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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 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 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

[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 (WHOCC). 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%26showdescription=no.

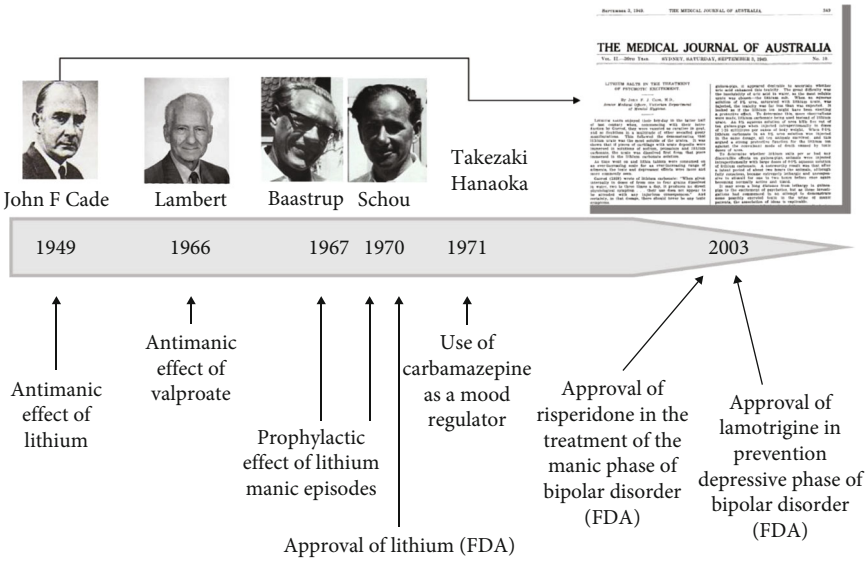

Figure 1: Historical process of the discovery of mood stabilizer drugs. Original figure created and designed by the authors.

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 pharmacological 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

