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Review Article

Serendipity in psychotropic drugs: Unearthing the origins

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ABSTRACT

This is a dive into the history of several groundbreaking psychiatric drugs and their discoveries.
The article begins by exploring the curious origin of the word "serendipity" following Horace Walpole's encounter with a fairytale. This captivating emergence of "serendipity" is followed by an account of lithium discovered in 1817. About a century and a half later, lithium would receive FDA approval, becoming a cornerstone in the treatment of mania.
The narrative meanders to other drugs that have a similar thread of serendipity woven into their beginnings— chlordiazepoxide, meprobamate, chlorpromazine, finally halting at iproniazid, an anti-tubercular agent that unexpectedly revealed its mood-enhancing potential and paved the way for the development of monoamine oxidase inhibitors as antidepressants.
The authors navigate through the intricacies of chance and discovery that have influenced the trajectory of psychiatric drug development, leading to unexpected breakthroughs that have forever left their mark on the undeniably vast landscape that is mental health.

1. Introduction

The word "serendipity" came into being in a letter by Horace Walpole to his friend, after he stumbled upon the translation of the Peregrinaggio. Walpole mentions in his letter that he 'once read a silly fairy tale, called The Three Princes of Serendip'.[1,2] It was a tale of three princes who were "always making discoveries, by accidents and sagacity, of things which they were not in quest of."

The history of Medicine is filled with such "happy accidents." But here's the thing, there is a common denominator in all of these serendipitous discoveries: "each was recognized, evaluated, and acted upon in the light of the discoverer's total intellectual experience."[3] The significance of this phrase lies in its recognition of the role of curiosity and preparedness in scientific exploration. It brings forth the idea that serendipity is not merely luck, but a combination of chance and the ability to recognize unexpected findings.

Even though the word "serendipity" is submerged in semantic confusion, the definition used here is that of Stedman's Medical Dictionary: "finding one thing while looking for something else."[4]

1.1. Lithium

The tale of lithium begins in 1817 when Johan August Asfwedson stumbled across the alkali metal during his analysis of petalite ore (Figure 1).[5]

A.B. Garrod, a London internist, observed that uric acid deposits in cartilage could be dissolved by the carbonate of lithium and subsequently introduced the use of lithium in the treatment of gout in his 1859 book, The Nature and Treatment of Gout and Rheumatic Gout.[6]

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During the latter half of the 19^{th} century, lithium gained traction as a medicinal product for many health conditions such as high blood pressure, angina, asthma, Raynaud's disease and gout.[6]

Lithium bromide emerged as a sedative, a treatment for insomnia and an antiepileptic towards the end of the 19^{th} century.[6] In 1871, William Hammond, professor of Diseases of the Mind and Nervous System at the Bellevue Hospital Medical College in New York, utilized lithium for the treatment of mania.[7] However, the dose Hammond suggested for the use of lithium bromide in mania (3.6 grams) may cause toxicity.[8] This could be the reason Hammond did not mention the use of lithium for mania in his future books again.

By the 1930s, many lithium-containing products, such as lithium tablets, were on the market for "uric acid diathesis," a predisposition for the accumulation of urea in the body that could cause a variety of disorders.[9]

The use of a 25% solution of lithium chloride also emerged in 1984 as a substitute for salt but soon lost popularity due to reports of toxicity.[10,11]

So, when John Cade rediscovered the use of lithium for mania and published his work in an obscure journal a year later in 1949, his findings went mostly unnoticed.[12] In this study, drawing parallels from thyroid disease, Cade had reasoned that if excess thyroid activity caused thyrotoxicosis and decreased thyroid function myxedema, there had to be some metabolite produced in the body that in excess caused mania and in deficiency, melancholia. He proceeded to inject guinea pigs with the urine of manic patients and that of normal patients. He soon found that Guinea pigs injected with the urine of patients with manic-depressive illness died more quickly. Thus, Cade concluded that the culprit responsible for the deaths of guinea pigs was urea and that uric acid increased its toxicity. To pursue this hypothesis further, he decided to inject lithium urate, the most soluble of urates, into the guinea pigs, expecting the toxicity to increase. Serendipity struck when, to his astonishment, the toxicity was less than expected. Cade also noticed that the guinea pigs appeared lethargic. He ascribed this effect to lithium. After testing lithium on himself for 2 weeks to identify side effects, he tested it on his patients— using lithium carbonate or citrate in ten manic, six schizophrenic, and five depressed patients. In 4-5 days, the patients with mania showed improvement.[12]

