The History of the Psychopharmacology of Schizophrenia

Heinz E Lehmann, MD[1], Thomas A Ban, MD[2]

Objective: *To review the historical development of the psychopharmacological treatment of schizophrenia.*

Method: *A chronological literature review of the clinical practices and theoretical models that have controlled drug treatment of schizophrenia at different times.*

Results: *Effective treatment of schizophrenia was achieved only after the introduction of antipsychotic drugs, in the 1950s, and is still progressing.*

Conclusion: *Close collaboration between basic neuroscience and careful and informed clinical practice are likely to lead to continued progress.*

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Kraepelin, in 1899, described the nature of dementia praecox as almost certainly involving heredity and as a "tangible affection of the brain, probably damage or destruction of cortical cells . . . which was the result of chemical disturbances" (1). Eugen Bleuler, in 1915, wrote about the etiology of schizophrenia: "One must acknowledge that, at least the great majority of clinical pictures, which are now collected under the name of dementia praecox, rests on some toxic action or anatomical process, which arises independently of psychic influences . . . The principal group is, in my opinion, certainly caused by organic changes" (2).

Thus the 2 key figures in the early history of the dementia praecox/schizophrenia concept were convinced of the biopathological factors underlying its apparent psychopathology. This somatic perception of schizophrenia, which was certainly not shared by North American psychiatry in the 1930s and 1940s, was proved to be correct only with the introduction of clinically effective pharmacotherapy in the 1950s. It is not often mentioned that the clinical discovery of antipsychotic (neuroleptic) drugs served as important, albeit indirect, evidence of schizophrenia's physical substrate which, in turn, led to essential new insights into the neuroscientific dynamics of schizophrenia.

The Period of Trials and Errors

Beginning soon after the nosological determination of the diagnostic category dementia praecox/schizophrenia, there have been countless attempts at physical or pharmacological treatment of this disease. Since the physiopathology of schizophrenia was completely unknown, all therapeutic efforts were launched on an almost random trial-and-error basis. These trials ranged from the prescription of cocaine (3), manganese (4), or castor oil (5) to the injection of animal blood (6). In the 1940s, one of the authors (HEL) injected oil of turpentine into the abdominal wall of a woman with schizophrenia in order to produce a large abscess with accompanying fever and leucocytosis. The abscess had to be opened, under sterile conditions, in the operating room. The patient was more rational for 2 or 3 days, as long as the fever lasted. (It had long been clinical knowledge that psychotic patients often became more lucid during a high fever or during critical illnesses [7]. Injections of sulphur in oil [8] also caused pyrexia. They were quite painful, but in some cases produced brief partial remissions.)

Some Success with Sleep Therapy

The Swiss psychiatrist Kläsi was more successful with a prolonged sleep treatment that he induced through multiple injections of the barbiturate, Somnifene (9). Some of his schizophrenic patients improved for longer periods of time, but the treatment involved major risks since patients not

[1]Professor Emeritus, Department of Psychiatry, McGill University, Montreal, Quebec.
[2]Professor Emeritus, Department of Psychiatry, Vanderbilt University, Nashville, Tennessee.
Address for correspondence: Dr HE Lehmann, 1033 Pine Avenue West, Montreal, QC H3A 1A1

infrequently developed pneumonia, often a fatal complication at a time when antibiotics were not available.

The Theory of Deficient Oxidative Processes

In the 1930s, the prevailing hypothesis was that schizophrenia was based on "a generalized inherent tendency to . . . deficient oxidative processes" (10). Loevenhart and others had reported, in 1929, that surprising cerebral stimulation was occurring in catatonic patients who were exposed to CO_2 inhalation (11). Five years later, Hinsie and others organized a large, systematic study of the effects of oxygen and carbon dioxide on catatonic symptoms. Eighteen schizophrenic patients were living in a special dormitory for 10 weeks. The dormitory was carefully sealed to maintain a 50% oxygen atmosphere, and some of the patients were also treated with short inhalations of carbon dioxide. The investigator's conclusion was that "it can neither be affirmed nor denied that there was any relationship between treatment and the clinical condition" (12). Nevertheless, the public press reported on the "gas cure" of the insane, when the treatment was given in combination with fever and psychotherapy (13).

There were quite robust findings about several different agents that would interrupt a catatonic stupor for short periods of time. In addition to the inhalation of carbon dioxide, injections of apomorphine (14) or the barbiturate sodium amytal (15) interrupted catatonic stupors in schizophrenic patients so regularly that one author coined the term "decatonisation" for the procedure (16).

Comas and Convulsions

The first physical treatments of schizophrenia giving more reliable therapeutic results and frequently leading to full remissions were hypoglycemic treatment, aimed at repeated, reversible comas induced by insulin (17), and convulsive treatment, carried out first with intramuscular injections of camphor and, later, with intravenous injections of metrazol (18). In some way, these may also be considered pharmacological treatments.