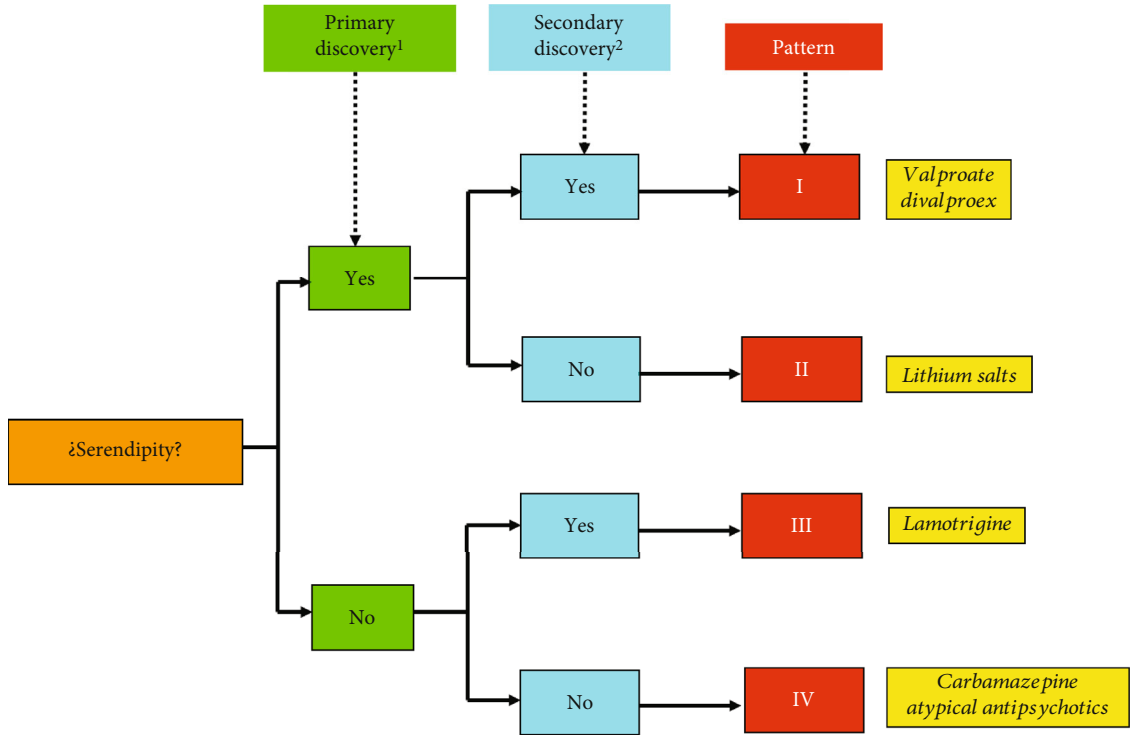

FIGURE 2: Illustration depicting the four attributability patterns in the discovery of pharmaceutical agents and their application to mood stabilizer drugs. [1]Typically, although not invariably, these findings are associated with outcomes observed in experimental animals; [2]discoveries concerning clinical 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

[a]Usually, but not always, they correspond to discoveries in laboratory animals; [b]discoveries 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 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 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 antikindling 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 D_2 receptors, also exhibited antagonism towards serotonin 5-HT_2 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 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 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-HT_7 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 nonserendipitous 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 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-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 *Lysergsäure-diethylamid*)
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.

References

[1] F. López-Muñoz, W. W. Shen, P. D'Ocon, A. Romero, and C. Álamo, "A history of the pharmacological treatment of bipolar disorder," *International Journal of Molecular Sciences*, vol. 19, no. 7, p. 2143, 2018.

[2] F. López-Muñoz, E. Vieta, G. Rubio, P. García-García, and C. Álamo, "Bipolar disorder as an emerging pathology in the scientific literature: a bibliometric approach," *Journal of Affective Disorders*, vol. 92, no. 2-3, pp. 161–170, 2006.

[3] E. Vieta, "Mood stabilization in the treatment of bipolar disorder: focus on quetiapine," *Human Psychopharmacology Clinical and Experimental*, vol. 20, no. 4, pp. 225–236, 2005.

[4] M. Bauer and A. Pfennig, "Epidemiology of bipolar disorders," *Epilepsia*, vol. 46, no. s4, pp. 8–13, 2005.

[5] F. K. Goodwin and K. R. Jamison, *Manic-Depressive Illness*, Oxford University Press, New York, 1990.

[6] M. S. De Lima, J. Tassi, I. P. Novo, and J. J. Mari, "Epidemiologia do transtorno bipolar," *Revista de Psiquiatría Clínica*, vol. 32, pp. 15–20, 2005.

[7] K. R. Merikangas, H. S. Akiskal, J. Angst et al., "Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication," *Archives of General Psychiatry*, vol. 64, no. 5, pp. 543–552, 2007.

[8] K. N. Fountoulakis, S. Kasper, O. Andreassen et al., "Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry," *European Archives of Psychiatry and Clinical Neurosciences*, vol. 262, no. S1, pp. 1–48, 2012.

[9] J. F. Cade, "Lithium salts in the treatment of psychotic excitement," *Medical Journal of Australia*, vol. 2, no. 10, pp. 349–352, 1949.

[10] F. López-Muñoz, C. Álamo, and E. Domino, *History of Psychopharmacology, 4 Volumes*, NPP Books, Arlington, 2014.

[11] E. Shorter, "A History of Psychiatry," in *From the era of the asylum to the age of Prozac*, Wiley & Sons, New York, 1997.

[12] T. L. Sourkes, "Sedatives and Hypnotics (I). The psychiatric history of bromides and chloral hydrate," in *History of Psychopharmacology, Volume 2, The Revolution of Psychopharmacology: The Discovery and Development of Psychoactive Drugs*, F. López-Muñoz, C. Álamo, and E. F. Domino, Eds., pp. 225–234, NPP Books, Arlington, 2014.

[13] F. López-Muñoz, R. Ucha-Udabe, and C. Álamo, "The history of barbiturates a century after their clinical introduction," *Neuropsychiatric Disease and Treatment*, vol. 1, no. 4, pp. 329–343, 2005.

[14] P. C. Baastrup and M. Schou, "Lithium as a prophylactic agent," *Archives of General Psychiatry*, vol. 16, no. 2, pp. 162–172, 1967.

[15] P. C. Baastrup, J. C. Poulsen, M. Schou, K. Thomsen, and A. Amdisen, "Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders," *Lancet*, vol. 2, no. 7668, pp. 326–330, 1970.

