines and hypnotics in the hope that they might have some other psychiatric benefit[8,9,26].

In this context, the Swiss psychiatrist Roland Kuhn, deputy medical director at the Cantonal Psychiatric Clinic in Münsterlingen (near Lake Constance), who had already studied the hypnotic and neuroleptic properties of certain Geigy phenothiazine agents[26,27], asked the Swiss company for new compounds from the phenothiazine family to test them in his psychotic patients. In early 1956, Kuhn received a preparation called G-22355, a substance with the same side chain as chlorpromazine, which had been synthesized by Franz Häfliger and Walter Schindler in 1948 from promethazine by replacing the sulfur bridge of phenothiazine with an ethylene bridge[28]. The substance had been registered in 1951 under United States license number 2554736[29].

Kuhn’s extensive clinical research in 1956 soon showed that the agent G-22355 had no appreciable neuroleptic activity. Even patients who had previously been treated with chlorpromazine developed more severe psychotic symptoms not schizophrenic and became clinically disturbed and agitated[30]. However, Kuhn observed that 3 patients diagnosed with depressive psychosis showed a pronounced improvement in their general condition in just a few weeks. The antidepressant effect of this substance, later named imipramine, was therefore completely unexpected and its discovery entirely accidental. In

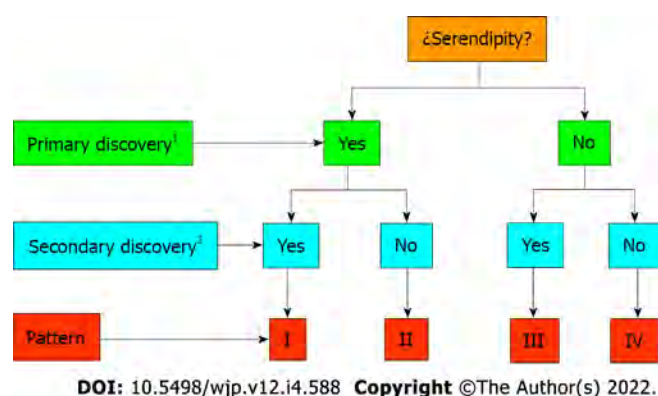


Figure 1 Diagram of the four patterns of serendipitous attribution in the discovery of pharmacological agents. ¹They usually, but not always, relate to findings in laboratory animals; ²Findings relating to clinical efficacy.

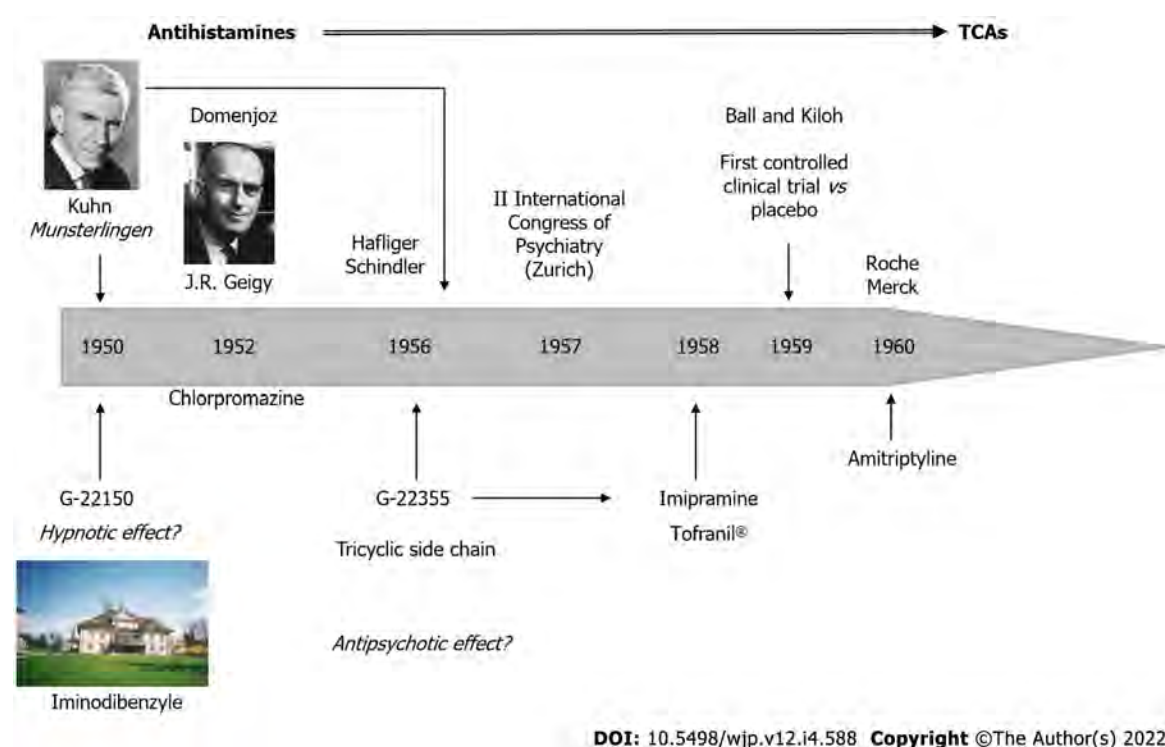


Figure 2 Historical process of the discovery of tricyclic antidepressants during the 1950s. TCAs: Tricyclic antidepressants.

this regard, the possibility that this substance could have a therapeutic antidepressant effect was first raised by Kuhn in a written communication to Geigy dated February 4, 1956[31].

Subsequently, a further 37 patients with depressive disorders received this drug, demonstrating its particular efficacy in treating depressive disorders[26,32,33]: “The patients appear, in general, more animated, their voices, previously weak and depressed, now sound louder; they are more communicative, the lamentations and sobbing have disappeared. The depression, which had manifested itself through sadness, irritation and a sensation of disaffection, now gave way to friendly, joyous and accessible feelings”[32]. Kuhn presented his results at the 2nd International Congress of Psychiatry in Zurich in September 1957 to an audience of just 12 people, using the data obtained from the clinical follow-up of these 40 depressed patients. The proceedings of the conference were published in the August issue of the *Schweizerische Medizinische Wochenschrift*[32]. However, the following year, Kuhn republished his data (with a larger sample of patients) in the *American Journal of Psychiatry*[33], thereby making his discovery internationally known. In this paper, Kuhn extensively described the pharmacological effects, data on efficacy and the adverse effects of imipramine and provided recommendations for its clinical use, dosage and duration of treatment. In this work, Kuhn stated that “the patients got up in the morning voluntarily, they spoke in louder voices, with greater fluency and their facial expression became more lively. They began to do some individual activities, they once more sought to make contact with other people, they began to train on their own, to participate in games, to become happier,

and to recover their ability to laugh"[33].

Geigy introduced imipramine to the local Swiss market at the end of 1957 under the trade name of Tofranil®. It was subsequently introduced in the rest of the European market in the spring of 1958[8,29] and represented a giant step forward in the treatment of depression, being the first representative of a new family of drugs, known as imipraminic or TCAs.

Kuhn had the sagacity to recognize an antidepressant drug when looking for an antipsychotic drug. Kuhn himself commented: "Chance admittedly had something to do with the discovery of imipramine. Chance was not decisive, however, to this had to be added a measure of intellectual achievement that was able to "invent" something completely new, something hitherto unknown, namely a new disease. Göthe put the sense of the matter in a nutshell when he wrote: 'Discovery needs luck, invention, intellect-neither can do without the other'"[34]. Something similar pointed more than a century ago the great Louis Pasteur: "In the realm of scientific observation, luck is granted only to those who are prepared"[35].

The discovery of the antidepressant properties of imipramine is a representative example of how a serendipitous finding, the observation of schizophrenic patients treated with this drug looking for an antipsychotic effect, leads to a planned and non-serendipitous discovery, *i.e.* the antidepressant effect. Therefore, the antidepressant effect of imipramine would fit into the type II pattern of our serendipitous attributability criteria. This pattern of a mixture of serendipitous and non-serendipitous findings was possibly the most common during the early stages of modern psychopharmacology. But it is precisely this dual quality that has been a major source of controversy in attributing serendipity to psychopharmacological discoveries.

Despite the remarkable success of imipramine, the next TCA, amitriptyline, was not introduced to the market until 1961. This molecule was also investigated as an antipsychotic by the pharmaceutical company Merck and Co. For this, they made modifications in the central ring of the thioxanthene family, and in this way, they got the first compound of the dibenzocycloheptadiene group[36]. Merck commissioned Frank J. Ayd Jr., one of the American pioneers in the study of chlorpromazine, to conduct clinical research on this new compound. But Ayd tried it as an antidepressant, following in the wake of imipramine. Ayd treated 130 patients at Baltimore Square Hospital with amitriptyline and found that the antidepressant effect was similar to that of imipramine. The Food and Drug Administration approved amitriptyline for marketing as an antidepressant on April 7, 1961 and it received the trade name Elavil®. This molecule would retain some of the tranquillizing effects of thioxanthenes, thus displacing imipramine in the treatment of patients with agitated or anxious depression.

The introduction of amitriptyline, the second tricyclic agent, by Merck and Co. increased the confidence in these drugs of both general practitioners and specialists. Thanks to the commercial strength of these two pharmaceutical companies and a marketing agreement between them (the joint marketing of both products, Elavil Merck and Tryptizol Roche worldwide, except in the United States where it was only marketed by Merck), amitriptyline quickly became the most prescribed antidepressant at the time.

Simultaneously, Hoffmann-La Roche and H. Lundbeck and Co. had succeeded in synthesizing amitriptyline by modifying the chemical structure of imipramine accordingly. Although due to the priority of their application, Roche received the European marketing rights under the name Saroten® [37].

The discovery of the antidepressant properties of imipramine and its commercial success led to the development of a number of compounds with similar structures and activities (now called "me-too" compounds) in order to identify specific comparative advantages[38]. This subsequently became quite common practice in the field of pharmacological therapeutics. As a result, a number of TCAs were developed during the 1960s. In 1963, nortriptyline was approved in Britain under the name Allegron®, while in the United States it was approved by the Food and Drug Administration in November 1964, when desipramine (J.R. Geigy), the principal urinary metabolite of imipramine, was also approved; in 1966, trimipramine was introduced in Britain and other European countries under the name Surmontil®. These agents were followed by other TCAs: in 1966 by protriptyline (called Concoridin® in Europe and Vivactil® in the United States); in 1967 by iprindole (Prondol®); in 1969 by dothiepin (Prothiaden®), an agent not approved in the United States; doxepin[39], introduced onto the European market by Galenus (Aponal®), a subsidiary of Boehringer, and in the United States by Pfizer (Sinequan®) [40]; and clomipramine (Anafranil®), introduced in Europe in 1970, which was not approved in the United States.

All components of the TCA series were developed specifically as antidepressant agents, following in the wake of imipramine and modifying its chemical structure, so they can all be included in the type IV pattern of our serendipitous attribution criteria, in which neither chance nor sagacity played a part (Table 2).

Discovery of the antidepressant properties of iproniazid and non-selective MAOIs

The origin of the first specific antidepressant drugs, MAOIs, can be traced back to hydrazide anti-tuberculosis agents, which had been used since the early 1950s[5,41] (Figure 3). In 1952, Selikoff *et al.*[42] began to study the clinical effects of iproniazid at Sea View Hospital on Staten Island (New York). They observed that compared to isoniazid iproniazid had a greater stimulatory power on the central nervous

Table 2 Attribution of serendipity in the discovery of classical antidepressant drugs

Group/Family	Drug	ATC code	Date of discovery (psychiatric introduction)	Effect/primary properties ¹	Effect/secondary properties ²	Pattern of discovery
TCAs	Imipramine	N06AA02	1951 (1957)	S	NS	II
	Amitriptyline	N06AA09	1958 (1961)	NS	NS	IV
	Trimipramine	N06AA06	1964 (1966)	NS	NS	IV
	Butriptyline	N06AA15	1964	NS	NS	IV
	Desipramine	N06AA01	1964	NS	NS	IV
	Clomipramine	N06AA04	1963 (1970)	NS	NS	IV
	Nortriptyline	N06AA10	1963 (1967)	NS	NS	IV
	Protriptyline	N06AA11	1967	NS	NS	IV
	Iprindole	N06AA13	1967	NS	NS	IV
	Doxepin	N06AA12	1969	NS	NS	IV
	Dibenzepin	N06AA08	1970	NS	NS	IV
	Maprotiline ³	N06AA21	1967 (1973)	NS	NS	IV
	Dosulepin	N06AA16	1977	NS	NS	IV
	Amineptine	N06AA19	1978	NS	NS	IV
	Amoxapine	N06AA17	1980	NS	NS	IV
	Quinupramine	N06AA23	1983	NS	NS	IV
	Lofepramine	N06AA07	1989	NS	NS	IV
MAOI	Iproniazid	N06AF05	1952 (1957)	S	NS	II
	Isocarboxazid	N06AF01	1959	NS	NS	IV
	Phenelzine	N06AF03	1960	NS	NS	IV
	Tranylcypromine	N06AF04	1961	NS	NS	IV
	Nialamide	N06AF02	1988	NS	NS	IV
OCA	Trazodone	N06AX05	1966 (1973)	NS	NS	IV
	Nomifensine	N06AX04	1977	NS	NS	IV
	Mianserin	N06AX03	1966 (1979)	S	NS	II

¹Usually, but not always, correspond to discoveries in laboratory animals.

²Discoveries related to clinical efficacy.

³Maprotiline is the first tetracyclic antidepressant and is included in the group of “second generation antidepressants.” Antidepressant drugs were classified by the Anatomical Therapeutic Chemical classification system controlled by the World Health Organization Collaborating Centre for Drugs Statistics Methodology. This system classifies the active ingredient of a drug into groups according to the organ or system on which they have their effect. https://www.whocc.no/atc_ddd_index/?code=N06AX&showdescription=no.

NS: Non-serendipitous discovery; S: Serendipitous discovery; TCAs: Tricyclic antidepressants; MAOIs: Monoamine oxidase inhibitors; OCA: Other classical antidepressants; ATC: Anatomical Therapeutic Chemical.

system, an effect initially interpreted as a secondary effect of the preparation[42]. The psychological changes observed in tuberculosis patients treated with iproniazid were particularly striking[5,8,43]; these patients showed increased vitality, even a desire to leave the hospital and a gradual increase in social activity. In other types of patients treated with iproniazid, such as patients with rheumatoid arthritis or cancer, similar psychostimulant effects were also observed[44].