Sakel, who developed insulin coma therapy, got the idea for this treatment when he treated heroin addicts in Berlin with small doses of insulin during their withdrawal periods. Once, one of the addicts, who also suffered from schizophrenia, accidentally went into hypoglycemic coma and after its reversal showed a remarkable improvement of his psychotic symptoms. Since Sakel was not allowed to follow up on this unique observation in Berlin, he went to Vienna, where he was able to develop his treatment in a systematic way.

Von Meduna, who developed his pharmacoconvulsive treatment in Budapest, arrived at its concept based on an erroneous theory. His hypothesis, built on the unconfirmed notion that there existed a "biological antagonism" between epilepsy and schizophrenia, led him first to infuse epileptic patients with the blood of schizophrenic patients. When this procedure did not result in the hoped-for reduction of seizure frequency in the epileptic patients, von Meduna reversed his therapeutic experiment by inducing convulsions in schizophrenic patients. This resulted in quite dramatic, symptomatic improvement that in most cases, however, lasted only a few weeks. It was soon determined that the real indication for convulsive therapy was depression, and the pharmacological induction of seizures was eventually replaced by electroconvulsive therapy.

One of the authors of this article (HEL) administered all these treatments and remembers that the camphor injections induced seizures at unpredictable times, sometimes when the patient was walking in hazardous places such as stairways. Metrazol injections induced extreme anxiety, sometimes lasting for more than a minute, for which the patient did not have amnesia, so that cooperation with continued treatment often became a major problem. Hypoglycemic treatments were not without risk, since, not infrequently, the insulin coma became irreversible (19).

Until that time, all pharmacotherapeutic interventions in schizophrenia that had had any reproducible, significant effects were those which had resulted in major, often critical, alterations of psychophysiological functioning, that is, fever, sleep, coma, and convulsions. The trend toward such treatments might well have been due to the fact that the first major therapeutic breakthrough in psychiatry had been Wagner-Jauregg's hyperpyrexic malaria treatment of general paresis (20).

Antipsychotic Psychopharmacology

Specific psychopharmacological treatment of schizophrenia that was targeted at the elimination of psychotic symptoms, rather than at the alteration of body states, started only in the second half of the 20th century with the seminal paper on chlorpromazine by the French psychiatrists Delay, Deniker, and Harl in 1952 (21).

This first antipsychotic drug had come to psychiatry in a somewhat convoluted way. The surgeon, Laborit, was experimenting with a form of anesthesia that he called hibernation, which consisted of the administration of a "lytic cocktail," that is, a mixture of narcotic, sedating, and hypnotic drugs (22). In that context, he had asked a pharmaceutical company (Rhone-Poulenc) to manufacture for him an antihistaminic drug with diminished antihistaminic but enhanced sedative effects. Chlorpromazine was the result. Laborit observed that this agent produced strange, pharmacodynamic effects which could be likened to a "chemical lobotomy." He recommended this drug to his psychiatric colleagues, which led to a new era of psychiatric therapy: psychopharmacology.

Chlorpromazine and the Phenothiazines

Chlorpromazine, the first antipsychotic drug, was a phenothiazine. The term neuroleptic is often used instead of antipsychotic. Other terms, like ataractics or major tranquillizers, are no longer employed. With the introduction of the first antipsychotic drugs, there appeared, in the form of side effects, the first secondary extrapyramidal symptoms.

Chlorpromazine was synthesized on December 11, 1950, by Charpentier and his collaborators, released for clinical studies on May 2, 1951, after completion of the initial pharmacological investigations by Courvoisier and her team, and given for the first time to a psychiatric patient on January 19, 1952, by Hamon, Paraire, and Velluz at Val de Grace, the famed military hospital in Paris.

After the unique therapeutic effects of chlorpromazine in psychotic patients were first reported by Delay, Deniker, and Harl, their observations were promptly confirmed by Staehelin and Kielholz in Europe (23) and Lehmann and Hanrahan in North America (24). It was only in the early 1960s, however, that the therapeutic effect of chlorpromazine was established beyond reasonable doubt by the US Veterans Administration Collaborative Study Group (25,26), and it was only by the end of the 1960s that it was determined that chlorpromazine must be given in adequate dosage, that is, at least 500 mg a day, in order to attain therapeutic effects (27).

With the employment of animal behavioural indicators for antipsychotic effects, such as induction of cataleptic immobility, reduction of spontaneous motility, inhibition of intracranial self-stimulation, and interference with classical conditioning and operant behaviour, pharmacological screening for chlorpromazine-like drugs began without delay; within a period of less than 10 years, 20 antipsychotic phenothiazines with 3 distinct side chain structures were in development. About twice as many antipsychotics were listed in the seventh edition of the *Index Psychopharmacorum* by 1990 (28). Of these, 12 were phenothiazines: chlorpromazine, methotrimeprazine, promazine, fluphenazine, perphenazine, prochlorperazine, thioproperazine, trifluoperazine, mesoridazine, pericyazine, pipotiazine, and thioridazine.

None of the phenothiazines is superior in overall therapeutic efficacy to chlorpromazine. They differ from each other only in so far as side effects and effective dosage are concerned. For instance, sedation is more of a problem with the aminoalkyls, like chlorpromazine; extrapyramidal signs with the piperazinylalkyls, like prochlorperazine; and anticholinergic effects with the piperidylalkyls, like thioridazine. Original expectations, regarding the differential therapeutic profile of antipsychotics with different side chains, were not borne out by clinical psychopharmacological experiments.

