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A History of Antipsychotic Drug Development

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The history of antipsychotic drug development has had a long and torturous course, often based on chance findings that bear little relationship to the intellectual background driving observations. In 1891, Paul Ehrlich observed the antimalarial effects of methylene blue, a phenothiazine derivative. Later, the phenothiazines were developed for their antihistaminergic properties. In 1951, Laborit and Huguenard administered the aliphatic phenothiazine, chlorpromazine, to patients for its potential anesthetic effects during surgery. Shortly thereafter, Hamon et al. and Delay et al. extended the use of this treatment in psychiatric patients and serendipitously uncovered its antipsychotic activity. Between 1954 and 1975, about 15 antipsychotic drugs were introduced in the United States and about 40 throughout the world. Thereafter, there was a hiatus in the development of antipsychotics until the introduction of clozapine treatment in the United States in 1990 opened the era of "atypical" antipsychotic drugs, which show a reduced potential to induce extrapyramidal symptoms (EPS), an increased efficacy for the negative symptoms of schizophrenia, no elevation of prolactin after chronic use (except risperidone), and, at least for clozapine, effectiveness in some patients previously regarded as treatment-refractory. This review describes the available atypical antipsychotic drugs and their characteristics, and concludes by highlighting those in the pharmaceutical "pipeline."

IN SEARCH OF AN ANTIMALARIAL DRUG

THE CHEMICAL CLASS of phenothiazines had its origin in the latter half of the 19th century and was associated with the flourishing dye industry in England. In 1856, W.H. Perkin produced an exquisite purple dye called mauve by oxidizing aniline, and due to its potential commercial value, various compounds related to aniline were quickly subjected to numerous types of chemical reactions.[1] As an outcome of this activity in 1876, Caro synthesized methylene blue, a phenothiazine derivative, and a few years later Bernthesen synthesized phenothiazine.[1]

For centuries, quinine—a constituent of the bark of the cinchona tree that grows in the tropics—was used to treat malaria throughout the world.[1] But during World War I, the Germans found themselves cut off from the world's primary supplies of quinine. Consequently, they had to look for a synthetic substitute. During their search, they uncovered the work by the German bacteriologist, Paul Ehrlich, who observed in 1891 that methylene blue was effective in treating the symptoms of malaria. Building on Ehrlich's earlier observations, W. Schulemann and his coworkers synthesized additional compounds related to methylene blue.[1] One of these was a diethylaminoethyl derivative of methylene blue. This derivative, which proved to have more active antimalarial activity than methylene blue, was too toxic to be clinically useful. Later, Schulemann and other German chemists discovered quinacrine, which together with quinine long provided the primary therapy for malaria around the world.[1]

During World War II, early Japanese victories in Southeast Asia again denied the Allies access to the quinine-producing area of the world. This time, as part of a program to find a synthetic antimalarial agent for the Allies, Gilman et al.[2] synthesized a group of compounds in which the aminoalkyl chains were attached to the central nitrogen atom of the phenothiazine ring. Unlike quinacrine, Gilman's phenothiazine derivatives were inactive as an antimalarial drug.[1]

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IN SEARCH OF BETTER ANTIHISTAMINES

Unaware of Gilman's work,[2] French researchers at the Société des Usines cliniques at Rhône-Poulenc Laboratories (Paris, France) studied phenothiazine derivatives identical to those developed by Gilman.[1] They confirmed that aminoalkyl phenothiazines do not possess significant antimalarial activity.[1,2] But these Rhône-Poulenc scientists did not give up, and they continued to evaluate these compounds for antihistamine effects.[1]

Before World War II, the best antihistamine agent was phenbenzamine (2339 RP [Rhône-Poulenc]).[1] During the War, as part of the further research to find antimalarial agents in the United States and France, numerous antihistamines were produced that were superior to phenbenzamine, one of which was chlorpheniramine. Later, scientists at Rhône-Poulenc Specia Laboratories found that one of the aminoalkyl phenothiazines, promethazine (3277 RP), which shares a common chemical structure with phenbenzamine, is a more potent antihistamine with a longer duration of action.[1]