But the adverse effects of iproniazid, observed in the first clinical trials with tuberculosis patients, were more frequent than in the case of isoniazid. Therefore, it was abandoned, except for specific cases, such as that of David M. Bosworth, Director of the Department of Orthopedics at St. Luke's and Polyclinic Hospital (New York), who continued to defend the use of iproniazid in bone tuberculosis [45]. But a few astute clinicians saw a “primary effect” in the psycho-stimulant type of “secondary effect” discussed above, which could be useful in other types of patients, mainly of a psychiatric nature. This was the case of Jackson A. Smith (Baylor University, Waco, Texas), who, evaluating the “tranquil-

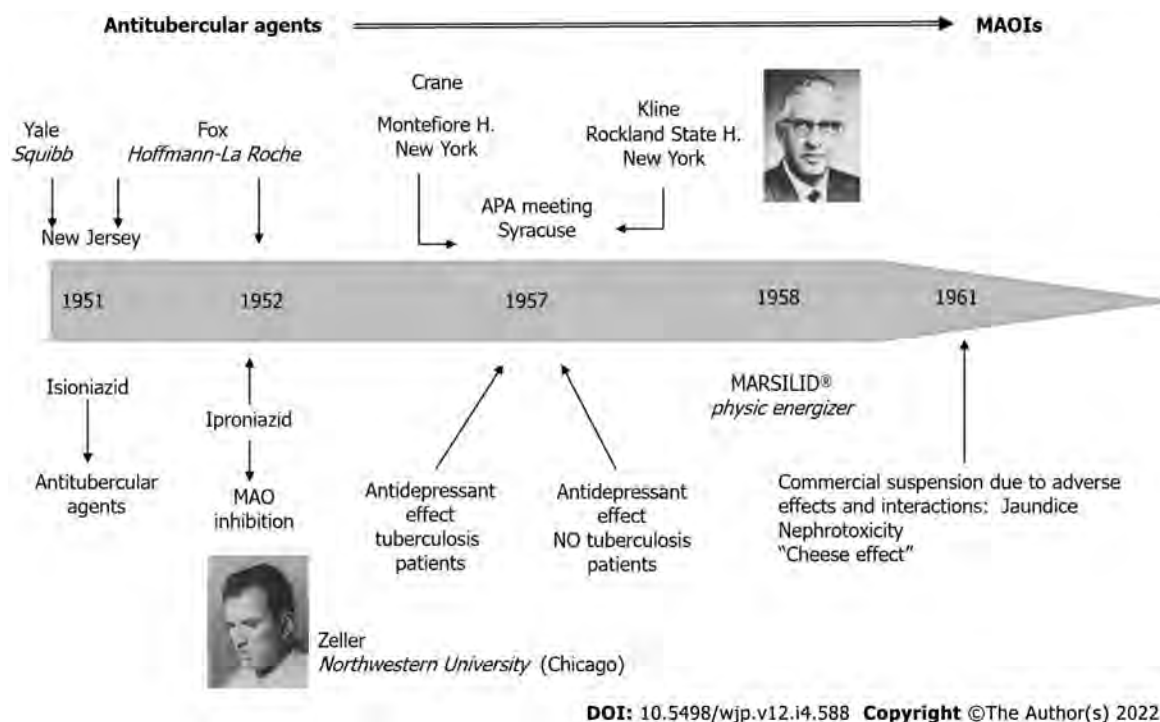


Figure 3 Historical process of the discovery of monoamine oxidase inhibitors during the 1950s. APA: American Psychiatric Association; MAOI: Monoamine oxidase inhibitors.

lizing" effect of iproniazid observed that of a group of 11 patients treated for 2 wk with this drug, 2 of them experienced a certain improvement (increased appetite, weight gain, increased vitality and improved sleep)[46]. The same was true of Gordon R. Kamman, of the University of Minnesota (Twin Cities)[47] and Carlos Castilla del Pino of the University of Cordoba in Spain, who described the euphoriant and mood-elevating effects of hydrazide therapy in tuberculosis patients[48]. Some studies were even published assessing the mood elevating effect of isoniazid in psychiatric patients[49-51]. In fact, one of these researchers, Max Lurie (Cincinnati), may have coined the term "antidepressant" precisely to describe the effect that this drug had on depressed patients[52].

The year 1957 was fundamental in the history of hydrazide drugs as antidepressants, as the first data on the effects of iproniazid on depression were presented at a meeting of the American Psychiatric Association in Syracuse in April of that year. Although its use was much more limited than isoniazid, George Crane of Montefiore Hospital in New York reported improvement in the mood of 11 out of 20 tuberculosis patients with concomitant depression[53], as did Frank Ayd, an intern at Taylor Manor Hospital in Baltimore[54]. However, these researchers never mentioned iproniazid as an "antidepressant" agent.

Meanwhile, Nathan S. Kline and his colleagues (Harry P. Loomer and John C. Saunders) from Rockland State Hospital (Orangeburg, New York), who were aware of the work of Charles Scott's team at Warner-Lambert Research Laboratories (Morris Plains, New Jersey) particularly the ability of iproniazid to prevent reserpine-induced immobility in mice[55], were the first psychiatrists to assess the efficacy of iproniazid in non-tuberculous depressed patients (chronic psychotic depression). They performed the same procedures on humans as Scott had done on animals. For their study, they recruited 17 severely inhibited patients with schizophrenia and 7 patients with depression from Kline's private practice and gave them a dose of iproniazid 50 mg, 3 times a day. Their results revealed the stimulating effect of iproniazid on depressed patients; 70% of the patients treated with this drug experienced a great improvement, including increased mood, increased appetite and increased interpersonal skills, interest in the environment and in themselves. These same effects were already provided at the Syracuse Meeting, although they were not released until a few years later when they were published[56].

In 1957, Kline[57] published the first neuropsychiatric experiments with iproniazid (previously reported at the American Psychiatric Association Annual Meeting in Syracuse) during a meeting of the Committee on Appropriations of the United States Senate in May[57], proposing the term "physic energizer" to designate the activity of this drug[58]. Two years later, Werner Janzarik proposed at a symposium held in Montreal the use of the term "thymereithics," *i.e.* compounds that act by increasing the stimulatory effects, to refer to all those drugs with effects similar to the new MAOIs.

Although iproniazid was only authorized (with the trade name of Marsilid) for the treatment of tuberculosis patients, its use in depressive patients was massive. Only 1 year after the Syracuse Meeting,

it was estimated that more than 400000 patients with depression were treated with iproniazid[59]. This opened the door to a group of specifically antidepressant drugs, later known as MAOIs, due to the research of Ernst Albert Zeller's team at Northwestern University Medical School (Chicago, Illinois). It was known in 1952 that iproniazid was able to inhibit MAO[60]. Despite all this, iproniazid was withdrawn from the United States market in 1961 following allegations that it induced a number of cases of jaundice and nephrotoxicity.

Serendipity played an important role in the discovery of iproniazid[11]. Thanks to the sagacity of healthcare professionals dedicated to the care of tuberculosis patients, it was realized that certain "secondary effects" of anti-tuberculosis medication of a psychostimulant nature, which appeared by chance, could be useful in psychiatric patients diagnosed with depressive disorders. Therefore, this would fall under a type II pattern under our serendipitous attribution criteria.

Iproniazid soon gave way to other agents with much higher MAO inhibitory potency[61], such as Hoffman-LaRoche's isocarboxazid (Marplan®), marketed in 1959, phenelzine developed by Warner-Lambert (Nardil®)[62], which became available in 1960, and tranylcypromine (Smith, Kline & French) (Parnate®)[63,64], which entered the market in 1961, as well as other hydrazine derivatives (nialamide, mebanazine and pheniprazine) and indole derivatives (etryptamine)[65,66]. The origin of this agent, synthesized in 1948 by Alfred Burger and William L. Yost, is part of the search for new analogues of amphetamines (trans,dl-2 phenylcyclopropylamine sulfate)[67], although its MAOI activity was discovered much later in 1959 by Smith, Kline & French Laboratories[63,68]. Indeed, the fact that tranylcypromine was not a hydrazine derivative aroused some clinical interest, and it was speculated that it could have a better hepatic safety profile than that of other MAOIs known to date[69].

But tranylcypromine was also withdrawn from the United States market in 1964, albeit for other safety reasons, when an increase in the number of drug-related hypertensive crises, some of them linked to intracranial subarachnoid hemorrhages, was reported. It was reintroduced in the same year at the request of specialists and is still in use today. Thanks to the contributions of Barry Blackwell, then a resident consultant in psychiatry at the Maudsley Hospital in London, it was confirmed that these crises were triggered by the concomitant consumption of certain cheeses, given their high tyramine content, hence the term "cheese effect"[70]. The link between the hypertensive crises described by Blackwell and the consumption of tyramine-rich foods is also a clear example of the phenomenon of "serendipity" in psychiatry, according to Blackwell himself[71]. A hospital pharmacist in Nottingham, called G.E.F. Rowe, read an article published by Blackwell[70] in 1963 in *The Lancet* on tranylcypromine and its adverse effects[70] and noted that the symptomatology described was alarmingly similar to that experienced by his own wife when she consumed certain cheeses. These episodes were described in detail in a letter Rowe sent to Blackwell, who was alerted to this dangerous association. Many other foods (yeast products, chicken liver, snails, pickled herring, red wines, some varieties of beer, canned figs, beans, chocolate and cream products, *etc.*) were subsequently found to contain indirectly acting amines (mainly tyramine), which could also cause hypertensive episodes in patients treated with MAOIs.

After the use of iproniazid as an antidepressant, the other agents in this family were incorporated into the antidepressant therapeutic arsenal thanks to recognition of their MAO inhibitory effect, meaning that they would fall into the type IV pattern under our serendipitous attribution criteria, where chance no longer played a role (Table 2).

Heterocyclic or "second-generation" antidepressants

During the 1960s, many changes were made to the dibenzazepine structure of imipramine in order to obtain new antidepressants with superior efficacy and/or an improved adverse effect profile. As a result, the tetracyclic, heterocyclic or "second generation antidepressants"[36], such as maprotiline (Ludiomil®), marketed by Ciba-Geigy in Europe and Japan in 1972[8], mianserin (Tolvon®), nomifensine (Merital®) and trazodone (Desyrel®), were developed. Compared to the classic TCAs, which had a very unspecific mechanism of action [serotonin (5-HT) and norepinephrine reuptake inhibition with blocking action of diverse receptors][72], these drugs had a slightly cleaner pharmacodynamic profile.

The first tetracyclic antidepressant was maprotiline, developed as an antidepressant by Max Wilhelm and Paul Schmidt in 1967 at Ciba. However, the four rings of its chemical structure are not fused together as is the case with other tetracyclic antidepressants. Clinical trials of this agent were also conducted by Kuhn[73]. By contrast, nomifensine is a tetrahydroisoquinoline antidepressant that is not chemically related to TCAs, MAOIs or heterocyclic antidepressants. It is a dopamine and norepinephrine reuptake inhibitor developed as an antidepressant in the 1960s. The pharmacological effects of nomifensine were similar to those of TCAs in animal models of depression but with a much lower rate of sedation[74]. However, it was withdrawn from the market in 1986 due to safety concerns (immune related hemolytic anemia), including some cases of dependence, given its similar mechanism of action to psychoactive drugs such as cocaine.

As far as trazodone is concerned, it is now known to have a dual mechanism of action whereby it inhibits the serotonin transporter and blocks the 5-HT₂ serotonin receptors (both the 5-HT_{2A} and 5-HT_{2C} receptors). But, like TCAs, it also exerts an antagonistic effect on α_1 - and α_2 -adrenergic receptors and histamine H₁ receptors, with almost no anticholinergic effects[75]. It was discovered in Italy in 1966 at Angelini Research Laboratories by Gorecki and Verbeeck[76] and developed as a second generation

antidepressant following the then current “mental pain” hypothesis, which postulated that clinical depression was associated with a reduced pain threshold[77]. Trazodone was patented and marketed in many countries around the world from 1973 and approved by the Food and Drug Administration as the first non-TCA, non-MAOI antidepressant in 1981. These three compounds can be included in our type IV pattern of attributability as serendipity was not involved in their discovery and development.

However, the development of mianserin is another example of serendipitous influence. As part of a research program carried out by Organon International, B.V. in Oss (The Netherlands), mianserin (a tetracyclic piperazino-azepine) was synthesized in 1966 by van der Burg *et al*[78], with the aim of confirming whether the antihistamine properties of phenbenzamine and the anti-serotonergic activity of cyproheptadine could be combined in a chemical structure that could be potentially useful for treating asthma, migraine or allergic diseases such as hay fever.

Early pharmacological studies confirmed that mianserin was capable of antagonizing the effects of serotonin in different samples of various animal tissues[79], including human blood vessels, and exhibited antihistamine properties[80]. These findings led to the launch of a pilot study in 1969, which was not published, in which the tetracyclic compound was administered to 10 asthmatic patients compared to an untreated control group. Patients who received mianserin had significantly fewer night-time asthma attacks. However, this line of research was not continued as a number of central adverse effects, mainly sedation, were also described[81]. Nevertheless, another study in Ireland also in 1969, found that mianserin had a marked positive effect in improving mood in some subjects, and they began to call mianserin the “good mood pill.” This observation about the hypothetical antidepressant properties of mianserin spurred on the clinical development of the molecule[81]. A number of experimental studies carried out using computer analyses of electroencephalogram recordings and comparative pilot trials with amitriptyline confirmed the antidepressant efficacy of this drug[82], which was presented as the first representative of a new generation of antidepressants (heterocyclic antidepressant compounds). Clinical trials over the next few years revealed antidepressant efficacy similar to that of classical TCAs, but superior to that of other “second generation” agents such as nomifensine or trazodone[81].

As in the case of the two group-leading agents of TCAs and MAOIs, mianserin falls within the type II pattern under our serendipitous attribution criteria, *i.e.* an initial serendipitous discovery when looking for an antihistamine drug leading secondarily to a non-serendipitous discovery of an antidepressant agent (Table 2).

NOTES FOR DIALOGUE

Serendipity is a phenomenon that has been regularly and constantly referred to when analyzing the great discoveries that supported the birth of modern psychopharmacology. But, as previously mentioned, the real role of serendipity in these processes has not been sufficiently well defined, possibly due to differences in opinion among authors given the semantic ambiguity of the term “serendipity” [83], and the degree of importance attributed at any given time to the two elements that make up the concept of serendipity: sagacity and unforeseen accidents. For this reason, our group[13,18] advocates the original meaning of the term, as “the discovery of something unexpected or not intentionally sought, in line with favors only the prepared mind”[35].