An initially commonly held belief, that the low-dose drugs which readily induced extrapyramidal signs (referred to as "incisive neuroleptics" in France) were more clinically effective, could not be verified (29). The same applies to the contention that only the "productive" or "positive" symptoms (type I syndrome) of schizophrenia respond to treatment. As early as 1965, Goldberg, Klerman, and Cole (30) recognized that productive symptoms of schizophrenia, such as delusions, hallucinations, memory deficit, and feelings of irritability, as well as slow speech and movement, lack of self-care, and indifference to the environment, all respond to pharmacological treatment.

Antipsychotic Action Mechanisms

Psychopharmacological research focused on the identification of the treatment-responsive population, and neuropharmacological research was investigating the action mechanism of phenothiazines. Since therapeutically effective phenothiazines act on a great variety of molecular structures, it appeared to be an insurmountable task to decipher which of these were relevant to their therapeutic effect. Because of biochemical speculations during the 1950s and 1960s regarding the nature of schizophrenia, the possibility was raised that the essential step in the action mechanism of phenothiazines was stabilization of the cell membrane, with a consequent interference with the pathophysiological action of alpha-2 globulin, the plasma protein factor then thought to be responsible for schizophrenia psychopathology (31). An alternative possibility was entertained that inhibition of the *N*-methyltransferase enzyme system, with a consequent decrease in the formation of epinephrine, the precursor of the psychotoxic adrenochrome, was responsible for the therapeutic effects (32). A third alternative considered the decrease of adenosine-triphosphate utilization, with a consequent involvement in the production of psychotoxic, dimethylated indoleamines and catecholamines (33).

While there were only isolated biochemical findings relevant to the action mechanism of phenothiazines in the late 1950s (for example, inhibition of the cytochrome oxidase enzyme system, uncoupling of oxidative phosphorylation, and changes in phospholipid metabolism), there was by that time an increasing body of evidence generated by neurophysiological research that the sedative effect of chlorpromazine was due to a suppression of afferent influences to the cerebral reticular formation, possibly by an action related to the afferent collaterals feeding this system (34).

Reserpine and the Rauwolfia Alkaloids

Soon after the introduction of chlorpromazine, another drug, reserpine, a derivative of the rauwolfia plant, was introduced in 1954 as an antipsychotic. The root of the plant had been used for hundreds of years as a remedy for mental illness. It was only in 1952, however, that Mueller, Schlittler,

and Bein, working with 18-hydroxyohimbin, isolated reserpine, which accounts for approximately 50% of the active—both psychotropic and antihypertensive—effects of the rauwolfia root (35). Subsequently, in less than 2 years, Steck recognized that the therapeutic effect of reserpine in psychoses, similar to that of the therapeutic effect of chlorpromazine, is associated with extrapyramidal signs (36).

The first paper on the use of *Rauwolfia Serpentina Benth* in neuropsychiatric conditions was published in 1954 by Nathan Kline (37). His interest in the rauwolfia root was triggered by the New York Times report (in March 1953) on Hakim, an Indian physician's paper on indigenous drugs in the treatment of mental illness. Kline's publication was followed, within a period of 6 months, by the reports of Delay, Deniker, Tardieu, and Lemperiere in France (38), who used reserpine, the active principle itself; Weber in Switzerland (39); and Noce, Williams, and Rapaport in the United States (40).

After a short-lived popularity from 1954 to 1957, the use of reserpine and other rauwolfia alkaloids rapidly declined. Nevertheless, well over 30 years later, Christison, Kirch, and Wyatt (41), on the basis of findings in 8 double-blind, placebo-controlled clinical studies, still suggest the use of reserpine as one of the alternative treatments in therapy-refractory schizophrenia patients.

While the place of reserpine among the different drugs used in the treatment of schizophrenia remains poorly defined to date, the different actions of reserpine, from the alleged decrease of "psychic energy" (42) to the measurable depletion of serotonin in the brain, have been described extensively. Brodie's postulation that the psychotropic effect of reserpine is intimately linked to the changes in the concentration of the neurotransmitter serotonin (43) provided the first building block for a bridge between neuropharmacology and psychopharmacology.

Haloperidol and the Butyrophenones

The building of this bridge progressed with the introduction of haloperidol in the late 1950s and with research on this drug's mechanism of action.

Haloperidol, the parent substance of the butyrophenone antipsychotics, was synthesized on February 15, 1958. It was the byproduct of research with meperidine (pethidine [Demerol]) aiming to find a more potent analgesic. Because the behavioural pharmacological profile of haloperidol was similar to that of chlorpromazine, clinical psychopharmacological research with the new drug proceeded rapidly. By the end of 1958, it had been shown that parenteral haloperidol, in single doses of 1 to 5 mg, could control motor agitation (44) regardless of its etiology. At the time of the first International Congress on haloperidol, on September 5, 1959, a target profile for the drug's effect was proposed: delusional psychoses, mania, and acute and chronic paranoid psychoses, but not hebephrenic schizophrenia. It was also recognized that the "pharmacologic action" of orally administered haloperidol was observed at doses from 2 to 5 mg a day. Signs of "extrapyramidal dysregulation" (handwriting tests) were a criterion that the dose was in the therapeutic range. Induction of motor disturbances was not considered a prerequisite for symptom relief.