AN AGENT TO POTENTIATE ANESTHESIA

Pharmacologic characterization of promethazine showed that it is associated with more pronounced sedation than any other antihistamine.[1] In 1950, H. Laborit, the French Navy anesthesiologist, found that promethazine potentiates the activity of other anesthetic agents, leading rapidly to its use in clinical anesthesia.[3]

Excitement over promethazine's anesthetic-potentiating effects led Rhône-Poulenc scientists on a search for other phenothiazine derivatives with similar activity.[1] In 1950, S. Courvoisier and her associates tested a new compound, chlorpromazine (4560 RP), which was previously synthesized by P. Charpentier.[1,3] Courvoisier et al. found that chlorpromazine prolongs sleep induced by barbiturates in rodents, prevents apomorphine-induced emesis in dogs, and also inhibits the conditioned avoidance-escape response in mice.[3] In 1951, Laborit and Huguenard reported that patients who are induced to a state of "artificial hibernation" by a "lytic cocktail" of chlorpromazine, promethazine, and an analgesic require lower doses of anesthetic agents and better withstand the stress of surgical trauma.[1,3,4] They also observed that chlorpromazine-medicated patients do not lose consciousness but do become sleepy and show a lack of interest in what occurs around them.[4]

CLINICAL TRIALS WITH CHLORPROMAZINE

Based on their fortuitous observations of the CNS effects of chlorpromazine, Laborit and Huguenard supplied chlorpromazine to two groups of psychiatrists: Hamon, Paraire, and Velluz at the Central Military Hospital—the Val de Grâce—in Paris[5] and Delay, Deniker, and Harl at the psychiatric clinic of Sainte-Anne Hospital in Paris.[3,6,7] The first reported chlorpromazine-treated case was a 57-year-old laborer who was admitted to the Val de Grâce because of erratic, uncontrollable behavior.[1,5] Prior to hospitalization, the patient made impassioned political speeches in cafes, proclaimed a love of liberty while walking down the street with a flower pot, and intermittently assaulted strangers.[5] Within 1 day of receiving chlorpromazine, he was noted to be calmer, and 1 week later he was joking with the medical staff.[1,5] After 3 weeks, the patient appeared nearly normal and was discharged.[5] Other patients treated with chlorpromazine for agitated and hyperactive behavior showed similar benefit.[1,6,7]

The identity of the first psychiatrists to administer chlorpromazine to patients remains a matter of dispute.[3,8,9] In 1957, three parties—Laborit, Lehmann, and Deniker—were awarded the Lasker Prize for their work with chlorpromazine,[10] but other awards in 1993 have recognized Laborit, Hamon, Paraire, and Velluz for their role in identifying chlorpromazine's therapeutic effects.[3,9] Apparently, Hamon et al. used chlorpromazine in conjunction with barbiturates in their patients on January 19, 1952, for the first time and then abandoned the field of chlorpromazine pharmacotherapy.[3] On the other hand, Delay et al. treated patients with chlorpromazine alone, reported their findings after Hamon et al., but remained interested in chlorpromazine pharmacotherapy for some time.[3,6,7] This confusion and dispute may account for the fact that the Nobel Prize Committee never recognized any of the discoverers of chlorpromazine despite its revolutionary clinical significance.[3]

In 1952 Rhône-Poulenc released chlorpromazine under the trade name of Largactil, meaning "large CNS effect,"[11] and in 1954 Smith, Kline and French (Philadelphia, PA) marketed it under the trade name of Thorazine. This made chlorpromazine available to investigators around the world, and the clinical findings of Hamon's and Delay's teams were promptly confirmed by Stähelin and Kielholz[12] in Germany, Lehmann and Hanra-

ham[13,14] in Canada, and Winkelman in the United States.[15] Findings from the United States and Canada were the first to be published in English. With the exception of one study in which the patients served as their own control,[16] these were all open-label studies. The therapeutic effect of chlorpromazine was not definitively established until the completion of a study by the US Veterans Administration Collaborative Study Group in the late 1950s.[17,18] However, long before the study was published, large decreases in psychiatric inpatient populations were witnessed around the world because of the widespread use of chlorpromazine or its related drugs.[8]