[16] W. W. Shen, *Clinical Psychopharmacology in the Twenty-First Century, Revised Edition (in Mandarin)*, Hochi Publishing Company, Taipei, 2004.

[17] A. Amerio, D. Russo, N. Miletto et al., "Polypharmacy as maintenance treatment in bipolar illness: a systematic review," *Acta Psychiatrica Scandinavica*, vol. 144, no. 3, pp. 259–276, 2021.

[18] F. López-Muñoz, A. A. Baumeister, M. F. Hawkins, and C. Álamo, "The role of serendipity in the discovery of the clinical effects of psychotropic drugs: beyond of the myth," *Actas Españolas de Psiquiatría*, vol. 40, no. 1, pp. 34–42, 2012.

[19] E. Robinson, "Psychopharmacology: from serendipitous discoveries to rationale design, but what next?," *Brain Neuroscience Advances*, vol. 2, article 239821281881262, 2018.

[20] F. López-Muñoz, P. D'Ocón, A. Romero, J. A. Guerra, and C. Álamo, "Role of serendipity in the discovery of classical antidepressant drugs: applying operational criteria and patterns of discovery," *World Journal of Psychiatry*, vol. 12, no. 4, pp. 588–602, 2022.

[21] E. Hargrave-Thomas, B. Yu, and J. Reynisson, "The effect of serendipity in drug discovery and development," *Chemistry in New Zealand*, vol. 4, pp. 17–20, 2012.

[22] A. A. Baumeister, M. F. Hawkins, and F. López-Muñoz, "Toward standardized usage of the word serendipity in the historiography of psychopharmacology," *Journal of the History of Neuroscience*, vol. 19, no. 3, pp. 253–270, 2010.

[23] R. S. El-Mallakh and J. W. Jefferson, "Prethymoleptic use of lithium," *American Journal of Psychiatry*, vol. 156, no. 1, p. 129, 1999.

[24] A. B. Garrod, *Gout and Rheumatic Gout*, Walton and Maberly, London, 1859.

[25] F. N. Johnson, *The History of Lithium Therapy*, MacMillan, London, 1984.

[26] J. F. Cade, "The anticonvulsant properties of creatinine," *Medical Journal of Australia*, vol. 2, no. 21, pp. 621–623, 1947.

[27] J. F. Cade, "The story of lithium," in *Discoveries in Biological Psychiatry*, F. J. Ayd and B. Blackwell, Eds., pp. 218–230, Lippincott Company, Philadelphia, 1970.

[28] G. F. S. Johnson, "Mood stabilizers (I). Discovering of antimanic properties of lithium salts," in *History of Psychopharmacology, Volume 2*, The Revolution of Psychopharmacology: The Discovery and Development of Psychoactive Drugs, F. López-Muñoz, C. Álamo, and E. F. Domino, Eds., pp. 161–168, NPP Books, Arlington, 2014.

[29] J. M. Talbot, "Use of lithium salts as a substitute for sodium chloride," *Archives of Internal Medicine*, vol. 85, no. 1, pp. 1–10, 1950.

[30] B. S. Burton, "On the propyl derivatives and decomposition products of ethylacetate," *American Chemical Journal*, vol. 3, pp. 385–395, 1882.

[31] M. Harris, S. Chandran, N. Chakraborty, and D. Healy, "Mood stabilizers: the archeology of the concept," *Bipolar Disorders*, vol. 5, no. 6, pp. 446–452, 2003.

[32] J. K. Penry and J. C. Dean, "The scope and use of valproate in epilepsy," *Journal of Clinical Psychiatry*, vol. 50, Supplement 3, pp. 17–22, 1989.

[33] T. R. Henry, "The history of valproate in clinical neuroscience," *Psychopharmacology Bulletin*, vol. 37, Supplement 2, pp. 5–16, 2003.

[34] G. Carraz, M. Darbon, S. Lebreton, and H. Beriel, "Proprietes pharmacodynamiques de l'acide n-dipropylacetique et de ses derives," *Thérapie*, vol. 19, pp. 469–475, 1964.

[35] G. Carraz, S. Lebreton, M. Boitard, S. Borselli, and J. Bonnin, "Apropos of 2 new anti-epileptic drugs of the N-dipropylacetic series," *Encephale*, vol. 54, no. 5, pp. 458–465, 1965.