The search for other psychotropic drugs proceeded through a test model that used the behavioural antagonism between haloperidol and amphetamine, as well as another dopamine agonist, apomorphine. The idea for this test model did not generate from sophisticated conceptualization, but was "suddenly inspired" by observations on the bicycle racetrack, where Janssen was struck by the fact that the champion, drugged with amphetamine, often kept racing after he had crossed the finish line and had to be stopped by force. This racetrack-inspired test model was successfully used several years before the dopamine hypothesis was scientifically formulated (45).

By 1990, 13 butyrophenones had been developed, of which 2, haloperidol and droperidol, are now available for clinical use in Canada (28).

No Single Antipsychotic Action Mechanism?

For some time during the 1960s, there seemed to be no single physiological or biochemical hypothesis that applied to schizophrenia. There appeared to be numerous schizophrenias: one that responded best to phenothiazines, that is, drugs which reduce arousal reactions, block adrenergic, intrareticular mechanisms, and decrease the cortical release of acetylcholine; another which responded best to butyrophenones that selectively decrease the responsivity of the caudal portion of the reticular formation, produce dopamine receptor blockade, and possibly occupy γ-aminobutyric acid receptors, thus making them inaccessible to glutamic acid (46).

It was thought that there might also be other schizophrenias associated with an abnormality of methylation processes with the production of psychotoxic metabolites in which a beneficial effect might result from the methyl acceptors niacin and niacinamide (32). Still other schizophrenias, for example, periodic catatonia (related to a positive nitrogen balance), might be successfully treated by administration of thyroxin (47).

The Dopamine Hypothesis

Eventually, formulation of the dopamine hypothesis was based in part on neuropharmacological research focused both on the study of the action mechanism of antipsychotic drugs and on the possible involvement of "dopamine structures" in the psychopathology of schizophrenia. Important steps in this development were observations that substances which can

increase or decrease brain serotonin levels, such as 5-hydroxy-parachlorophenylalanine and tryptophan, as well as drugs which can decrease brain norepinephrine levels, such as alpha-methylparatyrosine, had virtually no effect on schizophrenia symptoms. The administration of disulfiram, a dopamine-beta-hydroxylase inhibitor that can increase brain dopamine, however, had aggravating effects on schizophrenic symptoms.

On the basis of this and further neuropharmacological research with haloperidol and chlorpromazine, Carlsson and Lindquist, in 1963, founded their seminal hypothesis that the blockade of dopamine receptors was responsible for the clinical effects of antipsychotic drugs (48). Only 12 years later, however, Creese and collaborators demonstrated with X-ray crystallography that blockade of dopamine receptors actually takes place (49).

Based on the dopamine hypothesis, 4 different theories were proposed to explain the action mechanism of the "typical" (classic) antipsychotics: 1) blockade of the postsynaptic dopamine D_1 receptor (50); 2) blockade of the postsynaptic D_2 receptor (51); 3) interactive effects between D_1 and D_2 receptors (52); and 4) slowly developing decrease in presynaptic dopamine activity (53).

Typical Antipsychotics

Simultaneously with ongoing research on the action mechanism of such prototype antipsychotics as chlorpromazine, reserpine, and haloperidol, at least 6 other classes of antipsychotic drugs with therapeutic effect in schizophrenia were advanced. Of them, the thioxanthenes (chlorprothixene, clopenthixol, flupenthixol, thiothixene, and zuclopenthixol) and the azaphenothiazines, also referred to as benzothiazines (prothipendyl, isothipendyl, and oxypendyl) are structurally related to the phenothiazines; the benzoquinolizines (tetrabenazine and benzquinamide) are pharmacologically related to the rauwolfia alkaloids; and the diphenylbutylpiperidines (fluspiriline, penfluridol, and pimozide) are structurally and pharmacologically related to the butyrophenones. The dibenzoxepine (loxapine) and indole (oxypertine and molindone) derivatives are unrelated to any of the prototype antipsychotic drugs (54).

Availability of—as well as preference for—these numerous preparations shows considerable variation between and even within countries at different periods of time. In Canada, for example, 3 of the thioxantheses, namely, flupenthixol, thiothixene, and zuclopenthixol, 2 of the diphenylbutylpiperidines, that is, fluspiriline and pimozide, and the dibenzoxazepine, loxapine, are available at present for clinical use in the treatment of schizophrenia. Several others, as for example, the thioxanthene derivative chlorprothixene and the indole derivative molindone had been available in the 1960s and 1970s, respectively.