INTRODUCTION OF ANTIPSYCHOTIC AGENTS

The incredible clinical success of chlorpromazine stimulated a widespread search for other antipsychotic drugs at Rhône-Poulenc, where Charpentier and Courvoisier had previously identified the structural features necessary for potent biological activity, and thousands of additional phenothiazine derivatives were synthesized and tested.[19] Although chlorpromazine remained the most prescribed antipsychotic agent throughout the 1960s and early 1970s,[1] many drugs with similar antipsychotic efficacy but different chemistry, potency, and side-effect profiles were introduced to the market.[11] Among the 40 or more antipsychotic drugs introduced to the world by 1990[20] (about 15 in the United States[11]) were trifluoperazine, thioridazine, chlorprothixene, thiothixene, haloperidol, etc. The last of this series to be approved by the US Food and Drug Administration (FDA) was loxapine, a dibenzodiazepine, in 1975.[11] Despite this proliferation of antipsychotic drugs, only 11 depot preparations of eight different compounds were marketed in the world by 1990[20,21]; of these, only two (fluphenazine and haloperidol) were available in the US market.[11]

DESCRIPTION OF EXTRAPYRAMIDAL SYMPTOMS

In 1954, 2 years after chlorpromazine first came into clinical use, acute extrapyramidal symptoms (EPS) including parkinsonism, dystonias, and akathisia began to be described and recognized as side effects associated with the use of chlorpromazine and reserpine.[22] In a 1961 report,[23] the prevalence of EPS in patients treated with antipsychotic drugs was estimated as 38.9%. The majority of clinicians and pharmacologists became convinced of an absolute connection between EPS and the clinical effectiveness of antipsychotic drugs.[24,25] This attitude was reinforced with the introduction of haloperidol in 1958 by Haase and Janssen.[24,25] Tardive dyskinesia induced by chlorpromazine and its related antipsychotic drugs has been recognized as a concern since 1959 after the first report from France.[26,27]

INTRODUCTION OF CLOZAPINE

German psychiatrists working with G. Stille at Wander Pharmaceuticals in Bern, Switzerland, in the early 1960s worked to refute the concept that EPS and antipsychotic efficacy were linked.[25] Their work led to the introduction of clozapine, an antipsychotic with no EPS or minimally associated EPS.[11,26] Clinical confirmation of this profile for clozapine was provided in open studies by Austrian[28] and German[29] investigators in 1966, and later by Swiss researchers[30] in a double-blind study in 1971. The Wander Company, the manufacturer of clozapine at that time, found itself in a bizarre situation.[26] Clozapine was briefly marketed and quickly withdrawn.[26] Besides the embarrassment of lacking of EPS, the initial enthusiasm for clozapine was further dampened by (1) the purchase of Wander Pharmaceuticals Corp by Sandoz Pharmaceuticals Corp[31] and, most significantly, (2) reports from Finland that life-threatening incidents of agranulocytosis were associated with clozapine treatment.[32] However, enthusiasm for the drug was maintained by a small cadre of clinical investigators and G. Honigfeld at Sandoz, who observed that clozapine was remarkably effective in treatment-resistant patients. This led to a landmark double-blind study of clozapine in a well-defined group of treatment-resistant patients whose blood cell counts were closely monitored during treatment,[33] and ultimately to its introduction to the US market in 1990.

ADVENT OF ATYPICAL ANTIPSYCHOTIC DRUGS

Clozapine was first marketed in association with an intimately linked system of blood monitoring and drug availability in patients previously demonstrated to be treatment-resistant. Its initial use in studies and clinics established that it was useful not only for treating positive symptoms (such as hallucinations, delusions, disorganized behavior, and

disorganized speech) associated with schizophrenia but also for treating negative symptoms (such as severe social withdrawal, inactivity, apathy, affective flattening, and poverty of thought).[34] This activity rapidly destroyed the general conviction that the efficacy and EPS profile were linked, and led to an emerging concept of "atypical" antipsychotic drugs. Although no precise definition of this concept has ever been established, a drug with the property of "atypicality" shows a clinical profile with a low propensity to induce EPS (or EPS-sparing[35]) and with efficacy for the negative symptoms of schizophrenia. Other characteristics commonly identified as atypicality are an efficacy in treatment-refractory patients and, sometimes, a failure to induce a serum prolactin elevation.