[36] P. A. Lambert, S. Borselli, G. Marcou, M. Bouchardy, and G. Carraz, "Proprietes neuro-psychotropes du Depamide: action psychique chez les epileptiques et les maladies presentant des troubles caracteriels," in *Compte Rendus du Congrès des Psychiatristes et des Neurologistes de Langue Française*, pp. 1034–1039, Mason, Paris, 1966.

[37] P. A. Lambert, G. Cavaz, S. Borselli, and S. Carrel, "Action neuropsychotrope d'un nouvel anti-epiletique: le Dépamide," *Annales Médico-Psychologiques*, vol. 1, pp. 707–710, 1966.

[38] C. L. Bowden, A. M. Brugger, A. C. Swann et al., "Efficacy of divalproex vs. lithium and placebo in the treatment of mania," *Journal of the American Medical Association*, vol. 271, no. 12, pp. 918–924, 1994.

[39] H. Kutt, "Carbamazapine: chemistry and method of determination," in *Antiepiletic Drugs*, R. H. Levy, F. E. Dreifuss, and R. H. Mattson, Eds., pp. 457–471, Raven, New York, 3rd edition, 1989.

[40] W. Theobald and H. A. Kunz, "On the pharmacology of the antiepileptic 5-carbamyl-5H-dibenzo(b,f)azepine," *Arzneimittel-Forschung*, vol. 13, pp. 122–125, 1963.

[41] H. Takezaki and M. Hanaoka, "The use of carbamazepine (Tegretol) in the control of manic-depressive psychosis and other manic, depressive states," *Seishin Igaku*, vol. 13, pp. 173–182, 1971.

[42] N. Shinfuku, "What are happening in the mental health system in Japan: some observations," *Taiwanese Journal of Psychiatry*, vol. 26, pp. 70–76, 2012.

[43] J. W. Young, B. L. Henry, and M. A. Geyer, "Predictive animal models of mania: hits, misses and future directions," *British Journal of Pharmacology*, vol. 164, no. 4, pp. 1263–1284, 2011.

[44] R. Takehashi, A. Sakuma, and H. Itoh, "Comparison of efficacy of lithium carbonate and chlorpromazine in mania," *Archives of General Psychiatry*, vol. 32, no. 10, pp. 1310–1318, 1975.

[45] T. Okuma, I. Yamashita, and R. Takehash, "Comparison of the antimanic efficacy of carbamazepine and lithium carbonate by double-blind controlled study," *Pharmacopsychiatry*, vol. 23, no. 3, pp. 143–150, 1990.

[46] R. H. Weisler, J. R. Calabrese, C. L. Bowden, J. A. Ascher, J. DeVeaugh-Geiss, and G. Evoniuk, "Discovery and development of lamotrigine for bipolar disorder: a story of serendipity, clinical observations, risk taking, and persistence," *Journal of Affective Disorders*, vol. 108, no. 1-2, pp. 1–9, 2008.

[47] W. Sneader, *Drug Prototypes and Their Exploitation*, John Wiley & Sons, Ltd., Chichester, 1996.

[48] J. Fischer and D. P. Rotella, "Serendipitous Target-Based Drug Discoveries," in *Successful Drug Discovery, volume 1*, J. Fischer and D. P. Rotella, Eds., pp. 3–18, Wiley, New York, 2015.

[49] D. Smith, G. Baker, G. Davies, M. Dewey, and D. W. Chadwick, "Outcomes of add-on treatment with lamotrigine in partial epilepsy," *Epilepsia*, vol. 34, no. 2, pp. 312–322, 1993.

[50] R. Weisler, M. Risner, J. Ascher, and T. Houser, *Use of lamotrigine in the treatment of bipolar disorder*, American Psychiatric Association Annual Meeting, Philadelphia, P.A., 1994.

[51] C. L. Bowden, J. R. Calabrese, G. Sach et al., "A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder," *Archives of General Psychiatry*, vol. 60, no. 4, pp. 392–400, 2003.

[52] J. R. Calabrese, C. L. Bowden, G. Sachs et al., "A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder," *Journal of Clinical Psychiatry*, vol. 64, no. 9, pp. 1013–1024, 2003.