In spite of the differences in their structure, all these compounds produce a demonstrable, drug-induced blockade of dopamine (D_2) receptors in the mesolimbic (A10) pathways (55), with a subsequent decrease in the firing rate of ventral, tegmental dopamine neurons (56). In favour of the contention that this particular chain of events is causally related to, and not just associated with, their antipsychotic effect (57) are findings which indicate that the average doses of the different antipsychotics used in treatment are positively correlated with the affinity of the different drugs for the D_2 receptor (57,58). Chronic administration of these therapeutically effective antipsychotics produces a nearly complete inhibition of the firing of dopamine neurons, which project from the ventral tegmentum to the limbic forebrain (59).

Another common characteristic, shared by all "typical antipsychotics," is a marked blockade of D_2 receptors in the nigrostriatal pathways (59) involved in the refinement of movements and motor control. It is the removal of this modulation that is responsible for the acute extrapyramidal signs, in the form of akathisia, dystonia, and Parkinsonism, encountered by 50% to 90%, and the chronic extrapyramidal signs, in the form of tardive dyskinesia, encountered in 15% to 20% of the patients in the course of treatment (60). The problem is compounded by the therapeutic limitations (61) of these drugs: 30% to 50% of chronic schizophrenia patients remain unresponsive or are only partially responsive (62); negative symptoms poorly respond (63) to this treatment and so do neurocognitive deficits (64).

Pragmatic Considerations in Treatment

Before deciding to shift to an alternative treatment modality of schizophrenia, one must exclude the possibility that what appears to be refractoriness to treatment is the result of faulty diagnosis, wrong dose, noncompliance, and/or the selection of wrong medication.

Correcting Faulty Diagnosis

In spite of the emphasis on the importance of correct diagnosis, faulty (wrong) diagnoses are still common. Smith and his associates (65) found a faulty referral diagnosis at admission in 23 (46%) of 50 patients with treatment-refractory psychoses. In the same study, in the 12 of the 32 patients with the referral diagnosis of schizophrenia whose diagnosis was corrected from schizophrenia to mood disorder, the apparent refractoriness to treatment was resolved.

Dose Adjustment

Treatment with the wrong dose is frequently responsible for what appears to be refractoriness to antipsychotic treatment. It can often be resolved by proper adjustment of the dose. The problem of wrong dose may be compounded by the common practice of increasing the dose in cases of insufficient therapeutic response, in the hope that the increase

will improve the response to treatment. This outcome, however, does not necessarily result. A review of 6 double-blind clinical trials by Collins, Hogan, and Awad (66) revealed that in only one clinical trial was treatment with a higher dose superior to treatment with the standard dose. In 4 of the clinical trials, there was no difference in therapeutic effectiveness between the groups treated with high and with standard doses, and in one clinical trial, the group treated with a standard (low) dose actually fared better than the group treated with a high dose.

On the basis of pharmacokinetic findings, Van Putten and others (67) maintain that, apart from demonstrably low plasma levels—as a result of poor absorption and/or rapid drug metabolism—there is no known indication for an increase above the recommended dose of antipsychotics.

In keeping with this conclusion are the results of a recent study that showed that doses as low as 2 to 4 mg of haloperidol attained the dopamine D_2 PET occupancy associated with therapeutic response (68).

Replacement of Oral with Depot Preparations

Noncompliance is frequently the cause of apparent refractoriness to treatment. It is encountered in as high as 60% of schizophrenia outpatients within 6 weeks of starting treatment with an oral antipsychotic (69). Considering that approximately two-thirds (67%) of patients with schizophrenia relapse within a year if their antipsychotic medication is withheld (70), noncompliance is one of the most common findings in patients who responded to treatment initially but whose responsiveness to the antipsychotic seemed to wear off after a certain period of time (71).

The primary approach to overcoming noncompliance is the replacement of the oral with a long-acting, depot preparation. It is an effective measure in preventing relapse that results from noncompliance. The survival rate of discharged patients in the community within a period of 24 months is significantly longer (72), and the occurrence of relapse within a period of 30 months significantly lower in patients treated with a depot than with an oral antipsychotic.

There are 8 antipsychotics with 11 depot preparations listed in the seventh edition of the *Index Psychopharmacorum*, published in 1990. Of these 11 preparations, 6 are available in Canada for clinical use: the piperidylalkyl pipothiazine palmitate, the piperazinylalkyls fluphenazine decanoate and enanthate, the butyrophenone haloperidol decanoate, and the thioxanthenes flupenthixol decanoate and flupenthixol enanthate.

Substitution of One Antipsychotic with Another

Selection of the wrong medication for an individual patient is not infrequently the cause for apparent refractoriness to antipsychotics. This fact is remarkably understudied considering the problems it has created for all those treating schizophrenia patients. The problem is usually resolved by substituting the antipsychotic first prescribed by another antipsychotic drug. With consideration of the widely held belief in the 1960s that "sedative" antipsychotics like chlorpromazine differ from "incisive" antipsychotics like trifluoperazine, Lambert, as early as 1963, suggested the substitution of a "sedative" with an "incisive" antipsychotic or an "incisive" with a "sedative" antipsychotic in response to refractoriness to one or the other (73). This consideration of the type of antipsychotic in the substitution turned out to be unnecessary, however, because, as recognized in the early 1970s, the difference between the 2 types of antipsychotics is restricted to side effects (74). Nevertheless, the fact remains that a certain proportion of patients refractory to treatment with one antipsychotic will respond to another.