Clozapine's success quickly led to the development of other atypical antipsychotic drugs. The first of these, risperidone, was approved in 1994,[36] olanzapine in 1996,[37] sertindole in 1997 (in some countries outside of the United States),[38] and quetiapine in 1997.[39] Due to cardiac safety concerns raised by the FDA,[40] the manufacturer of sertindole has abandoned an effort to seek a US marketing license. Ziprasidone[41] was still under regulatory review as of February 1999.

CLINICAL CHARACTERISTICS OF ATYPICAL ANTIPSYCHOTIC DRUGS

All atypical antipsychotic drugs currently marketed in the United States belong to the group of mixed receptor antagonists.[42] Risperidone is an improvement from the chemical structure of haloperidol; olanzapine and quetiapine are derived from that of clozapine. Among the mixed receptor antagonists, clozapine, olanzapine, and quetiapine can be logically categorized as multireceptor clozapine analog antagonists, and risperidone, sertindole, and ziprasidone can be grouped together as serotonin/dopamine antagonists (written personal communication with John G. Csernansky, M.D., January 27, 1999). The chemical structures of typical antipsychotic drugs in the former class have a three-ring nucleus, but those in the latter class do not.

As a group, all of these marketed atypical antipsychotic drugs have been demonstrated in double-blind clinical trials to have reduced or minimal EPS at clinically effective doses and some efficacy in treating the negative symptoms of schizophrenia.[33,36-39] However, only clozapine has been demonstrated to provide efficacy in treatment-refractory schizophrenic patients.[33] In addition, none of these drugs except risperidone[43] show elevated serum prolactin levels after chronic administration. Table 1, which is expanded from a recent practice guideline for the treatment of patients with schizophrenia of the American Psychiatric Association, summarizes clinical characteristics of atypical antipsychotic drugs.[44]

Detailed receptor-binding profiles of atypical antipsychotic drugs have been generated in an attempt to understand their differences in pharmacodynamics and clinical activity. The attempt to explain how atypical antipsychotic drugs work and how they differ among themselves has caught the imagination of many basic scientists and clinicians. The comparison of the ratio of plasma K_i (pK_i) values for serotonin 2A ($5\text{-}HT_{2A}$) and dopamine 2 (D_2) binding activity has been most strongly proposed as providing the potential pharmacological basis of the unique clinical effects of atypical antipsychotic drugs,[45] but relationships between D_2 and D_3, D_4, and α_2 have also been proposed.[46,47]

Table 1. Brief Summary of Clinical Characteristics of Atypical Antipsychotic Available in the United States (haloperidol included for reference)

Antipsychotic	Year of US Introduction	Clinical Equivalent Oral Dose (mg/d)	Degree of EPS	Proven Enhanced Efficacy	Elevated Prolactin After Chronic Use	Effectiveness for Negative Symptoms
Clozapine	1990	50	0?	Yes	No	Yes
Risperidone	1994	1-2	+	No	Yes	Yes
Olanzapine	1996	2-3?	0-+?	No	No	Yes
Quetiapine	1997	50-100	0-+?	No	No	Yes
Sertindole*	—	2-3?	0-+?	No	No	Yes
Ziprasidone†	—	?	?	No	?	Yes
Haloperidol	1958	2	+++	No	Yes	No

Data are from Kane et al.,[33] Marder and Meibach,[36] Beasley et al.,[37] VanKammen et al.,[38] Arvantis et al.,[39] Prakash et al.,[41] and the American Psychiatric Association.[44]

*Licensing for the US market not currently pursued.

†Under application for release to the US market.

Researchers are still trying to interpret the information for the receptor profiles of atypical antipsychotic drugs.[48,49] However, pK_i values involving variable neurotransmission of the drugs are still useful to predict side effects, as shown elsewhere.[50]

DRUGS IN THE PIPELINE OR NOT AVAILABLE IN THE UNITED STATES

Pharmaceutical companies have numerous candidate antipsychotic compounds in various stages of the pharmaceutical pipeline.[42] Besides the previously described six atypical antipsychotic drugs, the mixed receptor antagonists also include zotepine, savoxepine, and amperozide. Zotepine is available in Europe[51,52] and Asia,[53] but not in the United States. It has three-ring structure[51,53] and should belong to the class of multireceptor clozapine analog atypical antipsychotic drugs. Amperozide is under development in Europe.[54]