In fact, in the field of psychopharmacology, contrary to what has been postulated, pure serendipitous discoveries are rather rare, and most of them are of a mixed nature. Some authors refer to these patterns as “pseudo-serendipity”[84] or discoveries that are “serendipity analogues”[85].

These mixed serendipitous discoveries usually consist of a pattern that starts from an initial serendipitous observation and culminates in an intentionally sought-after discovery. For this reason, some authors and scholars may fall into the interpretative error of ascribing merit to chance or luck alone, seeing the results of research processes as a mere continuation of the initial serendipitous findings rather than as two manifestly different events. The cases presented in this paper on the discovery of the two families of classical antidepressants are proof of this: TCAs and MAOIs. Many other discoveries during the 1950s are included within this type II serendipitous attribution pattern that we have defined (initial serendipitous discoveries, in some cases made in laboratory animals, leading secondarily to non-serendipitous discoveries), such as the discovery of the antipsychotic properties of chlorpromazine and clozapine and the experimental tranquillizing properties of meprobamate and its subsequent anxiolytic effect in clinical trials. However, the clearest example was the discovery of the lethargic effect of lithium salts in guinea pigs and their subsequent antimanic effect in humans. Most authors consider the discovery of the antimanic effects of lithium to be purely serendipitous. However, Cade himself pointed out that the link between his casual observation of the lethargic effect in guinea pigs and the subsequent confirmation of the antimanic efficacy of lithium salts was far from obvious[86]. For more information on the historical development of these drugs, see the work of our group[19,20,23,25,41,87-89].

There are also examples of mixed serendipitous discoveries in reverse, included in our type III pattern (non-serendipitous discoveries partnered secondarily with serendipitous discoveries). The most representative example of this group would have to be barbiturates and their intended hypnotic effects,

which made the later serendipitous discovery of their anticonvulsant and antiepileptic effects possible [90].

But although serendipity does not usually work alone, there are also cases of pure serendipitous discoveries (type I pattern of attributability), such as the discovery of the anticonvulsant and mood stabilizing effects of valproic acid and valproate, respectively, or the discovery of the psychotropic effects of lysergic acid diethylamide. Similarly, other discoveries in the field of psychopharmacology during the golden decade of the 1950s should be included under the type IV pattern, namely non-serendipitous discoveries, in line with our operational definition of an unintended finding. Notable here is the discovery of the anxiolytic effect of chlordiazepoxide, the first benzodiazepine agent [91], and the antipsychotic effect of haloperidol and reserpine [24,92,93].

The clinical introduction of psychotropic drugs during the 1950s can be considered one of the great advances in medicine of the 20th century, and a major part of this breakthrough can be attributed to the discovery of the antidepressant effects of iproniazid and imipramine [3], a process in which serendipity played an essential role. But it is worth highlighting another series of contributions to the progress of biological psychiatry in addition to this great clinical contribution [3]. First, from a strictly pharmacological point of view, the development of imipramine led to the introduction of new methods for assessing the antidepressant activity of different substances [94]. Second, the discovery and subsequent therapeutic use of TCAs and MAOIs played a major role in developing the first etiopathogenic theories on affective disorders [95]. During the 1960s, catecholaminergic theories of depression blossomed, postulating a functional impairment of brain noradrenergic neurotransmission as the primary cause of affective disorders based on observations made on the effects of newly discovered antidepressant drugs, such as the blocking of synaptic reuptake of norepinephrine by imipramine [96]. Later, in 1968, Carlsson *et al* [97] described for the first time how imipramine was able to block the reuptake of serotonin in brain pathways, thereby laying the groundwork for the “serotonergic hypothesis” of depression.

However, the story of these two families of antidepressants evolved in completely different ways. Consequently, while TCAs continue to be used in clinical practice in an important way and constitute first-line tools in clinical research, MAOIs have suffered a large reduction in their use, except in the specific case of atypical depressions, largely due to their problems of interactions with other psychostimulant drugs and with tyramine-rich foods, which can lead to tragic hypertensive crises. However, despite this divergence, the importance of imipramine and iproniazid in the history of psychopharmacology is paramount.

CONCLUSION

It is clear that during the 1950s and 1960s serendipity played an important role in the process of building modern psychopharmacology in general and the first groups of families of antidepressant drugs in particular giving way in later decades to another way of understanding scientific research in this field, namely the systematic and rational planning of projects to be developed. In recent decades, psychopharmacology is moving away from the influence of serendipity towards new scientific approaches, although this is a gradual process [98] as can be seen with the serendipitous introduction of ketamine into the antidepressant arsenal. In any event, the results of this work confirm that serendipity should be understood as more of an eminently scientific construct than a literary curiosity.

In the words of the discoverer of vitamin C, Albert Szent-Györgyi, “discovery consists of seeing what everybody has seen and thinking what nobody has thought” [99].

FOOTNOTES

Author contributions: All authors have contributed to this work; López-Muñoz F and Álamo C designed the study; López-Muñoz F and Guerra JA analyzed the data; López-Muñoz F, D’Ocón P and Romero A wrote the manuscript; López-Muñoz F approved the final manuscript; all authors reviewed and approved the final draft.

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Research Article

Discovery Patterns of Drugs Approved for Treating Bipolar Disorder by Applying Operational Criteria of Serendipity: A Historical Analysis

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While the scientific community has long acknowledged the significant role of serendipity in shaping the field of contemporary psychopharmacology, its impact has not undergone a comprehensive analysis using operational methodologies. Serendipity, originally defined as discoveries stemming from a blend of luck and astuteness by Walpole, has been operationalized by our research group. Our definition builds upon Walpole's notion of fortuitous accidents and keen insight leading to the unexpected revelation of something unintended. We have discerned four unique serendipitous attributability patterns. In this paper, we delve into the historical aspect of how serendipity has played a role in the discovery and advancement of drugs approved for addressing different stages of bipolar disorder. The revelation of valproate's antimanic properties aligns with the pure serendipitous pattern (type I). Conversely, the discovery of lithium's antimanic effects corresponds to the mixed type II pattern, where the initial serendipitous observation of sedation in research animals, prompted by adding lithium salts to enhance uric acid solubility, led to the planned discovery of its calming impact on manic patients. On the contrary, the recognition of the mood-stabilizing attributes of lamotrigine aligns with the type III archetype. This particular pattern is defined by serendipity emerging as a consequence of a discovery that was initially nonserendipitous, as mood-stabilizing efficacy was incidentally observed during the treatment of epileptic patients for whom the drug was originally developed. Finally, carbamazepine and, notably, atypical antipsychotics fall within the type IV pattern. In this category, serendipity is entirely absent, as the antimanic use of carbamazepine was a straightforward extension of the use of other antiepileptic drugs. Atypical antipsychotics were introduced into bipolar disorder therapy through a deliberate and targeted design process, seeking drugs capable of acting on specific biological targets.

1. Introduction

Although bipolar disorder is a mental disorder known since antiquity (“mania,” “manic-depressive psychosis,” and “psychotic excitement”) [1], until recently, it has not received adequate attention from science, and its etiopathogenesis is still largely unknown. Therefore, some authors contend that, in the context of current scientific research, bipolar disorder is regarded as a developing medical condition [2]. It is a severe, chronic affective disorder characterised by alternating episodes of mania or hypomania with euthymia and depressive episodes [3]. From an epidemiological point of view, this disorder has a high morbidity/mortality rate [4], with a lifetime prevalence estimated at 1-2% of the population over the age of 20 [5]. However, if we were to take the so-called “bipolar spectrum” into consideration, which includes the classic type I, type II, and cyclothymic disorders, giving this pathology a much wider scope, we could estimate rates of prevalence at between 2.8 and 6.5% of the population [4, 6–8].

Similarly, the history of the pharmacological approach to bipolar disorder is not a long one, as the only effective therapeutic tool for these patients was lithium salts, until the effectiveness of valproate in treating manic episodes was validated in the mid-1990s. The unearthing of lithium’s effectiveness in treating mania, made by the Australian psychiatrist John F.K. Cade in the late 1940s, was a significant revelation [9]. During the period known as the “modern psychopharmacology era,” which became well-established in the 1950s with the clinical introduction of the extensive groups of pharmaceutical agents still employed today, including the conventional neuroleptics and antipsychotics, the traditional tricyclic antidepressants, and the benzodiazepine anxiolytics [10], this is what is commonly referred to as the “psychopharmacology revolution,” as it not only provided the first specifically effective agents for managing psychiatric disorders, which drastically changed psychiatric care, but also allowed the neurobiological basis of mental illnesses to be understood.

In the specific case of bipolar disorder, until the antimanic effect of lithium was discovered, the therapeutic agents that had been used in clinical practice showed very low efficacy [10], with sedatives being the most commonly used drugs to manage manic patients. Opium and morphine were commonly used in the later part of the 19th century, along with alkaloids obtained from plants of the *Solanaceae* family, such as hyoscyamine and hyoscyne or scopolamine [1]. Later, chloral hydrate was used, which made it possible to treat manic patients at home [11], as were bromides [12], and then barbiturates in the 20th century. Barbitol was the first drug in this family and was introduced into clinical practice in 1903. It had already been shown to be capable of calming manic patients, among other properties, although the most widely used in these conditions was phenobarbital, marketed in 1912, thanks to its more prolonged pharmacological action. Even highly excited manic patients were given so-called “sleep cures” based on barbiturates and other compounds, which induced an extended and profound state of sleep, lasting for at least 6-7 days [13].

The efficacy of lithium salts in managing manic episodes became apparent during the 1950s. Nonetheless, it was not until the latter part of the 1960s that it was confirmed that lithium also possessed effectiveness in averting manic-depressive episodes in individuals diagnosed with bipolar disorder [14, 15]. However, the drug’s authorization for antimanic use by the US Food and Drug Administration (FDA) was delayed until 1970 [16]. Valproic acid was approved in 1995 by the FDA for antimanic use, and in 2004, carbamazepine was also approved, thereby giving classic anticonvulsants the status of established antimanic drugs. Finally, since 2000, the FDA and the European Medicines Agency (EMA) have authorized different atypical antipsychotic drugs (AADs) for antimanic use (olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, and cariprazine) or antidepressant use (quetiapine, olanzapine, lurasidone, lumateperone, and cariprazine), and lamotrigine, which belongs to the class of contemporary antiepileptic drugs, is used for the prevention of depressive episodes in individuals with bipolar disorder (see Table 1; Figure 1). In any event, it should be noted that polypharmacy with drugs from different therapeutic groups is a prevalent approach in the treatment of individuals with bipolar disorder [17].

Certain researches have demonstrated that serendipity may have significantly contributed to the uncovering of mood-stabilizing properties in some of the medications presently employed in bipolar disorder treatment (basically lithium salts and classic antiepileptic drugs), as it did with other drugs discovered at the beginning of the “era of modern psychopharmacology” [18, 19]. Nevertheless, a significant degree of dispute exists within the scientific literature regarding this matter, perhaps stemming from the absence of agreement on the conceptual delineation of this phenomenon. This disparity is noticeable even though there is a historical association between the 18th-century English writer, politician, and historian Horace Walpole and the British diplomat Sir Horace Mann. Their discussions revolved around the ancient Persian tale *The Three Princes of Serendip*, which initially referred to the two essential elements that would define “serendipity”: accident and sagacity [18], it gradually evolved until it was considered a synonym for chance or random phenomenon and lost the component of sagacity.

Sagacity has now been recognised once again, along with unexpected observation, as a key element of serendipity. However, our group has argued that, when it comes to serendipitous discoveries, sagacity is subsequent to the accidental observation, i.e., we would be addressing the uncovering of something unintended, irrespective of the steps that led to the fortunate observation [18, 20]. Following this approach, the incorporation of numerous psychotropic drugs discovered during the 1950s into clinical practice would be in line with the influence of serendipity. In this regard, Hargrave-Thomas et al. [21] postulate that a quarter of all existing drugs benefited from the phenomenon of serendipity at some point in their development, particularly psychotropic drugs.

Nevertheless, the extent of serendipity’s involvement in these endeavors has traditionally been conveyed subjectively

TABLE 1: Drugs approved by the Food and Drug Administration of the United States (FDA) or European Medicines Agency (EMA) for treatment of patients with bipolar disorder.

Group/family	Drug	ATC code	Mania (date approved)	Mixed mania/depression (date approved)	Maintenance/prevention (date approved)	Bipolar depression (date approved)
Salts	Lithium	N05AN01	1970	No	1978	No
Classic antiepileptics	Carbamazepine	N03AF01	2004	2004	No	No
	Valproate/divalproex sodium	N03AG01	1995	2005	No	No
New anticonvulsants	Lamotrigine	N03AX09	No	No	2003	No
Classic antipsychotics	Chlorpromazine	N05AA01	1973	No	No	No
Atypical antipsychotics	Aripiprazole	N05AX12	2004	2004	2005	No
	Asenapine	N05AH05	2009	2015	No	No
	Cariprazine ¹	N05AX15	2015	2015	No	2019
	Lumateperone ²	N05AD10	No	No	No	2021
	Lurasidone ³	N05AE05	No	No	No	2013
	Olanzapine	N05AH03	2000	2000	2004	2003 ^a
	Quetiapine	N05AH04	2003	2004	2008 ^b	2006
	Risperidone	N05AX08	2003	2003	2009	No
	Ziprasidone	N05AE04	2004	2004	2009 ^b	No

¹Not authorized by the European Medicines Agency for the treatment of the bipolar disorder, only for the treatment of schizophrenia; ²not approved by European Medicines Agency; ³not authorized by the European Medicines Agency for the treatment depressive phase of bipolar disorder, only for the treatment of schizophrenia; ^aneed to combine with fluoxetine; ^bneed to add lithium or divalproex. Mood stabilizers were categorized using the anatomical therapeutic chemical (ATC) classification system, overseen by the World Health Organization Collaborating Centre for Drugs Statistics Methodology (WHOCC). This system groups the active ingredients of drugs based on their impact on specific organs or systems within the body https://www.whooc.no/atc_dtd_index/?code=N06AX%26showdescription=no.