[53] R. F. Prien, E. M. Caffey, and C. J. Klett, "Comparison of lithium carbonate and chlorpromazine in the treatment of mania," *Archives of General Psychiatry*, vol. 26, no. 2, pp. 146–153, 1972.

[54] S. L. McElroy and P. E. Keck, "Pharmacologic agents for the treatment of acute bipolar mania," *Biological Psychiatry*, vol. 48, no. 6, pp. 539–557, 2000.

[55] M. Narasimhan, T. O. Bruce, and P. Masand, "Review of olanzapine in the management of bipolar disorders," *Neuropsychiatric Diseases and Treatment*, vol. 3, pp. 579–587, 2007.

[56] M. Tohen, T. G. Jacob, S. L. Grundy et al., "Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study," *Archives of General Psychiatry*, vol. 57, no. 9, pp. 841–849, 2000.

[57] P. E. Keck, M. Versiani, S. Potkin et al., "Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial," *American Journal of Psychiatry*, vol. 160, no. 4, pp. 741–748, 2003.

[58] P. E. Keck, R. Marcus, S. Tourkodimitris et al., "A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania," *American Journal of Psychiatry*, vol. 160, no. 9, pp. 1651–1658, 2003.

[59] S. Khanna, E. Vieta, B. Lyons, F. Grossman, and M. Kramer, "Risperidone monotherapy in acute bipolar mania," *Bipolar Disorders*, vol. 5, Supplement 1, 2003.

[60] A. B. Smulevich, S. Khanna, M. Eerdekens, K. Karcher, M. Kramer, and F. Grossman, "Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol," *European Neuropsychopharmacology*, vol. 15, no. 1, pp. 75–84, 2005.

[61] A. Cipriani, C. Barbui, G. Salanti et al., "Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis," *Lancet*, vol. 378, no. 9799, pp. 1306–1315, 2011.

[62] F. López-Muñoz and C. Álamo, "Neurobiological background for the development of new drugs in schizophrenia," *Clinical Neuropharmacology*, vol. 34, no. 3, pp. 111–126, 2011.

[63] M. Tohen and E. Vieta, "Antipsychotic agents in the treatment of bipolar mania," *Bipolar Disorders*, vol. 11, Supplement 2, pp. 45–54, 2009.

[64] X. Li, M. A. Frye, and R. C. Shelton, "Review of pharmacological treatment in mood disorders and future directions for drug development," *Neuropsychopharmacology Reviews*, vol. 37, no. 1, pp. 77–101, 2012.

[65] M. A. Frye, M. L. Prieto, W. V. Bobo et al., "Current landscape, unmet needs, and future directions for treatment of bipolar depression," *Journal of Affective Disorders*, vol. 169, Supplement 1, pp. S17–S23, 2014.

[66] J. R. Calabrese, P. E. Keck, W. MacFadden et al., "A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression," *American Journal of Psychiatry*, vol. 162, no. 7, pp. 1351–1360, 2005.

[67] M. E. Thase, W. MacFadden, R. H. Weisler et al., "Efficacy of quetiapine monotherapy in bipolar I and II depression," *Journal of Clinical Psychopharmacology*, vol. 26, no. 6, pp. 600–609, 2006.

[68] A. H. Young, S. L. McElroy, M. Bauer et al., "A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I)," *Journal of Clinical Psychiatry*, vol. 71, no. 2, pp. 150–162, 2010.

[69] S. L. McElroy, R. H. Weisler, W. Chang et al., "A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II)," *Journal of Clinical Psychiatry*, vol. 71, no. 2, pp. 163–174, 2010.

[70] F. López-Muñoz and C. Álamo, "Active metabolites as antidepressant drugs: the role of norquetiapine in the mechanism of

action of quetiapine in the treatment of mood disorders," *Frontiers in Psychiatry*, vol. 4, 2013.

[71] A. S. De Miranda, F. A. Moreira, and A. L. Teixeira, "The preclinical discovery and development of quetiapine for the treatment of mania and depression," *Expert Opinion on Drug Discovery*, vol. 12, no. 5, pp. 525–535, 2017.