Apart from the mixed receptor antagonist strategy, other mechanisms are also used in the current or recent development of antipsychotic drugs: (1) specific D_1/D_2 antagonists: amisulpride (D_2), raclopride (D_2), NNC 01-0687 (D_1), and NNC 01-0756; (2) partial D_2 agonists: SDZ HDC 912, MAR 327, pramipexode (SND 929), roxindole, talipexole (BHT 920), and terguride; (3) 5-HT antagonists: ondansetron (5-HT_3), zacopride (5-HT_3), and ritaserin (5-HT_2); and (4) miscellaneous mechanisms: bretazenil, milacemide, and peptides.[42] Some of these have been marketed for other indications. For example, the 5-HT_3 antagonist odansetron is used as an antiemetic drug.

Based on the concept that *N*-methyl-*D*-aspartate (NMDA) receptor hypofunction is the neuropharmacologic basis for schizophrenia,[55] D-serine is used as an add-on to an antipsychotic drug and is found to be effective in improving the negative symptoms of schizophrenia.[56] However, the development of D-serine as an add-on rather than a first-line antipsychotic drug is yet to be seen.

DISCUSSION

Table 2 summarizes the chronology of antipsychotic drug development and contains some events[57] that are not mentioned in the text of this article. Antipsychotic drug development has come a long way, from the serendipitous discoveries of chemicals by trial and error. Chlorpromazine came to the attention of psychiatry through a convoluted history.[58] It had taken almost 60 years to develop chlorpromazine since Ehrlich's clinical observation of methylene blue in 1891 from an antimalarial, to an antihistamine, to an anesthetic, and eventually to an antipsychotic medication. Because Ehrlich had a working relationship with Hoechst Pharmaceuticals,[59] he could afford to use a systematic "brute-force" approach to make things happen.[59,60] For example, there is the story of the famous discovery of arsphenamine (or salvarsan, the 606th compound) in a series of chemicals that Ehrlich and his Japanese collaborator Hata studied as possible treatments for syphilis.[59] Without the support of the pharmaceutical company, Ehrlich could not afford to have his relentless pursuit and to fail his screenings 605 times. Based on this historical review, all activities of antipsychotic drug development have been closely financed by pharmaceutical

Table 2. Chronology of Antipsychotic Drug Development

Year	Development
1956	Perkin synthesized mauve[1]
1896	Caro synthesized methylene blue, a phenothiazine derivative[1]
1878	Berthsen synthesized phenothiazine[1]
1891	Paul Ehrlich observed that methylene blue helped patients with malaria[1]
1944	Gilman et al. found a lack of antimalarial effect for phenothiazines[2]
1950	Laborit and Huguenard used promethazine in anesthesia[3,4]
1951	Laborit and Huguenard produced artificial hibernation with chlorpromazine[4]
1952	Hamon et al. and Delay et al. showed chlorpromazine's antipsychotic effect[5,6,9]
1953	Stähelin and Kielholz confirmed chlorpromazine's antipsychotic efficacy in Germany[12]
1954	Chlorpromazine marketed in the US by Smith, Kline and French Laboratories as an antivomiting agent[15]
	Lehmann and Hanrahan confirmed chlorpromazine's antipsychotic efficacy in Montreal[13,14]
	Winkelman confirmed chlorpromazine's antipsychotic efficacy in the US[15]
	Steck described EPS induced by chlorpromazine and reserpine[20]
1958	Haloperidol introduced to the market[22]
1959	Sigwald et al. described tardive dyskinesia[27]
1960	Veterans Administration Collaborative Study reported its double-blind results for antipsychotic agents[17,18]
1961	Ayd reported EPS incidence of ~38.9%[23]
1962	Carlsson and Lindquist demonstrated dopaminergic-blocking effect of antipsychotic drugs[57]
1975	Molindone introduced to the US market[11]
1990	Clozapine approved by the FDA[11,33]
1994	Risperidone approved by the FDA[11,36]
1996	Olanzapine approved by the FDA[37]
1997	Quetiapine approved by the FDA[39]

houses. Even today, the resources for antipsychotic drug development still originate from private industrial support rather than from public research organizations such as the National Institute of Mental Health.