Clozapine and Its Impact

Between the time that clozapine, the dibenzodiazepine derivative which was to become the prototype of "atypical antipsychotics," fell into disgrace in the mid-1970s and was resurrected in the mid-1980s, the clinical problems of typical antipsychotics, especially of tardive dyskinesia, began to cast threatening shadows over the pharmacological treatment of schizophrenia. Whether this could have been prevented if clozapine's development had not been interrupted is impossible to know.

The first paper on clozapine appeared in the *Medical Journal of Vienna* in 1966 (75). At about the same time as this publication, findings from a multicentre collaborative study conducted by a distinguished team of German psychiatrists—which included Bente, Engelmeier, Heinrich, Hippius, and Schmitt—were presented in Washington at the 5th Congress of the Collegium Internationale Neuropsychopharmacologicum (CINP) (76). In spite of promising findings by the Austrian and German investigators, however, the launching of clozapine for clinical use was delayed, even in Europe, until 1972, according to Ackenheil and Hippius (77), because the findings challenged the commonly held belief of a close relationship between antipsychotic effects and extrapyramidal disturbance.

Clozapine was not introduced at all during the first round in North America, probably because of its hypotensive effect, which, as later reports indicate, may occur in as much as 35% (78) or, even with conservative estimates, in 6% to 13% (79) of patients treated with the drug. Another possible hindrance was the risk for seizures with clozapine, a cumulative risk of 10% after 3.8 years of treatment, as shown recently (80).

Acceptance of clozapine suffered a serious setback by the report of Idanpaan-Heikkila and his associates on 18 (including 8 fatal) cases of agranulocytosis in Finland, published in the September 27, 1975, issue of *The Lancet* (81). It led to an

almost total withdrawal of clozapine for about a decade, which ended in a triumphant comeback with its introduction for specially selected cases in the United States. Recognition that, with proper precautions, fatalities from agranulocytosis—a total of 79 between 1972 and 1994 (82)—can be prevented shifted the balance in favour of clozapine. By the end of the 1980s, it was the general consensus that 1) the potential avoidance of extrapyramidal side effects with clozapine (33%) compared with typical antipsychotics (61%) (83), 2) the reduced propensity of tardive dyskinesia (84,85), and 3) the effectiveness of therapy in otherwise treatment-resistant schizophrenia (86,87) were important advantages. After all, this was the first antipsychotic that had been shown to be more effective clinically than the others. In addition, its therapeutic action in negative symptoms as well as in positive symptoms of schizophrenia (88,89), in the "deficit syndrome" (90), and in the cognitive dysfunction of schizophrenia (91) gave, for the first time in almost 3 decades, a new outlook to the pharmacotherapy of schizophrenia.

Atypical Antipsychotics

Originally, the term "atypical antipsychotic" was used exclusively in reference to clozapine with the purpose of focusing attention on the fact that it is not just one of the many "me too" drugs developed for the treatment of schizophrenia but a drug of its own class, which is just as effective in treatment as any of the others, but has a considerably lower propensity to induce acute and chronic extrapyramidal signs.

Since the late 1960s, that is, the time of completion of the first clinical studies, there has been a considerable interest in clozapine, with some accepting it, while others questioned whether it should be referred to as an "atypical antipsychotic"; with some impressed by the low incidence of extrapyramidal signs, and others concerned about the pronounced hypotensive effects. It was only after the introduction, in the later 1970s, of radioactive isotope receptor-binding techniques that the term "atypical antipsychotic" received a real meaning and grew into a heuristic concept. With the newly gained capability to characterize and classify antipsychotics on the basis of their receptor affinities, it became possible to channel the interest in clozapine into systematic research. During the 1980s, research focused on design and development of antipsychotics with particular profiles in terms of receptor affinities that are therapeutically effective in the treatment of schizophrenia, but, like clozapine, have a lower propensity for extrapyramidal side effects. To achieve this objective, initially 2 alternative strategies were pursued. First, "atypical antipsychotics" with higher affinity to mesolimbic than to nigrostriatal D_2 receptors were separated from "typical antipsychotics" with higher affinity to nigrostriatal than to mesolimbic D_2 receptors (92). Subsequently, the separation of "atypical antipsychotics," with affinities to both the D_2 and the serotonin-S_2 receptors, from "typical antipsychotics," with affinity to the D_2 receptor only, was proposed (93).

With the identification and cloning of D_3 and D_4 receptors by Sokoloff and his associates in 1990 (94), and Van Tol and his associates in 1991 (95), respectively, development of atypical antipsychotics entered a new phase. Since both of the newly identified receptors were found to be concentrated in the limbic system of the brain, involved in cognition and emotions, and since both receptors were implicated in the action mechanism of clozapine, D_3 and D_4 receptors provided new targets for the development of atypical antipsychotics. Furthermore, the finding of Seeman and his associates in 1993 (96) that the density of D_4 receptors in the autopsied brains of schizophrenic patients is 6 times that of normal subjects led to the dopamine-D_4 hypothesis of schizophrenia, the first major alternative to the dopamine-D_2 hypothesis.