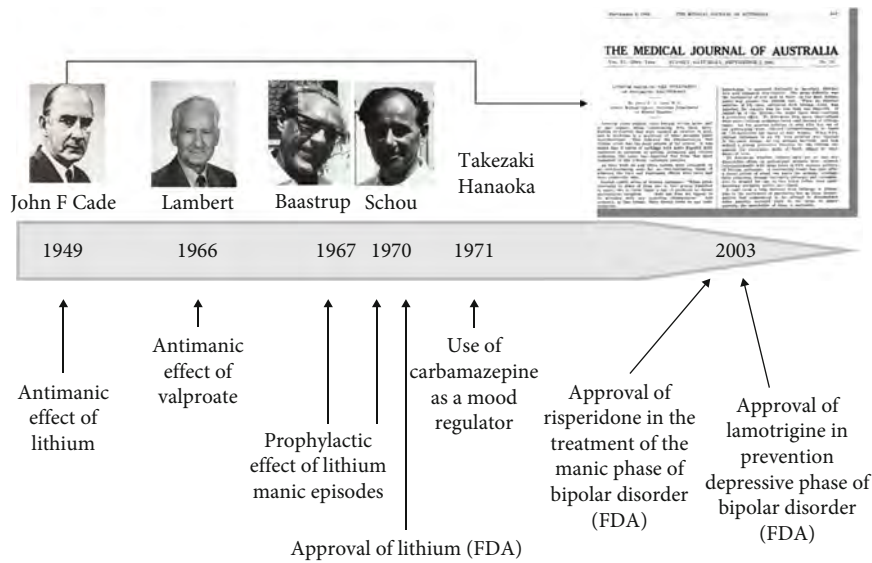


FIGURE 1: Historical process of the discovery of mood stabilizer drugs. Original figure created and designed by the authors.

by the scientists who made these discoveries. To tackle this matter, we have formulated a precise characterization of serendipity based on four specific patterns of attributability [18, 22]. This framework enables us to objectively discern the actual contribution of serendipity to the drug discovery process. In this paper, we will use this methodology to analyze the influence of serendipity in the discovery of the mood-stabilizing characteristics of drugs authorized for managing bipolar disorder.

2. Materials and Methods

In earlier studies, we have introduced a functional characterization of serendipity [18, 22] which relies on identifying four distinct patterns of attributing serendipity within the process of discovering drugs (Figure 2).

Pattern I: this includes purely serendipitous discoveries.

Pattern II: this is a modification of the preceding pattern, which outlines the initial chance findings leading to subsequent planned discoveries that lack serendipitous origins.

Pattern III: discoveries without serendipity that subsequently pave the way for serendipitous findings.

Pattern IV: this corresponds to purely nonserendipitous discoveries, outside the realm of chance or unintended accident. This last pattern includes all those discoveries of pharmacological drugs that fall within rational and systematic research programmes specifically designed to obtain agents with very specific effects on a given pathology.

While pattern I is exceptionally uncommon, mixed discoveries (patterns II and III) were prevalent during the initial era of modern psychopharmacology, with pattern II being most common, characterised by initial serendipitous discoveries, often observed in the laboratory during the process of animal research, which subsequently led to planned observations in the clinical setting.

Before applying the attributability criteria, we sourced the original manuscripts containing the initial pharmacolog-

ical and clinical information on presently approved mood-stabilizing drugs from the subsequent website:

- (1) The primary databases in the biomedical field (Medline, Embase, and Scopus)
- (2) The documentation resources provided by the pharmaceutical companies that distributed the mood-stabilizing medications
- (3) The documentation accessible through the International Network for the History of Neuropsychopharmacology (INHN), under the guidance of Thomas A. Ban (Vanderbilt University).
- (4) David Healy's *The Psychopharmacologists* series of interviews de (Arnold-Oxford University Press).
- (5) The history of psychopharmacology collection of the International College of Neuropsychopharmacology (CINP) (Collegium Internationale Neuro-Psychopharmacologicum), coordinated by Thomas A. Ban, David Healy and Edward Shorter and published by Animula
- (6) Prof. López-Muñoz's collection of documents on the history of psychopharmacology

3. Results

3.1. The Uncovering of Lithium Salts' Antimanic Characteristics. Lithium is an alkali metal that was first isolated by the Swedes Johann A. Arfwedson and Jöns J. Berzelius in 1817. In the mid-19th century, lithium was introduced therapeutically to treat gout, rheumatism, and kidney stones, as a chance result of the so-called "uric acid diathesis" theory [23], according to which lithium salts were able to dissolve urate deposits. In this regard, it was also hypothesised that mental disorders could be related to high

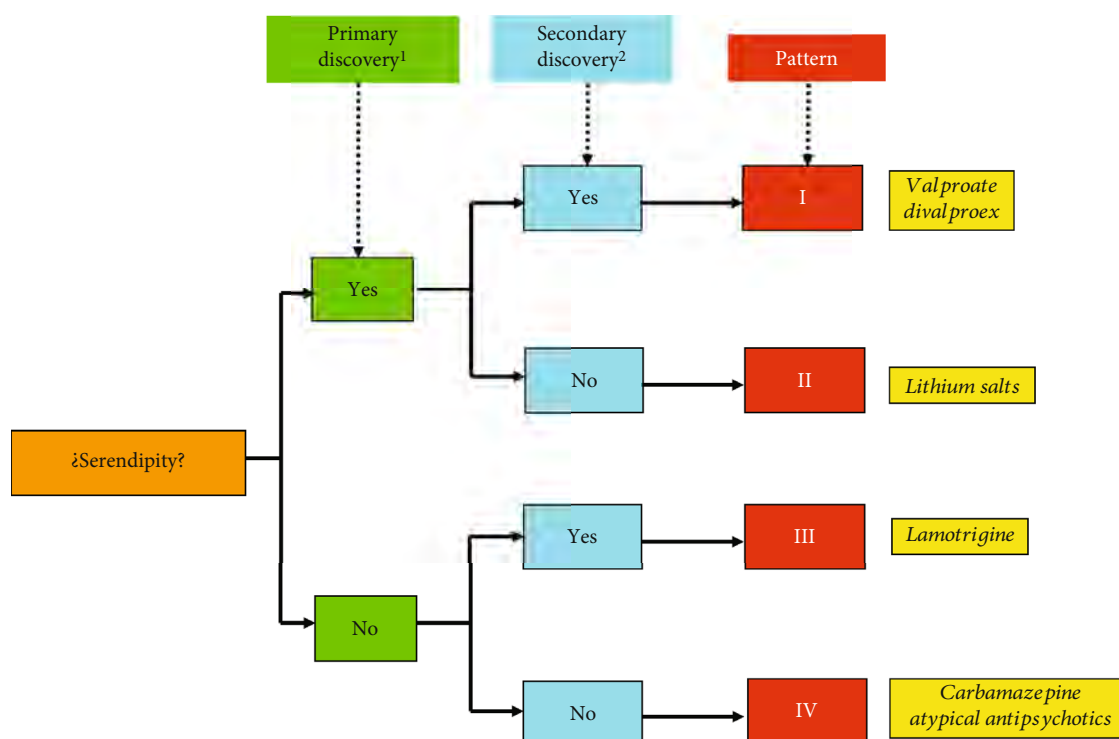


FIGURE 2: Illustration depicting the four attributability patterns in the discovery of pharmaceutical agents and their application to mood stabilizer drugs. ¹Typically, although not invariably, these findings are associated with outcomes observed in experimental animals; ²discoveries concerning clinical effectiveness. Figure adapted from the original created by the authors [18].

urate levels, referred to as “gout that affects the head” and “gouty mania” [24], for which lithium treatments were also recommended. However, excluding this anecdotal use, the actual introduction of lithium salts into psychiatric therapeutics took place in 1949, due to the remarkable foresight of the Australian psychiatrist John F.K. Cade, superintendent of the Bundoora Repatriation Mental Hospital (Victorian Department of Mental Hygiene of Australia) [1, 22, 25].

Cade’s keen observational skills allowed him to observe how patients with thyroid pathologies showed a symptomatology very similar to that experienced by patients with manic-depressive disorder. Therefore, patients with hyperthyroidism manifested some symptoms very similar to those presented by patients in the manic phase; conversely, the symptoms of hypothyroid patients resembled those of patients in the depressive phase [26]. This astute observation led Cade to think that manic-depressive illness might be related to endocrine dysfunction and that there might be some sort of toxin in these patients that could be eliminated in the urine. To test this hypothesis, Cade designed an interesting and unusual experimental animal study; several guinea pigs were subjected to intraperitoneal injections of varying concentrations of urine collected from individuals experiencing manic and melancholic states and individuals who were in a normal, healthy state. He noticed that those treated with high doses of urine, particularly from manic patients, exhibited convulsions, prolonged unconsciousness, and eventually succumbed. These outcomes prompted Cade to consider that urea in the urine of manic patients might be responsible for the observed toxic effects in guinea pigs.

However, he soon realized that the levels of urea and creatinine in the urine of manic individuals were similar to those of other patients. Therefore, he shifted his focus to uric acid to validate his hypothesis. He administered a solution containing urea and various concentrations of uric acid to the laboratory animals. Nevertheless, due to the limited solubility of uric acid, he turned to lithium carbonate, a significantly more soluble compound. By chance, he noticed that the administration of this salt at a concentration of 0.5% in an 8% urea solution prevented the occurrence of the previously observed convulsive symptoms, and all the animals survived [27]. In light of these findings, Cade decided to assess the effects of exclusively administering lithium carbonate to guinea pigs and observed that after 2 hours, the animals suffered a state of lethargy, which reverted 2 hours later [25, 28].

After analysing these experimental results, Cade considered the possible therapeutic effects of lithium salts on psychotically excited and manic patients and opted to provide a 54-year-old individual with 1200 mg of lithium citrate, thrice daily. The patient was diagnosed with manic excitement and had a 5-year history of manic episodes. The patient started to improve 5 days after starting treatment, and 4 months later, upon his discharge from the hospital, he received an outpatient treatment consisting of 300 mg of lithium carbonate daily, administered in two doses. This choice was made due to the reduced likelihood of nausea compared to citrate. The patient’s remarkable improvement was such that he managed to resume his prehospitalization job. Cade achieved comparable outcomes with nine

TABLE 2: Assigning serendipity's role in the finding of mood-stabilizing drugs.

Group/family	Drug	Date of discovery (psychiatric introduction)	Effect/primary properties ^a	Effect/secondary properties ^b	Pattern of discovery
Salts	Lithium	1817 (1949)	S	NS	II
Classic antiepileptics	Carbamazepine	1961 (1971)	NS	NS	IV
	Valproate/divalproex sodium	1881 (1966)	S	S	I
New anticonvulsants	Lamotrigine	1981 (2002)	NS	S	III
Atypical antipsychotics	Aripiprazole	1988 (2002)	NS	NS	IV
	Asenapine	1990 (2009)	NS	NS	IV
	Cariprazine	2008 (2015)	NS	NS	IV
	Lumateperone	2007 (2019)	NS	NS	IV
	Lurasidone	2003 (2010)	NS	NS	IV
	Olanzapine	1991 (1996)	NS	NS	IV
	Quetiapine	1985 (1997)	NS	NS	IV
	Risperidone	1988 (1993)	NS	NS	IV
	Ziprasidone	1987 (2001)	NS	NS	IV

^aUsually, but not always, they correspond to discoveries in laboratory animals; ^bdiscoveries related to clinical efficacy; NS: nonserendipitous discovery; S: serendipitous discovery.

additional patients diagnosed with mania or psychosis, observing the most favorable responses in highly agitated individuals. These findings were subsequently published in 1949 in *The Medical Journal of Australia* [8], in an article that is considered to be the start of the so-called “revolution in psychiatric pharmacology” [1].

However, lithium salts were not officially approved to treat mania until 1970 (Table 1; Figure 1), due to a number of circumstances that adversely affected their clinical development. These include lithium's poor reputation due to the high number of fatal poisonings in the USA in the late 1940s after lithium chloride was marketed as an alternative to sodium chloride or table salt for patients suffering from heart disease [29] and the subsequent rise of neuroleptic drugs from 1952 onwards, which led to scientific interest in lithium being abandoned [25].

The identification of the antimanic effects of lithium salts serves as a prime illustration of a serendipitous discovery (inducing a lethargic state in laboratory animals after adding these salts to improve the solubility of uric acid). Subsequently, this serendipitous discovery transformed into an intentional and nonaccidental finding, particularly the calming effect observed in manic patients. In this way, the antimanic effect of lithium salts could be classified as fitting our type II pattern of serendipitous attributability criteria, as outlined in Table 2. Nevertheless, this dual nature, a common feature in the discoveries of various psychotropic drugs in this period, has spurred debates concerning the actual influence of serendipity in these research and development procedures.

3.2. Valproic Acid and Valproate as Mood-Stabilizing Drugs. Valproic acid was synthesised in 1881 by the American chemist Beverly S. Burton as an organic solvent analogue of valeric acid [30], becoming a very popular diluent in the mid-20th century, particularly in the pharmaceutical indus-

try [31]. In 1963, Georg Carraz, a researcher at Laboratoire Berthier in Grenoble, conducted an assessment of the experimental anticonvulsant properties of several khellin compounds [32]. As was customary at that time, he employed valproic acid as a diluent. Employing the pentylenetetrazol convulsion model [33], Carraz et al. serendipitously discovered that every solution containing valproic acid exhibited anticonvulsant properties, irrespective of the specific khellin compound being tested. He also determined that valproic acid was the substance responsible for this effect [34].

Following this breakthrough, Carraz synthesised valpromide, a derivative of valproic acid designed to have increased lipid solubility and improved permeability through the blood-brain barrier in theory [31]. To evaluate its potential for human use, Carraz collaborated with Sergio Borselli, a psychiatrist who had received training under Pierre A. Lambert at the Hôpital Psychiatrique de Bassens in Rhône-Alpes. This collaboration paved the way for a series of clinical trials involving epilepsy patients [35, 36]. Initially, Borselli and Lambert observed that valpromide exhibited a sedative effect, especially when administered alongside other anticonvulsant drugs available at that time, such as phenobarbital. In any case, when valpromide and valproate were administered independently, these researches also appreciated, by chance, in 1966, that patients experienced a stabilisation of their mood, as well as an improvement in their neurological condition [36]. That same year, these researchers published, for the first time, in patients with bipolar disorder, the mood-stabilizing effects of valproate, such as an improvement in impulsivity, irritability, and emotional lability [37] (Figure 1). Nevertheless, valproate would not be licensed as an antimanic drug in the USA until 1995 (Table 1), after the publication of a series of clinical trials supported by Abbott Laboratories (Illinois, USA), the company that owns the patent for the divalproex sodium. The studies showed that both divalproex and lithium were significantly more

effective than placebo in reducing the symptoms of acute mania and that divalproex had antimanic efficacy similar to that of lithium [38].