It is unthinkable that chlorpromazine and other related compounds were released by the regulatory agents to the market before demonstrating efficacy with the clinical data from double-blind and placebo-controlled studies in 1960.[16-18] The thalidomine tragedy led to the passage of the Kefauver-Harris amendments to the Pure Food and Drug Act in 1962.[60] This legislation required that new drugs be shown to be efficacious and safe.[60] Since then, all marketed antipsychotic drugs have been subjected to this FDA standard for licensing.

From 1975 to 1990, there was a hiatus in antipsychotic drug development, during which no activities for developing new antipsychotic agents were seen. Based on the data of controlled comparative studies,[17,18] all typical antipsychotic drugs are equal in efficacy but their side effects are different. Thus, during that period, the manufacturers stressed the side effects of competitors' drugs to promote their own drugs.[61] For example, the manufacturers of low-potency antipsychotic drugs stressed the EPS side effects to promote their drugs, whereas the makers of high-potency antipsychotic drugs emphasized the cardiovascular side effects of low-potency antipsychotics. The lack of activity in antipsychotic drug development in those 15 years might be due to the dogmatic restraints of the dopamine hypothesis of schizophrenia[57] and Haase's concept of "no antipsychotic efficacy if no EPS."[24] When clozapine was developed, its manufacturer was hesitant to introduce it to the market, not due to the issue of its efficacy but to its absence of the EPS side effect.[26]

At present, the new antipsychotic drugs are synthesized with more precise receptor targeting according to the guidelines of psychopharmacologic principles, although the exact neurobiology and etiology of schizophrenia are still unknown. There is not a systematic guideline for antipsychotic drug development because the exact psychopathology of schizophrenia is still unknown. Only after sufficient clinical experience will clinicians be able to determine whether an individual atypical antipsychotic drug represents, as promised, a unique compound or just another "me-too" drug, as in the case of typical antipsychotic drugs, tricyclic antidepressants, or serotonin-specific reuptake inhibitors.

The newly released atypical antipsychotic drugs have yet to prove that they are as efficacious as clozapine, which is still considered the "gold standard."[26] For these reasons, research to alleviate clozapine-induced side effects[62] may be more cost-effective than developing brand-new atypical antipsychotic drugs. More studies on the treatment and prevention of clozapine-induced agranulocytosis[32] might be a better and cheaper answer than the development of a brand-new substitute drug, especially since granulocyte colony-stimulating factors have been used effectively to reverse this hematologic side effect.[63]

Noncompliance is an issue in the treatment of schizophrenia, and the formulation of depot preparations of atypical antipsychotic drugs is an urgent need if treatments with these new agents for schizophrenic patients are used more extensively.[21] Hopefully, a long-acting form of an atypical antipsychotic drug will be available soon.[21]

The experiences of atypical antipsychotic drug development have moved drug design from a pure dopamine antagonist strategy to other neurotransmission strategies with serotonin, glutamate (including NMDA), cholinergic, or even neuropeptide receptor-targeting. The involvement of other neurotransmitters in the activity of atypical antipsychotic drugs may make EPS less possible and an improvement of negative symptoms more possible. Recent activities in antipsychotic drug development not only have changed the pharmacologic concept of schizophrenia but also have fueled the enthusiasm in schizophrenia research, which in the past decade, after a 15-year hiatus, has been unprecedentedly active.

CONCLUSION

The history of antipsychotic drug development started with the serendipitous discovery of chlorpromazine in 1952. Most of the typical antipsychotic drugs were introduced between 1954 and 1975. The introduction of clozapine to the US market in 1990 heralded the new era of pharmacotherapy for schizophrenia with atypical antipsychotic drugs. As of February 1999, four atypical antipsychotic drugs (clozapine, risperidone, olanzapine, and quetiapine) are available in the United States. They are at least as effective as typical antipsychotic drugs in treating the positive symptoms of schizophrenia while causing fewer EPS side effects. They also show superiority over typi-

cal antipsychotic drugs in improving the negative symptoms of schizophrenia.

The advent of atypical antipsychotic drugs has brought unprecedented excitement to the research of schizophrenia. Hopefully, the pharmacological basis for atypicality will be identified and used as a basis to identify antipsychotic drugs with minimal side effects and a broader spectrum of efficacy.

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