Randomly controlled trials by Danish researcher Mogen Schou demonstrated the effectiveness of lithium in mania.[13] This was a major breakthrough, opening the door for more international trials. Lithium attained FDA approval in 1970.[7]

1.2. Chlordiazepoxide

The mid-20^{th} century stands out as the time of development of benzodiazepines (Figure 2). It started with Leo Henryk

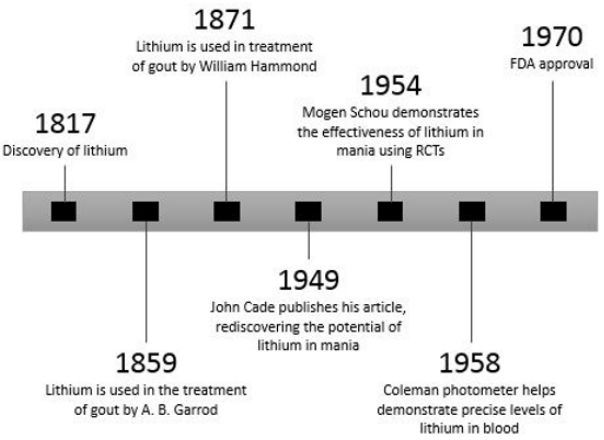

Figure 1: Milestones in the discovery of lithium

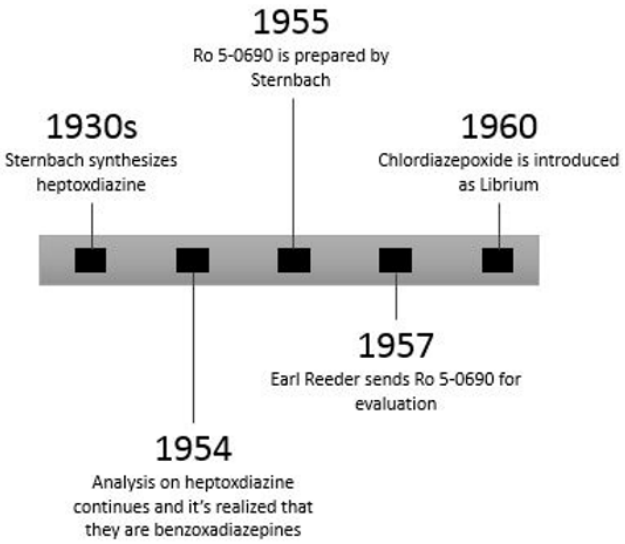

Figure 2: Milestones in the discovery of chlordiazepoxide

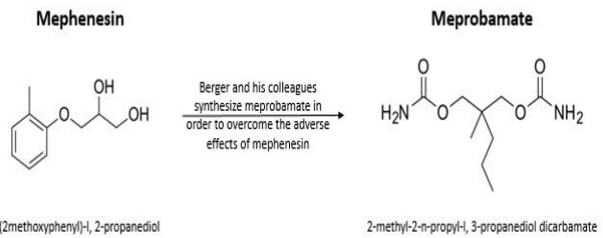

Figure 3: The structures of mephenesin and meprobamate

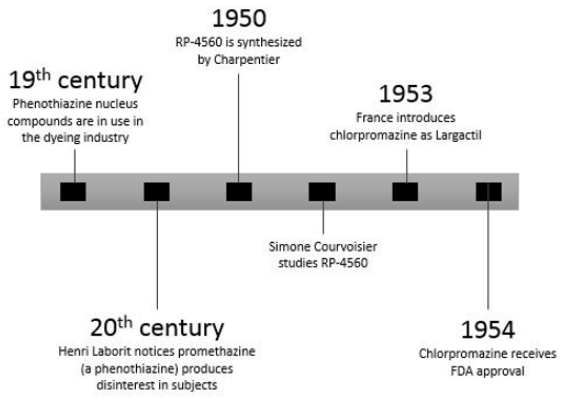

Figure 4: Milestones in the discovery of chlorpromazine

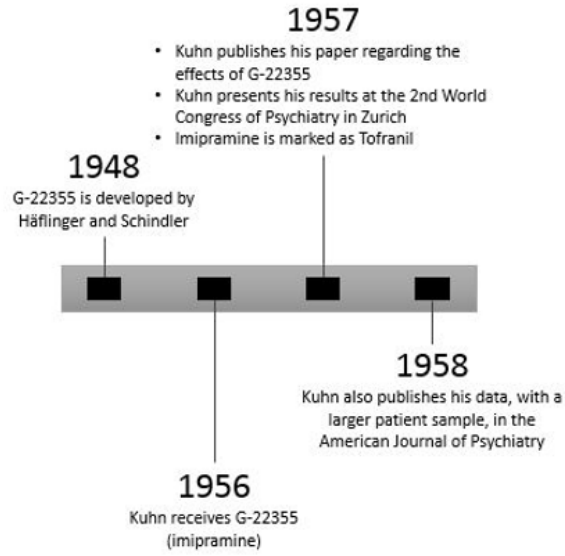

Figure 5: Milestones in the discovery of imipramine

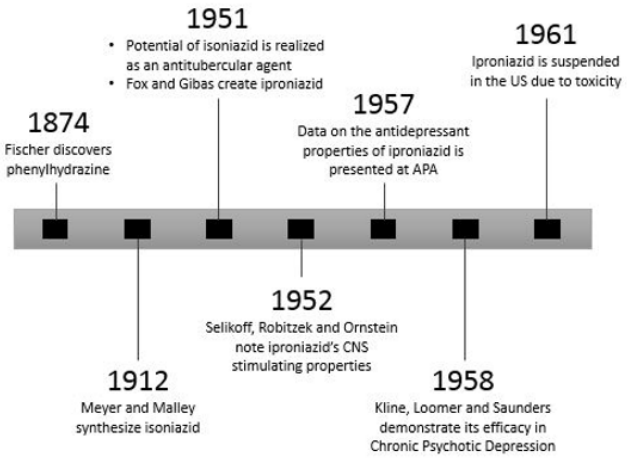

Figure 6: Milestones in the discovery ofiproniazid

Sternbach, a Polish immigrant, working in the Chemical Research Department of Hoffmann-La Roche, U.S.A. in Nutley, New Jersey.[14]

In 1954, he continued his analysis of some heterocycles (heptoxdiazine) that he had synthesized in the 1930s, during his time at Jagiellonian University, Poland where he had worked in the field of dyestuff chemistry.[14]

The recent discovery of chlorpromazine and its tricyclic structure drove his research and he soon realized that the materials he had thought of as heptoxdiazine compounds were, in fact, benzoxadiazepines.[15] The Polish researcher produced forty such compounds in due course, but all of them proved to be inert, so the studies were halted soon after this.[15]

In the April of 1957, almost two years later, during a laboratory clean-up, Earl Reeder (Sternbach's colleague) drew his attention to Ro 5-0690.[16] Sternbach had prepared Ro 5-0690 in 1955 by the treatment of quinazoline N-oxide with methylamine but had let it remain untested.[16] On Reeder's insistence, it was sent for evaluation with the expectation of a negative result. However, luckily, this would not prove to be the case. The compound showed some promising results instead, similar to meprobamate.[15]

Sternbach wanted to find out why of the 40 such compounds that he had synthesized, none had demonstrated similar properties.[16] The answer to this would come to light when he reexamined the structure of Ro 5-0690 and realized that instead of using a secondary amine in the synthesis of Ro 5-0690, as he had done with all the other compounds, he had instead used methylamine, a primary amine.[15] As a result, it followed a different pathway and undergone molecular rearrangement to become 1, 4-benzodiazepine.[15]