Both the revelation of valproic acid's anticonvulsant properties and the discovery of valproate's mood-stabilizing effects serve as remarkable instances of unplanned scientific observations, exemplifying pure serendipity (Table 2).

3.3. The Finding of the Mood-Stabilizing Effects of Carbamazepine. Carbamazepine is a tricyclic anticonvulsant compound that was formulated in the laboratories of J.R. Geigy, situated in Basel, Switzerland, during the latter part of the 1950s [39]. The anticonvulsant characteristics of carbamazepine were elucidated in 1963 by Walter Theobald and H. A. Kunz [40]. However, its initial introduction to treat manic patients in Japan was due to the concurrence of several factors, such as the lack of availability of lithium on the Japanese market in the early 1970s [41] and the preponderance of psychiatry over neurology in Japan [42], which resulted in the widespread use of this drug agent in Japanese hospitals after being marketed as an antiepileptic drug during the 1960s [41]. Furthermore, anticonvulsant drugs had been evaluated as mood stabilizers since the early 1970s, based on the hypothesis that epilepsy and bipolar disorder might share similar underlying properties, such as kindling [43].

In this setting, Japanese psychiatrists began to use carbamazepine on manic patients due to its sedative properties, rather than other less well-tolerated drugs such as barbiturates, particularly after learning that valpromide was being used for manic patients [31]. In 1971, Haruhiko Takezaki and Masanori Hanaoka, in Tottori, published the first clinical data on manic-depressive patients treated with carbamazepine [41] (Figure 1). It was an open study in which 20 patients were evaluated for periods between one and eleven months, with an improvement of "symptomatic manic-depressive" symptoms in 85% of them, although the authors did not mention whether the patients were treated previously with lithium. However, although controlled studies between carbamazepine and lithium showed similar efficacy [44], this input was not taken up in the West [45], where carbamazepine was not licensed by the FDA for this indication until 2004 (Table 1), with the introduction of an extended-release galenic formulation.

The identification of carbamazepine's antimanic properties aligns with our type IV attributability pattern, as serendipity played no part in its introduction into the management of bipolar disorder, which was merely an extrapolation concerning the application of different antiepileptic medications, like valproate (Table 2).

Although serendipity actively participated in the introduction of classical antiepileptic agents in terms of observing the clinical improvement of manic patients, the pharmacological actions that justified them took many more years to begin to be discovered. And also, coincidentally, it was found that many of them were shared with lithium, such as the enhancement of gabaergic neurotransmission, the decrease in dopamine turnover, the decrease in the release of noradrenaline, or the increase in synaptic levels of serotonin.

However, despite the advances made in recent years, the mechanism of antimanic action of anticonvulsant drugs is not yet well determined, and there is no evidence of whether or not it coincides with their antiepileptic mechanism of action [1].

3.4. Lamotrigine and Its Efficacy in Preventing Depressive Episodes in Bipolar Disorder. Lamotrigine, a phenyltriazine compound, was synthesised in the early 1980s at Wellcome Research Laboratories in Beckenham, Kent, England. This development was part of an initiative to create novel antiepileptic drugs that offered improved tolerability compared to existing options during that period [46]. This initiative was founded based on the assumption developed in the mid-1960s concerning the potential proconvulsant properties of folates whereby antiepileptic drugs would exert an antagonistic action on folic acid [47]. A number of phenyltriazines were synthesised taking pyrimethamine, a substance developed in 1950 as a malaria agent, as a reference, including BW288U, a compound exhibiting strong anticonvulsant efficacy while displaying limited antifolate properties. Attempts were made to optimise this compound, resulting in lamotrigine [48]. Phase I clinical trials were quickly initiated and it demonstrated excellent pharmacological properties. It was finally approved as an antiepileptic drug in Ireland in 1990 and by the FDA in 1994. In addition, it had an improved profile in terms of side effects compared to classical antiepileptic drugs, despite the problematic but rare Stevens-Johnson syndrome.

During the first clinical studies on epileptic patients with the new substance, Smith et al. [49] observed its positive impact on the emotional state and communication abilities of the individuals undergoing treatment with it, which made it possible to test it on bipolar patients in a psychiatric setting. The initial researcher to present scientific evidence regarding the effectiveness of lamotrigine in the context of bipolar disorder was Weisler et al., affiliated with the University of North Carolina Chapel Hill School of Medicine in Chapel Hill, NC, USA, who, as he himself acknowledged [46], knew about this molecule before it was authorized in the USA, due to the fact that he had attended several international congresses. Following the importation of the medication from Europe and the submission of an application to the FDA for compassionate use authorization, in 1993, he employed this drug in combination with other treatments to manage two patients who had been grappling with bipolar disorders for an extended duration, who were resistant to all of the pharmacological treatments available at the time [1]. A marked clinical improvement was confirmed in both patients within several weeks. Weisler's group presented their results at the 1994 Annual Meeting of the American Psychiatric Association (APA) in Philadelphia [50] and defended its use based on the molecule's mechanism of action (a strong antkindling effect, inhibition of sodium channels, and suppression of glutamatergic activity).

Following the publication of several other clinical cases, GlaxoSmithKline launched an ambitious programme of clinical trials using lamotrigine on bipolar disorder between 1996 and 2001. A total of 2,400 patients from 4 continents

were enrolled in this phase III, controlled, double-blind trials [46]. Unlike classic antiepileptic drugs, which are more effective in controlling mania than depression, lamotrigine was shown to be particularly effective in patients with predominantly depressive phases. Lamotrigine yielded its most favorable outcomes in studies focused on preventing relapses in individuals with bipolar disorder, demonstrating its superiority over lithium and a placebo [51, 52], which led to its authorisation by the FDA for this indication in 2003 (Table 1; Figure 1). These findings corroborated lamotrigine's primarily antidepressant characteristics as a mood stabilizer, in comparison with the agents available up to that time.

The discovery of lamotrigine's mood-stabilizing attributes could align with the criteria for type III serendipitous attributability in our framework, characterised by the presence of serendipity secondary to a nonserendipitous discovery (Table 2), as it was developed specifically as an antiepileptic agent, but the discovery of its mood-stabilizing efficacy was serendipitous in the context of its use in the treatment of epileptic patients. However, at the time of this discovery, the antimanic effects of the classic anticonvulsant drugs, valproate, and carbamazepine, were already known.

3.5. Atypical Antipsychotics and their Role in Managing the Bipolar Spectrum. Chlorpromazine stands as the sole classic neuroleptic drug licensed by the FDA for the treatment of manic episodes in bipolar disorder, a designation granted in 1973. This authorisation was justified by the results of several clinical trials that confirmed their efficacy in acute mania [53] and their hypothetical faster action than classic mood regulators [54]. However, their use was very limited due to their high incidence of adverse effects and, above all, to the clinical introduction of the new, much better-tolerated AADs.

Olanzapine was the first among the atypical antipsychotics to receive authorization for the treatment of acute mania. Eli Lilly (Indianapolis, USA) initiated a series of clinical trials that were published from 1999 to 2003. These trials assessed the effectiveness of olanzapine in comparison to placebo, divalproex, and haloperidol in the treatment of acute mania or mixed episodes. Later, the efficacy of olanzapine in acute mania was confirmed, with better results than valproate and lithium [55]. As a result, in the year 2000, olanzapine achieved the distinction of being the inaugural AAD to receive approval from the US FDA for the treatment of manic episodes in bipolar disorder (Table 1).

Subsequent to these developments, the effectiveness of AADs in the management of manic conditions was established through randomized, placebo-controlled studies [3, 56–60]. These studies indicated a class-wide efficacy among AADs in the treatment of mania. Consequently, one by one, nearly all AADs obtained approval for the treatment of mania; risperidone and quetiapine in 2003, ziprasidone and aripiprazole in 2004, asenapine in 2009, and cariprazine in 2015 were granted FDA approval as antimanic drugs for use in monotherapy (Table 1). In this sense, their indications were broadened to encompass the management of all three clinical phases of bipolar disorder. Certain medications were

authorized for the purpose of averting the recurrence of manic episodes in patients with bipolar disorder who had previously exhibited a positive response to treatment with these antipsychotic drugs (Table 1), while others were sanctioned for the treatment of depressive episodes. This included olanzapine (in combination with fluoxetine) in 2003, quetiapine in 2006, lurasidone in 2013, cariprazine in 2019, and more recently, lumateperone in 2021. Currently, AADs constitute the frontline treatment for manic phases [61].

The particular neurochemical properties of AADs, notably their ability to inhibit dopamine receptors, as well as other elements of their drug receptor profiles and their influence on various neurotransmitter systems [62], prompted considerations of their potential efficacy in treating mania [63]. Neurobiological studies confirmed that AADs, in addition to antagonizing dopamine D₂ receptors, also exhibited antagonism towards serotonin 5-HT_{2A} and 5-HT_{2C} receptors, particularly 5-HT_{2A} and 5-HT_{2C}. Additionally, some AADs, such as aripiprazole, ziprasidone, and asenapine, acted as partial agonists of the 5-HT_{1A} receptor [62]. These mechanisms collectively led to heightened noradrenergic and dopaminergic neurotransmission [64]. Nevertheless, the precise mechanisms by which AADs exert their influence on mania remain undisclosed. It is important to highlight that these substances exhibit a unique antimanic impact, regardless of the presence of concurrent psychosis or the degree of sedation induced by the medication [43].

Bipolar depression is more difficult to treat than manic episodes, and different pharmacologic approaches are required for unipolar depression [65]. Quetiapine became the initial AAD to secure FDA authorization for the standalone treatment of bipolar depression. This achievement was realized through a clinical trial initiative initiated by Astra-Zeneca (London, UK). In these studies, quetiapine demonstrated markedly superior and more rapid response and remission rates in cases of acute bipolar depression compared to placebos, with discernible benefits evident as early as the first or second week [66, 67] and significantly better clinical improvement than lithium [68] and the antidepressant paroxetine [69]. From a neurobiological perspective, the active metabolite of quetiapine, norquetiapine, facilitates the transmission of serotonin by behaving as a partial agonist of 5-HT_{1A} receptors, and also strongly inhibits the noradrenaline transporter, leading to heightened functionality of the noradrenergic system [70, 71].

Meanwhile, lurasidone was the first AAD to be tested in bipolar disorder, although its efficacy was only analyzed in the treatment of the depressive phase. This decision was influenced by three major factors [72]: its special pharmacological profile with receptor affinity (primarily its 5-HT_{1A} receptor and 5-HT₇ receptor agonist and antagonist activity, respectively) [73], its efficacy in animal models of acute and chronic depression [74], and the results obtained in previous efficacy studies on schizophrenia [75], which found that patients treated with lurasidone showed a significantly greater reduction in scores on scales of depression than patients in the control group. Consequently, starting in 2009, Sunovion Pharmaceuticals, Inc. (Marlborough,

Massachusetts, USA) devised a series of clinical trials aimed at evaluating the effectiveness and safety of lurasidone. These trials encompassed both standalone use and combined treatment with lithium or valproate in adult patients grappling with bipolar depression [72, 76]. The favorable outcomes from these trials culminated in the FDA granting approval for this medication in June 2013 to treat depressive episodes in bipolar type I patients. The trail of lurasidone was followed by lumateperone, developed by IntraCellular Therapies (under licence from Bristol-Myers Squibb) and licensed only to treat the depressive phase of bipolar disorder, possibly due to its moderate selective serotonin transporter reuptake inhibition and simultaneous modulation of dopamine and glutamate [77].

The antidepressant effects of some AADs can be explained by their modulating properties of the three monoaminergic systems (noradrenergic, serotonergic, and dopaminergic) related to the etiopathogenesis of depression [78].

The clinical introduction of AADs in bipolar disorder did not involve either chance or sagacity, implying that the uncovering of their antimanic and antidepressant characteristics aligns with the Type IV pattern in our framework for serendipitous attributability criteria (Table 2). This family of drugs was introduced into the therapy of bipolar disorder following a rational and targeted design procedure, i.e., following a preplanned strategy, in which drugs capable of acting on specific loci of action were sought.

4. Discussion

Many scientific contributions have tangentially commented that serendipity played a prominent part in the identification of the initial psychotropic drugs during the mid-20th century's golden era. However, the true role of serendipity has not been studied sufficiently from the perspective of scientific methodology. This is partly because the very concept of serendipity has not been defined precisely [79], often assimilating it to the involvement of luck or chance (happy discoveries), without valuing the key role of the sagacity of researchers and clinicians. This led to our group developing operational criteria for serendipitous attributability in line with the original approach to the term, where sagacity shares preponderance with the accidental discovery of something not intentionally sought [22]. This is very much in line with Louis Pasteur's postulate: "In the field of scientific observation, chance favours only the prepared mind" [80].

Following our approach and contrary to what many authors propose, we can affirm that purely serendipitous discoveries in the field of psychopharmacology do not occur very often and that discoveries characterised by a mixed pattern are much more common. Other researchers have categorized these findings, denoted as type II and type III in our operational criteria, namely "pseudoserendipity" (accidental discoveries of ways to achieve an end sought for) [81] or findings that can be likened to "serendipity analogs" [82]. In both cases, the discovery of the antibiotic effect of penicillin is always used as a characteristic example, in addition to many others outside of pharmacology and medicine, such as the process of vulcanization of rubber by Charles Goodyear, after many years of hard

work [81]. But even other authors only highlight the role of luck or chance in making these discoveries, deeming the end result of the process to be a formal continuity of previous serendipitous discoveries, rather than the occurrence of two clearly distinct events.

The most common pattern in these mixed serendipitous discoveries is usually an initial serendipitous observation that ends with a rational and intentional discovery that does not involve accident. This is what we have termed the type II pattern, which includes one of the most important contributions in the history of psychopharmacology in the field of mood-regulating agents: the identification of lithium salts' antimanic properties, particularly the widely held belief that it was a result of pure serendipity, has been a subject of discussion among authors. However, Cade contended that his incidental observation of the sedative impact of lithium on guinea pigs was not inherently linked to the subsequent verification of the agent's antimanic effectiveness in humans [27]. This type II pattern, characterised by initial serendipitous findings, frequently in laboratory animals, that subsequently lead to planned and nonserendipitous findings, includes a multitude of additional revelations in the field of psychotropic medications throughout the 1950s. This includes the discovery of imipramine and iproniazid, which served as prototypes for the first two classes of antidepressant drugs, tricyclic antidepressants and monoamine oxidase inhibitors. It also involves the unearthing of the antipsychotic effects of chlorpromazine and clozapine, along with the accidental discovery of meprobamate's experimental tranquilizing properties and the subsequent confirmation of its distinct anxiolytic effects.