[72] A. Loebel, J. Xu, J. Hsu, J. Cucchiaro, and A. Pikalov, "The development of lurasidone for bipolar depression," *Annals of New York Academy of Sciences*, vol. 1358, no. 1, pp. 95–104, 2015.

[73] T. Ishibashi, T. Horisawa, K. Tokuda et al., "Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity," *Journal of Pharmacology and Experimental Therapeutics*, vol. 334, no. 1, pp. 171–181, 2010.

[74] L. N. Cates, A. J. Roberts, S. Huitron-Resendiz, and P. B. Hedlund, "Effects of lurasidone in behavioral models of depression: role of the 5-HT7 receptor subtype," *Neuropharmacology*, vol. 70, pp. 211–217, 2013.

[75] H. A. Nasrallah, J. Cucchiaro, Y. Mao, A. A. Pikalov, and A. D. Loebel, "Lurasidone for the treatment of depressive symptoms in schizophrenia: analysis of 4 pooled, 6-week, placebo-controlled studies," *CNS Spectrums*, vol. 20, no. 2, pp. 140–147, 2015.

[76] C. Álamo, F. López-Muñoz, and P. García-García, "The effectiveness of lurasidone as an adjunct to lithium or divalproex in the treatment of bipolar disorder," *Expert Review Neurotherapeutics*, vol. 14, no. 6, pp. 593–605, 2014.

[77] J. Greenwood, R. B. Acharya, V. Marcellus, and J. A. Rey, "Lumateperone: a novel antipsychotic for schizophrenia," *Annals of Pharmacotherapy*, vol. 55, no. 1, pp. 98–104, 2021.

[78] C. Álamo and F. López-Muñoz, "Eficacia de quetiapina de liberación prolongada en la sintomatología afectiva," *Revista de Psiquiatría y Salud Mental*, vol. 5, Supplement 1, pp. 3–19, 2012.

[79] R. K. Merton and E. Barber, *The Travels and Adventures of Serendipity*, University Press Princeton, Princeton, 2004.

[80] A. Hofmann, "LSD My Problem Child," in *Reflections on Sacred Drugs, Mysticism, and Science*, McGraw Hill, New York, 1980.

[81] R. M. Roberts, *Accidental Discoveries in Science*, John Wiley & Sons, New York, 1989.

[82] C. L. Diaz de Chumaceiro and O. G. E. Yaber, "Serendipity analogues: approval of modifications of the traditional case study for a psychotherapy research with music," *Arts in Psychotherapy*, vol. 22, no. 2, pp. 155–159, 1995.

[83] F. López-Muñoz, C. Álamo, and P. García-García, "The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: half a century of anxiolytic drugs," *Journal of Anxiety Disorders*, vol. 25, no. 4, pp. 554–562, 2011.

[84] F. López-Muñoz, V. S. Bhatara, C. Álamo, and E. Cuenca, "Historical approach to reserpine discovery and its introduction in psychiatry," *Actas Españolas de Psiquiatría*, vol. 32, no. 6, pp. 387–395, 2004.

[85] F. López-Muñoz and C. Álamo, "The consolidation of neuroleptic therapy: Janssen, the discovery of haloperidol and its introduction into clinical practice," *Brain Research Bulletin*, vol. 79, no. 2, pp. 130–141, 2009.

[86] H. Oh, T. D. Prevot, D. Newton, and E. Sibille, "From serendipity to rational drug design in brain disorders: in silico, in vitro, and in vivo approaches," *Current Opinion on Pharmacology*, vol. 60, pp. 177–182, 2021.

[87] A. A. Pieper and J. M. Baraban, "Moving beyond serendipity to mechanism-driven psychiatric therapeutics," *Neurotherapeutics*, vol. 14, no. 3, pp. 533–536, 2017.

[88] D. F. Klein, "The loss of serendipity in psychopharmacology," *Journal of the American Medical Association*, vol. 299, no. 9, pp. 1063–1065, 2008.

[89] A. A. Baumeister, J. L. Pow, K. Henderson, and F. López-Muñoz, "On the exploitation of serendipity in drug discovery," *Clinical and Experimental Pharmacology*, vol. 3, no. 3, article e121, 2013.

[90] D. Healy, *The Psychopharmacologists III*, Arnold, London, 2000.