First called methaminodiazepoxide, then chlordiazepoxide, the drug almost didn't receive assent due to symptoms of ataxia and dysarthria in geriatric patients.[17] However, its effectiveness was soon established and the US Food and Drug Administration approved its use.[17] It was introduced under the trade name Librium in 1960.[16] Chlordiazepoxide was followed three years later by diazepam under the brand name, Valium.[15]

1.3. Meprobamate

The development of meprobamate is closely entwined with mephenesin (Figure 3) because it was due to the latter that the former came to be. Frank Berger and William Bradley, in a British drug company, were in pursuit of an antibacterial drug that would be effective against gram-negative bacteria not responding to penicillin.[18] Berger and Bradley turned their attention towards phenoxetol, a phenylglycerol ether compound known to possess the ability to destroy gram-negative bacteria.[18] Bradley, a chemist, developed compounds with related structures in hopes of discovering a substance that would contain the required antibacterial properties. Berger tested these compounds

on mice and discovered to his astonishment that they produced reversible flaccid paralysis of the voluntary skeletal muscles.[18] He stated in his 1946 publication, "A number of α-substituted ethers of glycerol produced transient relaxation and paralysis of skeletal muscles in small laboratory animals."[18] 143 compounds were analyzed and mephenesin, or 3-(2methoxyphenyl)-l, 2-propanediol, was found to have the most profound muscle relaxing ability and widest safety margin.[18]

Mephenesin was introduced for clinical use during light anesthesia in the next few years.[19] Its propensity as an anxiety drug was soon noticed but three main issues limited its use.[19] These were—short duration of action, more effect on the spinal cord than on supraspinal structures and requirement for large doses due to its weak action.

Thus, Berger and his colleagues set themselves on finding a way to overcome the adverse effects of mephenesin.[20] This search paved the way for the discovery of 2-methyl-2-n-propyl-l, 3-propanediol dicarbamate, that is, meprobamate by J. Ludwig, working at the Wallace Laboratories of Carter Products, who published his findings in 1951.[20] It was a tranquilizer, just like mephenesin, but its duration of action was about eight times longer.

Meprobamate was introduced under the trade name, Miltown, in 1955.[21] From the time of its introduction to the 1960s, it gained explosive popularity, especially in Hollywood.[21] But meprobamate's fame was short-lived, its crown usurped by the introduction of Valium in 1963.[21]

1.4. Chlorpromazine

The discovery of the phenothiazine nucleus can be traced back to the late nineteenth century when compounds containing the nucleus had utility in the dyeing industry.[22] They were also utilized in the first half of the twentieth century as antiseptics, antihelminthics and antihistaminics.[22]

Henri Laborit, a surgeon in the French Navy, observed that promethazine, a phenothiazine compound, in an intravenous dosage of 50 to 100 mg, produced a sense of disinterest and a tendency to sleep without loss of consciousness.[22] He found it helpful as a pharmacological tool for preventing surgical shock. In 1950, he persuaded a French pharmaceutical company, Rhône-Poulenc, to produce a similar compound that would potentiate anesthesia while simultaneously decreasing the patients' anxiety.[22] Simone Courvoisier began studying the phenothiazines that had been developed by Paul Charpentier since 1944.[22] Her attention soon fell on RP-4560, a compound that had been created in the winter of 1950 by Charpentier. This substance was chlorpromazine and it met the properties that Henri Laborit had been in search of. It was released for use the next year and Henri Laborit soon saw its potential beyond the management of surgical shock and potentiation of anesthesia, in the treatment of burns, Raynaud's disease and psychiatric disorders.[22,23]

Chlorpromazine (or, "Laborit's Drug" as it was known by many authors during that time) was released in France under the trade name Largactil in 1952 (Figure 4).[24]