On the contrary, there are also, within the framework of our type III pattern, mixed discoveries that were initially non-serendipitous and that later caused serendipitous discoveries. In the case of current drugs approved to treat bipolar disorder, the only available example is lamotrigine, which was initially developed as an antiepileptic agent. This subsequently led to the serendipitous discovery of its mood-stabilizing and preventive effects on bipolar depressive episodes. Other historical examples of this pattern can be found in barbiturates [13].

Similarly, in the history of psychopharmacology, there have also been instances of purely serendipitous discoveries, as exemplified by our type I pattern. These include the chance of uncovering the anticonvulsant effects of valproic acid, the antimanic properties of valproate, and the psychotropic attributes of lysergic acid diethylamide (LSD). Conversely, during the initial years of the modern psychopharmacology era, there were discoveries where serendipity played no role whatsoever, aligning with our type IV pattern. A notable example is the revelation of the anxiolytic effect of the first benzodiazepine, chlordiazepoxide [83], or the antipsychotic effect of haloperidol and reserpine [84, 85]. However, it should be noted that this pattern was consolidated from the 1970s onwards, as a consequence of the implementation of rational design processes for pharmacological drugs, particularly aimed at their interaction with specific biological targets, such as specific receptors, related to the etiopathogenesis of mental disorders [86].

Tables 1 and 2 show all of the drugs approved by the FDA and the EMA to treat patients with bipolar disorder.

While 11 drugs have been approved as antimanic drugs, only 5 have received approval to treat depressive episodes of bipolar disorder, including olanzapine, which has to be prescribed together with fluoxetine. Similarly, 7 drugs have been licensed for the maintenance treatment and prevention of any types of episodes of this disorder, including quetiapine and ziprasidone, which have to be administered together with lithium salts or divalproex. And only two drugs, olanzapine and quetiapine, include all three phases of bipolar disorder among their indications. Currently, including chlorpromazine, despite its anecdotal use, the therapeutic arsenal for treating bipolar disorder consists of 14 drugs, with only AADs having been added in the last 20 years. It is clear that the process that John Cade started with the discovery of the antimanic effect of lithium salts 73 years ago is still far from complete, not least because of the limited knowledge of the neurobiological basis underlying this pathology, and that we are a long way from having the ideal mood-stabilizing agent.

We do not know what the role of serendipity will be in the future of research on mood-stabilizing agents, although it is clear that, over recent decades, the influence of serendipity is decreasing in the progress of psychopharmacology [87], which has evolved, like other areas of pharmacology, towards much more planned and rational developments [85]. Some authors have claimed the role of serendipity in the scientific research process today. Klein [88] attributes, in part, the relative lack of innovation in the specific field of psychopharmacology during the last 40 years to the absence of serendipity and defends its promotion through an adequate structuring of the environments of the processes of investigation. Our group has also identified various “antiserendipity” factors [89] that could explain this phenomenon pointed out by Klein, such as the decrease in the time available to researchers to observe and follow up on their patients, the imposition of the “double-blind” methodology in the design of clinical trials, which limits the possibility of identifying individual markers of response to drugs, or the use, in mental health, of evaluation scales to measure the effects of drugs, instead of longitudinal clinical observation. Two other relevant factors would be the scientific turn of pharmacology towards a rational drug design based on translational research, which has put an end to specific observations of the effects of drugs on the behaviour of animals or humans, and the change in the structure of the pharmaceutical industry, which is closely linked to the phenomenon of lack of innovation in the field of psychopharmacology. The result of this change has been the continuous clinical introduction of multiple drugs that are practically equivalent in mechanism of action and effectiveness, the so-called “me too” drugs, whose final profitability would exceed the innovative and novel agents. The restriction on the diversity of compounds selected for clinical trials, which is inherent in this reductionist approach, minimizes the possible role of serendipity in this process and its importance in the discovery of new drugs.

In any case, there is no doubt that currently available psychopharmacological agents have many limitations and that current knowledge of the aetiology of psychiatric disorders

is still quite limited. All this suggests that serendipitous discoveries can still take place in this new technical environment of the 21st century [19]. However, it is indisputable that serendipity played a significant role in the advancement of modern psychopharmacology throughout the latter half of the 20th century. In one of David Healy's interviews with one of the pioneers of the “psychopharmacology revolution,” Jean Thuillier, this influence is clear: “Healy: How did it all start? /Thuillier: It was by chance” [90]. In any case, the outcomes of this research underscore the notion that serendipity ought to be regarded as a legitimate scientific concept rather than a mere literary curiosity.

Acronyms

5-HT:	5-Hydroxytryptamine or serotonin
AAD:	Atypical antipsychotic drug
APA:	American Psychiatric Association
ATC:	Anatomical therapeutic chemical
CINP:	Collegium Internationale Neuro-Psychopharmacologicum-International College of Neuropsychopharmacology
EMA:	European Medicines Agency
FDA:	Food and Drugs Administration
INHN:	International Network for the History of Neuropsychopharmacology
LSD:	Lysergic acid diethylamide (from German <i>Lysergsäure-diethylamid</i>)
NS:	Nonserendipitous discovery
S:	Serendipitous discovery
UK:	United Kingdom
US:	United States
WHOCC:	World Health Organization Collaborating Centre for Drugs Statistics Methodology.

Data Availability

Data are available from the first author.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

All listed authors must have made a significant scientific contribution to the research in the manuscript, approved its claims, and agreed to be an author. FL-M and CA designed the study; FL-M and JAG analyzed the data; FL-M, PDO, DB, and AR wrote the manuscript; FL-M approved the final manuscript; all authors reviewed and approved the final draft.

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Original Article

Did Serendipity Contribute to the Discovery of New Antidepressant Drugs? Historical Analysis Using Operational Criteria

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Abstract

Objective: Given their great importance, as one of the most prescribed types of therapeutic drugs worldwide, we have analyzed the role of serendipity in the discovery of new antidepressants, ranging from selective serotonin reuptake inhibitors to more contemporary developments. **Methods:** We carried out a historical analysis of the discovery of new antidepressants, resorting to the original articles published on their development (initial pharmacological and clinical information) and applied an operational criterion of serendipity developed by our group. **Results:** Selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline, and escitalopram), selective dopamine and noradrenaline reuptake inhibitors (bupropion), noradrenaline and serotonin reuptake inhibitors (venlafaxine, milnacipram, duloxetine, and desvenlafaxine), selective noradrenaline reuptake inhibitors (reboxetine), noradrenergic and specific serotonergic antidepressants (mirtazapine), melatonergic agonists (agomelatine), and serotonin modulators and stimulators (vortioxetine, vilazodone, tianeptine) correspond to the type IV pattern. Moclobemide, a reversible monoamine oxidase inhibitor, corresponds to the type II pattern, for which the initial serendipitous findings (i.e., the chance discovery of the inhibitory effects of monoamine oxidase (MAO) whilst being studied for their antihyperlipidemic properties) led to subsequent non-serendipitous discoveries (clinical antidepressant efficacy). Ketamine, a glutamatergic modulator, corresponds to the type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using). **Conclusion:** The majority of new antidepressants adhere to a type IV pattern, characterized by a rational and targeted design process where serendipity played no part, except moclobemide (type II pattern) and ketamine (type III pattern).

Keywords: antidepressants; history of medicine; psychopharmacology; serendipity

Main Points

1. Serendipity is a phenomenon that requires the convergence of accident and sagacity.
2. In pharmacology, purely serendipitous discoveries (type I pattern of imputability) are relatively rare. This pattern has not been found in the discovery of any of the new antidepressants.
3. The development of new antidepressants, from selective serotonin reuptake inhibitors (SSRIs) to the present, has been characterized by a pattern IV, based on rational and systematic research programs and where there is no intervention of serendipity.
4. Moclobemide can be classified under the type II pattern, wherein initial serendipitous findings (the chance discovery of MAO inhibitory effects in a molecule being studied for its antihyperlipidaemic properties) led to sub-

sequent non-serendipitous discoveries (clinical antidepressant efficacy).

5. Ketamine follows a type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using).

1. Introduction

The 1950s, renowned in the field of pharmacology as the "golden decade" of psychotropic drugs, ushered in the introduction of the primary groups of agents still used today in treating mental disorders: antipsychotics, anxiolytics and antidepressants [1]. These psychotropic drugs drastically altered psychiatric patient care and provided insight into the neurobiological underpinnings of mental illnesses for the



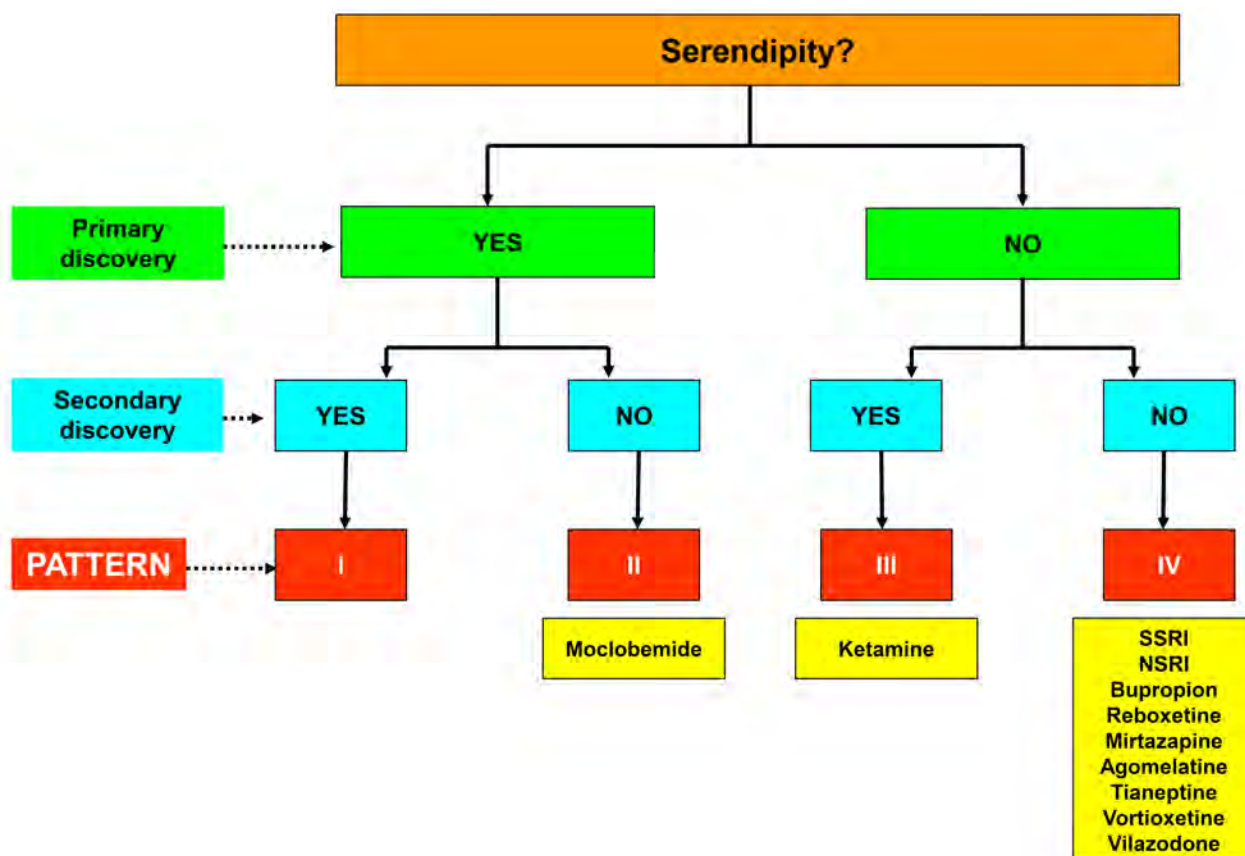


Fig. 1. Diagram of the four patterns of serendipitous attribution in the discovery of pharmacological agents and their application to new antidepressant drugs. SSRI, selective serotonin reuptake inhibitors; NSRI, noradrenaline and serotonin reuptake inhibitors. Figure adapted from the original created by the authors [7,13].

first time in the history, an approach often referred to as “pharmacocentric” [2].

The two main families of antidepressant drugs discovered during this period, tricyclics (TCAs) [3] and monoamine oxidase inhibitors (MAOIs) [4], exhibited significant efficacy in managing affective disorders [1,5]. However, their substantial clinical contributions were overshadowed by therapeutic challenges primarily associated with tolerability and safety profiles. Consequently, a major challenge in psychopharmacology was overcoming these drawbacks, a feat realized in the 1980s with the clinical introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs). SSRIs revolutionized depression therapy [5], offering undeniable advantages over classical antidepressants, particularly in terms of safety and tolerability. While zimelidine was the first SSRI introduced, it was subsequently withdrawn from the market, the “new” or “modern” antidepressant era began with the clinical introduction of fluoxetine [6] paving the way for new antidepressant families (see Table 1).

These new drug families, similar to classical drugs in terms of their mechanisms of action, primarily modulate monoaminergic neurotransmission at a synaptic level [2,5]. Nonetheless, additional antidepressant drug fami-

lies targeting different neurotransmitter pathways, such as glutamatergics or melatonergics, have also been introduced into clinical practice.

Serendipity is a phenomenon frequently invoked when examining scientific discoveries, including those in pharmacology. Serendipitous discovery is understood as the revelation of something unforeseen, independent of the systematic process leading to the accidental observation [7]. However, the attribution of this phenomenon remains highly contentious, likely due to the semantic ambiguity surrounding the term “serendipity” [8], which has been employed with a wide array of meanings. Traditionally associated with concepts like chance, fortune, randomness, or coincidence (“happy accident”, “pleasant surprise”, etc.), we adopt the approach proposed by the introducer of this term, the English writer, politician and historian Horace Walpole, 4th Earl of Oxford, in his commentary on the classic Persian tale *The Three Princes of Serendip* (1557) [9]. Walpole suggested that serendipity requires the convergence of accident and sagacity, with sagacity being the factor conditioning a serendipitous discovery in the presence of a significant accidental event [7]. This is evidenced by the book *Serendipity. Accidental discoveries in Science* [10].