Triggered by the shifting targets for developing new drugs for schizophrenia, a rapidly growing number of atypical antipsychotics were rendered accessible for clinical investigation and/or introduced into clinical use, including selective $D_{2/3}$ receptor blockers (for example, benzamides such as amisulpride, emonapride, raclopride, remoxipride, and sulpiride) and selective serotonin-S_2 or S_3 receptor blockers such as ritanserin and olansetron (97). By the mid-1990s, they included $D_{1/2/3/4}$ and serotonin-$S_{a/2a/2c/3/6/7}$ antagonists alone and in different combinations. From the numerous atypical antipsychotics, the first to follow clozapine were remoxipride, risperidone, and olanzapine, while others, including ilperidol, seroquel, sertindole, and ziprasidone, are still in different stages of clinical development. Among the different atypical antipsychotics, clozapine has remained the one with the broadest activity within the dopamine family of receptors ($D_{1/2/3/4}$) combined with effects on serotonin-$S_{2a/2c}$ and alpha-$_{1/2}$ adrenergic receptors (98–102).

Seen from the clinical perspective, the term "atypical antipsychotic" is somewhat loosely defined as a drug that is therapeutically more effective in both positive and negative schizophrenia symptoms than the antipsychotics before clozapine and causes no, or very few, acute and chronic extrapyramidal side effects.

Alternative Treatments

Psychopharmacological Approach

The psychopharmacological is an empirical approach for the selection of alternative treatment for therapy-refractory patients. It is based on findings in clinical investigations, regardless of theoretical considerations.

In their comprehensive review of the literature in 1991, Christison, Kirch, and Wyatt found that a wide variety of treatments—from substances with an effect on the gabaminergic system (for example, baclofen) through

narcotic antagonists (for example, naloxone, naltrexone), endorphins (for example, betaendorphin), and vitamins (for example, nicotinic acid), to calcium channel blockers (for example, nimodipine, verapamil)—have been tried, but there are only 7 alternative pharmacological treatments to typical antipsychotics for which there is some evidence of effectiveness. The 7 treatment modalities are clozapine, lithium, benzodiazepines, reserpine, carbamazepine, propranolol, and L-dopa (41).

The evidence for the effectiveness of these 7 approaches is based on an analysis of 52 double-blind studies. In the case of reserpine and clozapine, the evidence is supportive of the use of these medications alone. For carbamazepine, however, there is evidence for its effectiveness only as an adjunctive medication, that is, for its use in combination with an antipsychotic. As in the case of carbamazepine, the evidence supports the use of lithium, benzodiazepines, and propranolol only as adjunctive medications in combination with an antipsychotic. By contrast, the evidence concerning L-dopa is supportive of its use either alone or in combination with an antipsychotic in schizophrenia with prevailingly negative symptoms.

In terms of clinical strategy, the same authors suggest that clinicians use clozapine first. Only if treatment with clozapine fails should one try lithium and benzodiazepines (in that order) as adjunctive medications. Reserpine, carbamazepine, and propranolol (in that order) are left as last resorts.

Neurophysiological Approach

The neurophysiological approach for the selection of alternative treatment is based on the detection of neurophysiological abnormality and on choosing treatment for the correction of the abnormality found. Most frequently, sleep electroencephalogram measures are used for the primary orientation because impairment in the different sleep continuity measures, such as slow-wave sleep and shortened rapid eye movement (REM) latency, in the absence of abnormality of sleep architecture (including REM time and density), are frequently encountered in treatment-refractory schizophrenia.

Considering that "impaired sleep continuity" might be explained by cholinergic hyperactivity, and in view of a frequently presumed dopaminergic hyperactivity in schizophrenia, Tandon and others speculate that increases of cholinergic and dopaminergic activity might play a role in the pathophysiology of schizophrenia. Since they found that the administration of anticholinergics, for example, biperiden or trihexyphenidyl, produced significant improvement in negative symptoms while worsening the pathology of positive symptoms, they suggested that the increase of cholinergic activity is intimately linked to the presence of negative symptoms, whereas the increase of dopaminergic activity is linked to the presence of positive symptoms of schizophrenia (103,104).

If these findings can be substantiated by further evidence, it would explain the favourable effects of drugs with central anticholinergic properties, such as methotrimeprazine, a phenothiazine antipsychotic (105), and clozapine, an atypical antipsychotic, on the negative symptoms of schizophrenia. The notion that a concomitant increase of cholinergic and dopaminergic activity is the underlying pathophysiology of schizophrenia, however, is not consistent with the findings that concomitant administration of anticholinergic drugs may reduce the effectiveness of antipsychotics (106).

New Perspectives

Seeman, in a 1993 study (107), showed that if the effects of clozapine and thioridazine on negative symptoms were attributable to their action on central acetylcholine receptors, then other antipsychotics, such as chlorpromazine, chlorprothixene, flupenthixol, mesoridazine, and trifluprom azine, should also have such effects. Similarly, if the clinical, therapeutic effects on negative symptoms of clozapine and thioridazine were due to their action on the serotonin-S_2 receptors, then again other antipsychotics, such as chlorpromazine, chlorprothixene, loxapine, mesoridazine, methotrimeprazine, perphenazine, risperidone, trifluprom azine, and zuclopenthixol, should have the same effects.