1.5. Imipramine

The success of drugs like reserpine and chlorpromazine formed the backdrop of the discovery of imipramine, the first tricyclic antidepressant (Figure 5). Roland Kuhn, a Swiss psychiatrist collaborating with the pharmaceutical company Geigy, asked for phenothiazine compounds to be used in psychotic patients, in hopes of finding a drug effective in schizophrenia.[25] In 1956, Kuhn received G-22355, a compound similar in structure to chlorpromazine, which had been created by Franz Häflinger and Walter Schindler from promethazine in 1948.[25] As it were, G-22355 proved ineffective in schizophrenia.[25]

Electroshock and psychotherapy were the only modalities of depression treatment during this time.[26] However, Kuhn decided to administer G-22355, later named imipramine, to patients with depression, having earlier noticed that it decreased depressive symptoms in patients of schizophrenia.[26] This led to him publishing his first paper, in German, regarding his findings in 1957.[27] He also presented his results at the 2nd World Congress of Psychiatry in Zurich the same year to a dozen participants.[15] The next year, Kuhn also published his data, with a larger patient sample, in the American Journal of Psychiatry, leading to widespread recognition.[28]

Imipramine was introduced for the treatment of depression in Europe towards the end of 1957 by Geigy, under the name Tofranil.[15]

1.6. Iproniazid

The development of iproniazid and its recognition as an antidepressant is a complex one (Figure 6). The story begins in 1874, when Emil Fischer accidently discovered phenylhydrazine.[29]

Hans Meyer and Josef Malley synthesized isonicotinylhydrazine (isoniazid) in 1912.[30] Apart from this, two teams, one led by Herbert Hyman Fox and the other by Harry L. Yale in 1951 realized independently the potential of isoniazid as an antitubercular agent.[30]

In attempts to improve the tuberculostatic effect of isoniazid, Herbert H. Fox and John T. Gibas of Hoffmann-La Roche Laboratories ended up synthesizing iproniazid.[30] It was a potent antitubercular drug but its Central Nervous System stimulating adverse effects were of particular concern, as noted by Irving J. Selikoff, Edward Robitzek and Ornstein in 1952.[31] The same year, E. A. Zeller and colleagues at Northwestern University, Chicago, discovered that iproniazid was a monoamine oxidase (MAO) inhibitor.[32]

Jackson A. Smith, Gordon R. Kamman and Carlos Castilla del Pino soon recognized that these adverse effects could be used to benefit psychiatric patients.[33–35]

In April 1957, at a meeting in Syracuse of the American Psychiatric Association, many groups of scientists presented data on the effects of iproniazid on depressed patients but none of them used the term "antidepressant" for iproniazid.[36] Next year, Nathan S. Kline, Harry P. Loomer and John C. Saunders, of Rockland State Hospital, were able to demonstrate the efficacy of iproniazid, marketed as an antitubercular drug, in non-tuberculotic depressed patients (chronic psychotic depression). They attributed iproniazid's antidepressant activities to its MAO-inhibiting effect.[36]

Even though iproniazid was only marketed as an antitubercular agent (Marsilid), in 1958, over 400,000 depressed patients had been treated with the drug. Iproniazid opened the door for development of Monoamine Oxidase Inhibitors as antidepressants.[37]

2. Conclusion

The history of the medications mentioned in the article demonstrates how unexpected observations may lead to revolutionary treatments for psychiatric conditions.

In tracing the origins of lithium, chlordiazepoxide, meprobamate, chlorpromazine, imipramine and iproniazid, we encounter a common thread: serendipity. From the accidental discovery of lithium's mood-stabilizing properties to the chance observation of chlorpromazine's calming effects, these stories highlight the unpredictable nature of scientific advancement.

Serendipity often intertwines with meticulous research and astute observation. It's not merely stumbling upon a discovery, but recognizing its significance and acting upon it with informed insight. The journey from initial observation to practical application involves a blend of curiosity, perseverance, and sometimes, sheer luck.

3. Source of Funding

Nome.

4. Conflict of Interest

None.

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