Table 1. Classification of new antidepressants according to action mechanism and historical perspective on their clinical introduction.

FAMILY	Acronym	Prototype substance	Period
Selective 5-HT reuptake inhibitors	SSRI	Fluoxetine	1975–1990
Reversible MAO inhibitors	RIMA	Moclobemide	1975–1990
Selective DA and NA reuptake inhibitors	SDRI	Bupropion	1975–1990
NA and 5-HT reuptake inhibitors	NSRI	Venlafaxine	1980–2000
Selective NA reuptake inhibitors	SNRI	Reboxetine	1980–2000
Noradrenergic and specific serotonergic antidepressants	NaSSA	Mirtazapine	1980–2000
Melatonergic agonists		Agomelatine	1990–2010
Glutamatergic modulators		Esketamine	1970–2020
Serotonin modulators and stimulators	SMS	Vortioxetine	2000–2020

5-HT, serotonin; MAO, monoamine oxidase; DA, dopamine; NA, norepinephrine; SSRI, selective serotonin reuptake inhibitor; RIMA, reversible monoamine oxidase inhibitors; SDRI, selective dopamine and noradrenaline reuptake inhibitor; NSRI, noradrenaline and serotonin reuptake inhibitor; SNRI, selective inhibitors of noradrenaline reuptake; NaSSA, specific noradrenergic and serotonergic antidepressants; SMS, serotonin modulators and stimulators.

Hargrave-Thomas *et al.* [11] noted that 24% of all commercially available drugs at the time were positively influenced by serendipity during their development, particularly psychopharmacological agents. Confirming this, we found that the discovery of most psychotropic drugs during the 1950s occurred under these parameters of serendipitous influence, including classical antidepressant drugs [7,12,13]. To this end, we have established an operational definition of serendipity based on four different attributability patterns [7,12], allowing us to clarify its role in drug discovery. This paper, following our established approach, examines the role of serendipity in the discovery of new or modern antidepressant drugs.

2. Methods

2.1 Operational Criteria of Serendipity

In previous research, we have employed a functional characterization of serendipity [7,12,13], which involves identifying four distinct patterns of attributing serendipity within the drug discovery process (Fig. 1, Ref. [7,13]):

(a) Pattern I, encompasses purely serendipitous discoveries.

(b) Pattern II, a modification of the former pattern, delineates chance findings initially leading to planned discoveries devoid serendipitous origins.

(c) Pattern III, comprises discoveries lacking serendipity but subsequently leading to serendipitous findings.

(d) Pattern IV, corresponds to purely non-serendipitous discoveries, occurring outside the realm of chance or unintended accident. This pattern includes discoveries of pharmacological drugs within rational and systematic research programs specifically tailored to produce agents with specific effects on a given pathology.

2.2 Archives and Documents on the History of Psychopharmacology

Before applying the attributability criteria, we accessed the original manuscripts containing the initial pharmacological and clinical information on new antidepressant drugs from the various sources:

(a) Primary databases in the biomedical field (Medline, Embase, Scopus).

(b) Documentation resources provided by the pharmaceutical companies distributing the new antidepressants.

(c) Documentation accessible through the International Network for the History of Neuropsychopharmacology (INHN), under the guidance of Thomas A. Ban (Vanderbilt University).

(d) David Healy's *The Psychopharmacologists* series of interviews de (Arnold – Oxford University Press).

(e) The History of Psychopharmacology collection of the International College of Neuropsychopharmacology (CINP) (*Collegium Internationale Neuro-Psychopharmacologicum*), coordinated by Thomas A. Ban, David Healy and Edward Shorter and published by Animula.

(f) Prof. López-Muñoz's collection of documents on the history of psychopharmacology.

3. Results

3.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

The first SSRI synthesized and developed was fluoxetine, considered the prototype molecule of this antidepressant family. Its development stemmed from 1960s studies on TCAs with supported the serotonergic hypothesis of depression by demonstrating the potent inhibition of 5-HT uptake by imipramine and similar agents [1]. A lecture on "synaptosomes" technique, given in 1971 by Solomon H. Snyder from John Hopkins University later influenced fluoxetine's development. That same year, pharmacolo-

gist Ray W. Fuller, an expert in 5-HT research, and biochemist David T. Wong formed a “serotonin-depression study team”, which also included organic chemist Bryan Molloy and pharmacologist Robert Rathbun [1]. In the early 1970s, this team focused on developing molecules that selectively inhibited 5-HT uptake, aiming to create antidepressants without the cardiotoxicity and anticholinergic properties of TCAs [1]. They noted that diphenhydramine and other antihistamines could inhibit monoamine uptake, leading them to synthesize a series of phenoxyphenyl-propylamines, including nisoxetine [14]. Among the 55 derivatives in this series, fluoxetine hydrochloride (LY-110140) was identified in 1972 as the most potent and selective 5-HT uptake inhibitor [15]. Fluoxetine’s structure, particularly the *p*-trifluoromethyl group, was key to its efficacy and selectivity, resulting in fewer adverse effects compared to TCAs [16]. Despite indirect testing methods, studies suggested an increase in extraneuronal 5-HT concentrations [1]. The first publication on fluoxetine appeared in 1974, highlighting its potential utility in studying serotonergic functions and mental disorders [15]. Fluoxetine’s clinical development began in 1980, with initial studies conducted at John Feighner’s private psychiatric clinic in La Mesa (California). By 1983, results demonstrated fluoxetine’s efficacy as an antidepressant with significantly fewer side effects compared to TCAs, marking the advent of a “New Generation of Antidepressants” [17]. Extensive clinical trials between 1984 and 1987 culminated in its approval by the US Food and Drug Administration (FDA) in December 1987.

Following fluoxetine, other SSRIs were introduced, including zimelidine, marketed in 1982, which was withdrawn due to adverse effects (hypersensitivity issues, including fever, myalgias, increased levels of aminotransferases and notably, various cases of neurological complications linked to Guillain-Barré syndrome) [18]. The rest of the SSRIs were marketed later through targeted research strategies. Fluvoxamine was developed by Welle and Claassen [19] in the mid-1970s at Belgium, and marketed in Switzerland in 1983. Citalopram was synthesized in 1972 by chemist Klaus Bøgesø [20] and it was first marketed in Denmark in 1989. Paroxetine, a phenylpiperidine derivative, was discovered in 1975 and patented in the US in 1977. The patent was subsequently transferred in 1980 and was first marketed in Sweden in 1991 [21]. Sertraline’s development began in 1977, led by pharmacologist Kenneth Koe and chemist Willard Welch [22]. This SSRI was launched in the UK in 1990. Finally, in 1997 began the development of escitalopram, (S)-enantiomer of the racemate citalopram [20]. In 2002, escitalopram was launched in Europe and the US and subsequent clinical studies confirmed its superiority over escitalopram, particularly in patients with severe depression [23].

The development of SSRIs marked a shift in psychopharmacology towards rational, directed drug design

rather than serendipitous discovery, aligning with our type IV pattern of serendipitous attribution (Table 2).

3.2 Reversible Monoamine Oxidase Inhibitors (RIMA)

The development of reversible and selective monoamine oxidase A (MAO-A) inhibitors, with moclobemide as the prototype, emerged from efforts to improve the safety profile of classical MAOIs. Moclobemide (Ro 11-1163), a benzamide derivative of morpholine, was first synthesized in 1972 by Pierre-Charles Wyss in Basel (Switzerland) [24]. This synthesis was part of a research programme focused on developing new lipid-lowering agents without antiviral activity. Despite failing to exhibit significant hypolipidemic effects and yielding negative screenings, moclobemide was found to possess intriguing monoamine oxidase (MAO) inhibitory activity in rat studies, prompting a shift towards its development as an antidepressant [24]. *In vitro* studies evidenced moclobemide to be a weak but highly selective MAO-A inhibitor, with a relatively short enzyme inhibition period of 8 to 10 hours [25]. Furthermore, its safety profile was significantly better than that of classical MAOIs, with rare instances of problematic hypertensive crises [26].

Clinical trials began in 1977, and moclobemide, was introduced into clinical practice in the UK and Europe in 1992 as the first drug of the new RIMA class. Although it was marketed in various countries and used as a first-line treatment in Finland and Australia, it was never approved in the US.

The serendipitous discovery of moclobemide, originally intended as an antihyperlipidemic, led to its development as a leading example of the new class of antidepressants. This development fits within the type II pattern of our serendipity attribution criteria (Table 2).

3.3 Other Monoamine Reuptake Inhibitors

Over the past four decades, numerous new antidepressant drugs have been developed to enhance the basic and clinical profiles of SSRIs. These new drug families, with diverse pharmacodynamic properties, primarily act on the central nervous system (CNS) by modulating monoamine neurotransmission [5]. This includes noradrenaline and serotonin reuptake inhibitors (NSRIs) (venlafaxine, duloxetine, milnacipram, desvenlafaxine, levomilnacipram); selective dopamine and noradrenaline reuptake inhibitors (SDRIs) (bupropion); and selective inhibitors of noradrenaline reuptake (SNRIs) (reboxetine).

Bupropion, originally known as amfebutamone, is a chloropropiophenone derivative primarily inhibiting dopamine (DA) reuptake, with minimal effect on 5-HT transporters [27]. Developed by Nariman Mehta in 1969 [28], bupropion was introduced to the US market in 1985 but withdrawn in 1986 due to seizure risks, which were later linked to dosage. Reintroduced in 1989 with a maximum daily dose of 450 mg, sustained-release (SR) and

Table 2. Attribution of serendipity in the discovery of new antidepressant drugs.

Group/Family	Drug	ATC code	Date of discovery (psychiatric introduction)	Effect/primary properties	Effect/secondary properties	Pattern of discovery
SSRIs	Fluoxetine	N06AB03	1972 (1987)	NS	NS	IV
	Citalopram	N06AB04	1972 (1989)	NS	NS	IV
	Paroxetine	N06AB05	1973 (1991)	NS	NS	IV
	Sertraline	N06AB06	1979 (1990)	NS	NS	IV
	Fluvoxamine	N06AB08	1978 (1983)	NS	NS	IV
	Escitalopram	N06AB10	1988 (2002)	NS	NS	IV
RIMA	Moclobemide	N06AG02	1972 (1992)	S	NS	II
SDRI	Bupropion	N06AX12	1969 (1985)	NS	NS	IV
NSRI	Venlafaxine	N06AX16	(1993)	NS	NS	IV
	Milnacipran	N06AX17	(1996)	NS	NS	IV
	Duloxetine	N06AX21	1986 (2004)	NS	NS	IV
	Desvenlafaxine	N06AX23	(2008)	NS	NS	IV
	Levomilnacipran	N06AX28	(2013)	NS	NS	IV
SNRI	Reboxetine	N06AX18	1984 (1997)	NS	NS	IV
NaSSA	Mirtazapine	N06AX11	1989 (1994)	NS	NS	IV
MA	Agomelatine	N06AX22	1998 (2009)	NS	NS	IV
GM	Esketamine	N06AX27	1962 (2019)	NS	S	III
	Tianeptine	N06AX14	1981 (1989)	NS	NS	IV
SMS	Vortioxetine	N06AX26	2002 (2013)	NS	NS	IV
	Vilazodone	N06AX24	2004 (2011)	NS	NS	IV

NS, non-serendipitous discovery; S, serendipitous discovery; SSRI, selective serotonin reuptake inhibitors; RIMA, reversible monoamine oxidase inhibitors; SDRI, selective dopamine and noradrenaline reuptake inhibitors; NSRI, noradrenaline and serotonin reuptake inhibitors; SNRI, selective inhibitors of noradrenaline reuptake; NaSSA, specific noradrenergic and serotonergic antidepressants; MA, melatonergic agonists; GM, glutamatergic modulators; SMS, serotonin modulators and stimulators.

Antidepressant drugs were classified by the Anatomical Therapeutic Chemical (ATC) classification system controlled by the World Health Organization Collaborating Centre for Drugs Statistics Methodology (WHOC). This system classifies the active ingredient of a drug into groups according to the organ or system on which they have their effect.

https://www.whocc.no/atc_ddd_index/?code=N06AX&showdescription=no.

extended-release (XL) formulations were approved by the FDA in 1996 and 2003, respectively, to improve patient's adherence to treatment [29]. Reboxetine, the first, SNRI, was developed at Italy in the mid-1980s and approved in Europe in 1997 [30]. Another potent and selective SNRI is atomoxetine. Initially developed as an antidepressant, it proved more efficacious for the treatment of attention-deficit/hyperactivity disorder (ADHD) and was FDA-approved for this indication in 2002.

Venlafaxine, the first NSRI, was designed to inhibit both 5-HT and norepinephrine (NA) reuptake (with three times greater selective for 5-HT than NA), proving effective with minimal action at other receptors [31]. By optimizing of ciramadol, an opiate analgesic lead, through a three-step synthesis, reducing its chiral centres from three to one, and incorporating an alkylamine pharmacophore, venlafaxine was introduced to the US market in 1993. In 1997, the XL formulation of venlafaxine was also approved for depression [32]. To mitigate potential drug interactions in patients with varying metabolizing capabilities, desvenlafax-

ine was developed, the primary active metabolite of venlafaxine (O-desmethyl metabolite) [33], and was approved in the US in 2008 [31]. Duloxetine emerged from observations made during research on the molecule LY227942, whose (+)-enantiomer exhibited twice the potency inhibiting 5-HT reuptake compared to the (-)-enantiomer. This antidepressant was introduced to the market in 2004 [34]. Finally, milnacipran, a cyclopropane derivative with 5-HT and NA reuptake inhibitory properties, was approved for use in France in 1996 [35]. Levomilnacipran, the levorotatory enantiomer of milnacipran, was commercialized in 2013 [36].

The development of these drugs was based on rational hypotheses rather than serendipity, reflecting a type IV pattern of drug discovery (Table 2).

3.4 Noradrenergic and Specific Serotonergic Antidepressants (NaSSA)

Mirtazapine, known as ORG 3770, is a tetracyclic piperazine-azepinet derived from the antidepressant mi-

anserin. It chemically differs from mianserin by the addition of a nitrogen atom in one of the rings [37]. This atypical tetracyclic antidepressant blocks α_2 adrenoreceptors, 5-HT₂ and 5-HT₃ receptors. By antagonizing somatodendritic α_2 autoreceptors and heteroreceptors located in the pre-synapses, it enhances the firing rate of the neurons and neurotransmitter release [38]. Additionally, its blockade of 5-HT₂ and 5-HT₃ receptors helps to moderate some of the known serotonergic adverse effects and improves pharmacological efficacy [39]. The initial data on mirtazapine were published in 1989, and its clinical introduction occurred in the Netherlands in 1994.

