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THE ROLE OF SERENDIPITY IN THE DISCOVERY OF CLASSICAL ANTIDEPRESSANT DRUGS: APPLYING OPERATIONAL CRITERIA AND PATTERNS OF DISCOVERY

Serendipity and classical antidepressant drugs

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Abstract

BACKGROUND

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.

AIM

In this paper, we have analysed the role of serendipity in the discovery and development of classical antidepressant drugs, basically tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), as well as heterocyclic, "atypical" or "second generation" antidepressants.

METHODS

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.

RESULTS

The discovery of the antidepressant properties of imipramine and iproniazid, the prototypes of TCAs and MAOIs, respectively, fits the mixed type II pattern; initial serendipitous discoveries (imipramine was an antipsychotic and iproniazid was an anti-tuberculosis agent) leading 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, characterised by the complete absence of serendipity. Among the heterocyclic drugs, mianserin (originally developed as an antihistamine) also falls into the type II pattern.

CONCLUSION

Serendipity played an important role in the discovery of the first antidepressant drugs.

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.

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 categorised as traditional antidepressants (Table 1).

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 analysed 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 revolutionised the care of mental illnesses during the 1950s has not escaped this conceptualisation 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.

MATERIALS AND METHODS

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):

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

II) 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.

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

IV) 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 programmes specifically designed to develop effective drugs for different pathological conditions.

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 analysed 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.

RESULTS

Discovery of the antidepressant properties of imipramine and tricyclic antidepressants

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].

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 synthesised by Franz Häfliger and Walter Schindler in 1948 from promethazine by

replacing the sulphur bridge of phenothiazine with an ethylene bridge[28]. The substance had been registered in 1951 under US licence 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 tricyclic antidepressants.

Kuhn had the sagacity to recognise 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 tranquillising 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 synthesising 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 Concordin® 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 USA.

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 monoamine oxidase inhibitors

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].

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 "thymerethics", 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 realised 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 haemorrhages, 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 tetrahydoisoquinoline 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 haemolytic anaemia), 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-HT_2 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 H_1 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 programme carried out by Organon International, B.V. in Oss (The Netherlands), mianserin (a tetracyclic piperazino-azepine) was synthesised 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 antagonising 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).

DISCUSSION

Serendipity is a phenomenon that has been regularly and constantly referred to when analysing 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 favours 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 tranquillising 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 stabilising 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].

ARTICLE HIGHLIGHTS

Research background

Serendipity refers to discoveries made through a combination of accidents and sagacity.

The role played by serendipity in the origin of modern psychopharmacology has proven to be controversial in scientific literature.

Research motivation

Know the role played by serendipity in the discovery of the first antidepressant drugs.

Research objectives

Analyze the true role of serendipity in the discovery and development of classical antidepressant drugs: tricyclic antidepressants, monoamine oxidase inhibitors, and heterocyclic, "atypical" or "second generation" antidepressants.

Research methods

Application of our operational definition of serendipity: the discovery of something not sought.

Application of our four different patterns of serendipitous attributability.

Research results

Imipramine meets a type II pattern of serendipity: initial serendipitous discoveries (imipramine was an antipsychotic drug) leading secondarily to non-serendipitous discoveries.

Iproniazid meets a type II pattern of serendipity: initial serendipitous discoveries (iproniazid was an anti-tuberculosis agent) leading secondarily to non-serendipitous discoveries.

Mianserin meets a type II pattern of serendipity: initial serendipitous discoveries (mianserin was an antihistamine drug) leading secondarily to non-serendipitous discoveries.

The rest of tricyclic antidepressants, monoamine oxidase inhibitors, and heterocyclic, "atypical" or "second generation" antidepressants meet a type IV pattern of serendipity: complete absence of serendipity.

Research conclusions

Serendipity played an important role in the discovery and clinical introduction of the first antidepressant drugs.

Research perspectives

The role of serendipity in the discovery of new antidepressant agents seems to be diminishing.

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