In the 1980s, radioactive binding techniques yielded observations that led to testable hypotheses relevant to the differential therapeutic effects of antipsychotic drugs. In the 1990s, advancing genetic technology opened a new perspective through the tailoring of antipsychotics in relation to receptor affinities (108).

Paul established a CNS Drug Discovery Program using the molecular genetic techniques as a screening device for compounds that interact with cell lines "transfected" with a cloned receptor. This "computational structural biology" may be used to find chemicals that fit specific receptors and thus produce specific neurotransmitter–receptor profiles (109).

Other current research in the field proceeds along more traditional lines by focusing on such pivotal D_2 receptor agonists (110,111) as, for example, preclamol and talipexole, which decrease dopaminergic transmission by reducing the firing of dopamine neurons and producing a weak blockade of postsynaptic receptors (112).

One strategy in the search for novel treatments of schizophrenia is the selection of a receptor system like that of clozapine (111). Another strategy seeks to develop drugs that counteract the psychosis induced by phencyclidine (PCP) or other antagonists of the *N*-methyl-D-aspartate (NMDA) system. A third strategy is aiming at the neuropeptide modulators of conventional neurotransmitters such as neurotensin,

somatostatin, neuropeptide Y, and the corticotrophin-releasing factor (CRF). Still another strategy is directed to the control of immediate, early genes, such as *c-fos*, which appear in the nucleus accumbens with the administration of antipsychotic drugs (113–115).

Returning to the ancestry of the first antipsychotic, chlorpromazine, that is, to the antihistamines, we note that some clinical research is studying the therapeutic effects on negative symptoms of schizophrenia that have been observed with the administration of a recent specific H_2 histamine antagonist: famotidine (116).

Finally, some research is proceeding on the treatment of schizophrenia with unsaturated fatty acids. The rationale for this treatment dates back to the 1970s, when Horrobin observed that schizophrenia patients are resistant to pain and inflammation and relatively free of rheumatoid arthritis. He postulated that schizophrenia is a prostaglandin deficiency disease and suggested a treatment with arachidonic acid, or polyunsaturated fatty acid, which is the precursor of prostaglandin (117). This hypothesis has been revived by recent observations that there is low phospholipase A_2 enzyme activity in schizophrenia patients. This enzyme is responsible for the cleavage of arachidonic acid from the cell membrane. About 80% of schizophrenia patients have a low arachidonic acid level. In addition, a considerable proportion of schizophrenia patients do not flush when receiving the vitamin niacin, which is a prostaglandin-dependent reaction (118). Recent observations of favourable therapeutic results occurring within 6 weeks in schizophrenia patients have been reported after the administration of 10 g of fish oil, which is high in unsaturated fatty acids (119,120).

Summary

Kraepelin and Bleuler, the earliest pioneers of the dementia praecox/schizophrenia concept, were convinced that this disease complex had a physical substrate. When, after more than half a century of useless, wide-ranging trials and errors, no proof for this conviction could be produced, however, academic orientation veered to the teaching that further search for any biological treatment of schizophrenia was no longer acceptable. Then, clinical serendipity uncovered the first antipsychotic drugs—the phenothiazines—in the 1950s. This revolutionary discovery jump-started neuroscientific research into the action mechanism of these new drugs and further led to the dopamine hypothesis for the etiology of schizophrenia. For several decades the search for new and better psychopharmacological agents was contained by this theory and made no therapeutic progress until another lucky clinical finding, clozapine, broke the dopamine receptor barrier and, with the help of rapid progress in molecular biology and brain imaging, resulted in new perspectives and methodologies that promise continued steady progress from purely empirical to rational procedures which will integrate basic research and clinical approaches.

Clinical Implications

- Clinicians are responsible for the first effective treatments of schizophrenia, both with unspecific and with symptom-targeted therapies.
- More recently, neuroscience has provided workable theories and methods to the clinicians in the field.
- Collaboration between basic neuroscience and clinical practice has been most successful in the development of rational drug treatment of schizophrenia during the last decade.

Limitations

- The historical method of data collection, which was employed in this review, does not lend itself readily to objective and statistical validation.
- Much of the current knowledge reviewed in this article is theoretical.
- Some of the theories reviewed are not yet based on empirical evidence and must still be considered to be speculative.

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Résumé

Objectif : *Passer en revue l'évolution du traitement psychopharmacologique de la schizophrénie.*

Méthode : *Examen chronologique de la documentation traitant des pratiques cliniques et des modèles théoriques qui ont déterminé le traitement pharmacologique de la schizophrénie à différentes époques.*

Résultats : *Le traitement efficace de la schizophrénie n'existe que depuis l'introduction des antipsychotiques, durant les années 1950, et les progrès dans ce domaine continuent.*

Conclusion : *Une étroite collaboration entre les neurosciences fondamentales et une pratique clinique attentive et informée devrait mener à d'autres progrès.*