As the discovery process of mirtazapine as an antidepressant did not rely on serendipity at any stage, this development aligns with our type IV pattern (Table 2).

3.5 Melatonergic Agonists

The hypothesis that led to the discovery of the first melatonergic agent, agomelatine, was based on the manipulation of the circadian rhythm, which is often disrupted in depressive patients [40]. Consequently, a series of naphthalene derivatives were synthesized, and their ability to displace [¹²⁵I]-melatonin in the pituitary gland was investigated [41]. Concurrently, electrophysiological studies were conducted, revealing that one of the derivatives, S20098, acted as an agonist of melatonin receptors. This molecule was selected for further development and named agomelatine [42]. Subsequent studies confirmed that this agent could normalize circadian rhythms in a dose-dependent manner [43] and pharmacological screenings for antidepressant properties yielded positive results [40]. The receptor profile of agomelatine is different from other antidepressant drugs. Agomelatine acts as an agonist of the MT₁ and MT₂ melatonin receptors [44], while also functioning as an antagonist of the 5-HT_{2C} receptors [45]. Moreover, it does not inhibit the reuptake of monoamines and lacks the capacity to block other receptors. With its properties as a melatonergic receptor agonist, agomelatine can be regarded as an agent capable of synchronizing distorted rhythms.

Following successful testing of agomelatine in various animal models of depression, the first clinical trial of agomelatine was launched in 2002 by L  o *et al.* [46] (H  pital Sainte Anne, Paris), confirming its antidepressant efficacy compared to paroxetine. In March 2006 clinical trials began in the US. However, development for the US market was discontinued in October 2011. Agomelatine was approved for clinical use in Europe in 2009. Despite numerous studies confirming the clinical efficacy of agomelatine in treating depression [47], no further melatonergic drugs have been developed.

The development of agomelatine followed a systematic research program specifically designed to obtain a drug with a melatonin-like profile, devoid of serendipity (type IV pattern of serendipity) (Table 2).

3.6 Glutamatergic Modulators

Ketamine (CI-581), a short-acting derivative of phenylcyclidine, was synthesized in 1962 by Calvin Lee Stevens [48]. It was initially used as a dissociative anaesthetic from 1970 [49] and gained attention for its use in the Vietnam War [50]. Despite its clinical potential, ketamine began being abused recreationally as “Special K” in the mid-1990s, leading to its classification as a Schedule III of the Controlled Substance Act in 1999. Interest in its antidepressant effects emerged in the 1970s [50,51], but clinical research was delayed for more than two decades by its association with recreational use [1]. A until the first pilot study in 2000 demonstrated that intravenous ketamine at subanaesthetic doses improved depressive symptoms in major depression patients 72 hours after administration [52], leading to a surge in studies confirming its efficacy for treatment-resistant major depression, bipolar disorder and suicidal ideation [53]. Ketamine primarily functions as a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor [54]. Its antidepressant effects are also attributed to other mechanisms such as α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated signalling, increased DA levels in the prefrontal cortex and nucleus accumbens [55]. Following the discovery that, esketamine, the S enantiomer of ketamine, was higher NMDA receptor affinity [51], a double-blind clinical trial showed its rapid antidepressant effects in treatment-resistant depression after intravenous infusion [56]. Subsequently, the possibility of administering low doses of esketamine intranasally was explored [57] and was approved by the FDA and European Medicines Agency (EMA) in 2019 for use in resistant depression in combination with an SSRI or SNRI, with administration monitored in clinical settings [58]. Despite its benefits, esketamine has a higher incidence of dissociative effects and potential abuse risk due to its hallucinatory properties [59].

Tianeptine, discovered by the French Society of Medical Research in the 1960s and patented by researchers Antoine Deslandes and Michael Spedding in 1981 [60], differs from traditional TCAs, as amineptine, by not affecting 5-HT reuptake [61]. Instead, it has a weak action on μ -opioid receptors and modulates glutamatergic mechanisms [62]. Although initially developed for major depressive disorder, its US development was discontinued in 2012 [63]. Tianeptine was later marketed as a nootropic supplement but faced scrutiny due to high abuse potential and legal concerns [64]. This led to the coining of the term “gas station heroin”. Since 2023, products containing tianeptine have been gradually withdrawn.

Ketamine has garnered significant attention in psychiatric research as a prototype for a new generation of antidepressants following the discovery of its profound and rapid effects on depressive symptoms. However, it stands as a clear example of serendipity resulting from a non-

serendipitous discovery (type III pattern) (Table 2). Originally developed as an anaesthetic agent, its antidepressant efficacy was stumbled upon coincidentally when improvement in depressive symptoms was observed in individuals using the substance as a drug of abuse.

3.7 Serotonin Modulators and Stimulators (SMS)

Vortioxetine is a bis-aryl-sulfanyl amine and piperazine derivative, whose rationale and synthesis (Lu AA21004) was detailed in 2002 [65]. It was introduced into the US market in 2013. This compound represents a new class of antidepressants known as SMS or “multi-modal”, due to its high binding affinity and complementary mechanisms of action on several 5-HT receptors and 5-HT transporters. Specifically, vortioxetine acts as a 5-HT_{1A} receptor agonist, 5-HT_{1B} receptor partial agonist, 5-HT_{3A} and 5-HT₇ receptor antagonist, and a potent 5-HT reuptake inhibitor [66]. Additionally, vortioxetine exhibits significant affinity for DA and NA transporters, being 3 to 12 times more selective for 5-HT transporters, respectively [67].

Vilazodone received approval medical use in the US in 2011. Classified as a SMS or serotonin partial agonist/reuptake inhibitor (SPARI), vilazodone possesses SSRI properties and acts as an activator of the 5-HT_{1A} receptor [68].

The development of SMS drugs was driven by rational planning based on an understanding of the role of serotonergic neurotransmission in affective disorders, with minimal reliance on serendipity (type IV pattern of serendipity) (Table 2).

4. Discussion

As articulated by Albert Szent-Györgyi, the discoverer of vitamin C, “a discovery consists of seeing what everybody has seen and thinking what nobody has thought” (p. 57) [69]. Therefore, in line with the original conceptualization, we contend that “*serendipity*” pertains to the discovery of something unexpected or not deliberately sought [7,12], i.e., a finding that arises without the observer anticipating it.

In pharmacology, purely serendipitous discoveries (our type I pattern of imputability), are relatively rare, contrary to popular belief. Most discoveries exhibit a mixed character (Patterns II and III), blending serendipitous and non-serendipitous elements. Typically, this follows a consistent pattern that starts with an initial serendipitous observation, often encountered in laboratory-based animal research, which subsequently prompts deliberate investigations in a clinical setting (our Pattern II). These circumstances contribute to the existence of the aforementioned discrepancies among authors. Some interpret these findings solely through the lens of chance, positing that the results of clinical trials represent a *continuum* of the initial serendipitous findings and should be regarded as part of a unified

discovery rather than separate events. Other authors refer to these patterns as “pseudoserendipity” [10] or “serendipity analogous” discoveries [70].

However, it is evident that serendipity, to varying degrees, played a fundamental role in the initial decades of modern psychopharmacology, particularly in the discovery of the first two families of antidepressant drugs (TCAs and MAOIs) [3,4,13]. This process yielded revolutionary outcomes in the realm of mental health, influencing various aspects of socio-health reality. These include the progressive phenomenon of “deinstitutionalization” in psychiatry and the involvement of primary care into mental health services, both mitigating the historical stigmatization associated with psychiatric care. Moreover, this “revolution” spurred scientific advancements, including the formulation of initial biological hypotheses concerning the genesis of mental illnesses, particularly affective disorders [2,71]. At the nosological level, the introduction of these drugs contributed, to some extent, to shaping new diagnostic criteria. Furthermore, the emergence of classic psychotropic drugs enhanced clinical research by facilitating the synthesis of numerous drugs for mental disorder treatment.

The development of new drugs for affective disorders benefited significantly from the tenets of monoaminergic theories of depression, which dominated scientific discourse in specialized journals during the 1960s and 1970s following the discovery of imipramine and iproniazid. These theories posited a functional deficiency in noradrenergic or serotonergic neurotransmission [2,5] in specific brain regions as a primary cause of these pathologies [72], paving the way for new families of antidepressant drugs characterized by modulating monoaminergic functionalism.

Hence, the findings of our study appear to affirm that since the 1980s, the development of new antidepressant agents have followed a different dynamic, marked by a systematic and deliberate pursuit of outcomes, with minimal reliance on serendipity (our Pattern IV). Some authors have underscored the role of serendipity in contemporary scientific research in this field. Donald Klein [73], in his article *The Loss of Serendipity in Psychopharmacology*, partly attributes the relative dearth of innovation in psychopharmacology over the past five decades to the absence of serendipity. He advocates for fostering serendipity through structured research environments [73]. In our editorial, we identified several “anti-serendipity” factors that may explain this phenomenon outlined by Klein; (a) the scientific shift towards rational drug design grounded in translational research; (b) reduced time for researchers to observe and engage with patients; and (c) pharmacology’s reliance on clinical trials employing double-blind, placebo-controlled designs as the primary method for demonstrating drug efficacy [74]. Additionally, other authors highlight more specific factors, such as advances in genetic and diagnostic imaging techniques, including nuclear magnetic resonance,

combinatorial and computational chemistry, X-ray crystallography, etc. [75].

Over the past four decades, the discovery and identification of new chemical entities (NCE) have predominantly focused on elucidating the molecular targets with which these agents interact. This approach, often termed “targophilia”, by some authors, adopts a reductionist perspective that emphasizes the specific sites of drug action [76]. This paradigm has prevailed in the development of new antidepressant drugs, leading to a practical decline in serendipitous discoveries within this process, as evidenced by the findings of our study. Nonetheless, certain exceptions have been noted, such as in the cases of moclobemide and ketamine. Serendipity played a pivotal role in the discovery of the antidepressant properties of both drugs, as previously mentioned, thereby categorizing them within our type II and III patterns of imputability, respectively.

Despite the considerable clinical advantages of new antidepressants, which are largely attributed to their improved tolerance, safety profile, and greater convenience, several challenges persist in antidepressant therapy. Notable among these challenges are the delayed onset of antidepressant response and the estimated percentage of non-responsive patients, which stands at around 30% [77]. Additionally, inadequate antidepressant response affects 40–50% of patients. This may be influenced by the convergent pharmacodynamic properties of these new antidepressants, which often enhance aminergic function: Examples include NSRI (venlafaxine, duloxetine, milnacipram), NaSSA (mirtazapine), SDRI (bupropion), and SNRI (reboxetine, atomoxetine) [5]. Moreover, some recent antidepressants target non-aminergic receptors, albeit not entirely selectively. For instance, agomelatine, a melatonergic agonist (MT₁ and MT₂) also blocks 5-HT_{2A} receptors, thereby facilitating the release of DA and NA in the prefrontal cortex [78]. The antidepressant arsenal has further expanded with vortioxetine, characterized as SMS or “multi-modal”, given its impact on the functionalism of several monoamines. Its primary mechanism involves a combination of SSRI, 5-HT₃ receptor antagonism and 5-HT_{1A} receptor agonism, thus, affecting monoaminergic pathways as well. Lastly, tianeptine is an antidepressant with a complex mechanism involving glutamatergic functionalism, along with esketamine, which influences opioidergic and DA release in the nucleus accumbens and prefrontal cortex. Therefore, these latter antidepressants also engage monoaminergic mechanisms [62].

Depression is a complex pathology characterized by pathophysiological mechanisms that extend beyond solely aminergic pathways. As a result, research into the mechanisms of action of antidepressants has begun to explore alternative directions. These include investigations into neurotrophic factors such as neurotrophins and brain-derived neurotrophic factor (BDNF), corticotrophin releasing hormone (CRH), glucocorticoids, and various other potential

targets as the opioid system, interleukins, substance P, somatostatin, neuropeptide Y, melatonin, nitric oxide, among others. Moreover, studies are delving into intraneuronal molecular signal communication pathways. Therefore, the quest for antidepressants with clinical profiles distinct from conventional ones involves a deeper exploration of depression’s pathogenesis and the use of pathophysiological findings as potential therapeutic targets. In this evolving landscape, serendipity may once again emerge as a relevant factor.

5. Conclusion

The discovery of the majority of new antidepressants adhere to a type IV pattern, characterized by a rational and targeted design process where serendipity played no part. This is the case of SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline, and escitalopram), SDRI (bupropion), NSRIs (venlafaxine, milnacipram, duloxetine, desvenlafaxine), SNRI (reboxetine), NaSSA (mirtazapine), melatonergic agonists (agomelatine), and SMS (vortioxetine, vilazodone, tianeptine). However, there are two exceptions: moclobemide and ketamine. Moclobemide, a RIMA, can be classified under the type II pattern, wherein initial serendipitous findings (such as the chance discovery of MAO inhibitory effects in a molecule being studied for its antihyperlipidaemic properties) led to subsequent non-serendipitous discoveries (clinical antidepressant efficacy). Ketamine, a glutamatergic modulator, follows a type III pattern, characterized by a non-serendipitous origin (initial development as an anesthetic agent) leading to a serendipitous observation (the discovery of antidepressant efficacy in individuals illicitly using ketamine).

Since the 1980s, psychopharmacology has been evolving outside the influence of serendipity, but this phenomenon eventually becomes apparent, as has happened in the case of ketamine. However, the results of this work are limited by the data provided by the discoverers themselves in their scientific articles and in their memoirs. In addition, the scientific construct of the serendipity phenomenon itself has varied over time and its role has been interpreted differently by each researcher. Fortunately, the operational criteria of serendipity developed by our group has allowed us to address this issue in a fairly objective and satisfactory way.

Availability of Data and Materials

All data analyzed in the current study is included in the manuscript.

Author Contributions

Conception–FL-M; Design–FL-M; Supervision–FL-M, PD’O, AR, DDB, CÁ; Materials–FL-M; Data Collection and/or Processing–FL-M; Analysis and/or Interpretation–FL-M, PD’O, AR, DDB, CÁ; Literature

Review–FL-M; Writing–FL-M; Critical Review–FL-M, PD'O, AR, DDB, C.Á. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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