A Historical Perspective of Clozapine

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Having challenged the established view that extrapyramidal symptoms are an intrinsic feature of antipsychotic activity, clozapine was developed as the first atypical antipsychotic with activity against both the positive and negative symptoms of schizophrenia. Following its partial withdrawal due to concerns over agranulocytosis, clozapine was reintroduced in response to pressure from psychiatrists and is now used worldwide in patients with treatment-resistant schizophrenia, having demonstrated its superiority over typical antipsychotic agents. This, combined with its low propensity to cause tardive dyskinesia, has transformed the management of patients with schizophrenia. This article outlines the history of clozapine's development, from its discovery in 1958 to its current position as the "gold standard" therapy for treatment-resistant schizophrenia.

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The year 1998 marked the 10-year anniversary of the publication of the U.S. Clozaril Multicenter Trial,[1] which led to the worldwide use of clozapine for treatment-resistant schizophrenia. However, the history of clozapine encompasses a considerably longer period than the past 10 years and can be divided into 2 distinct phases: from chemical synthesis in 1959 to 1988 and from 1988 to the present time.

1959–1988: DISCOVERY OF CLOZAPINE—FROM CHEMICAL SYNTHESIS TO CONTESTED PSYCHOTROPIC DRUG

The introduction in the 1950s of the first thioxanthene and phenothiazine neuroleptics followed by the early tricyclic antidepressants stimulated research into the mechanisms of neurotransmission and also led to early and naive speculation on the relationship between chemical structure and clinical effect. In 1958, Wander Laboratories initiated the screening of tricyclic compounds for antidepressant activity and were surprised to discover drugs with a chemical structure comparable to the tricyclic antidepressants but with neuroleptic properties. Clozapine was subsequently identified in 1959. At this time, Janssen hypothesized that a butyrophenone cataleptic effect and apomorphine antagonism were prerequisites for neuroleptic efficacy,[2] and this led to the introduction of haloperidol in the early 1960s. Based on this hypothesis, the early pharmacologic investigations with clozapine revealed that the drug had a "defective" or "atypical" profile. Clozapine was also found to have marked analgesic potential.

The "neuroleptic dogma" that extrapyramidal symptoms (EPS) were necessary for pharmacologic activity developed and was one of the factors that limited interest in clozapine for many years. Additionally, many of the early studies with clozapine were of an open-label design and were published only in German.[3–5] The first double-blind study of clozapine, compared with levomepromazine, was also published solely in German.[6]

In the early 1970s, Stille and Hippius challenged the neuroleptic dogma with pharmacologic and clinical data derived with clozapine demonstrating that antipsychotic activity was not dependent on the development of EPS.[7] However, other factors continued to limit interest in clozapine: in 1972, Wander Laboratories became part of the Sandoz organization, but more importantly, in 1974, 8 patients in Finland who were taking clozapine in conjunction with a variety of other drugs died as a result of agranulocytosis.[8] This led to the withdrawal of clozapine in those countries where it was already marketed and suspension of clinical trials elsewhere.

Subsequently, a number of patients who had previously responded to clozapine experienced relapses, and protests from German psychiatrists led to the reintroduction of clozapine in a few countries under rigorous controlled conditions. The therapeutic use of clozapine increased in these countries over the ensuing years, but very little clinical research was conducted. In other countries, especially in the United States, there was increasing research interest in clozapine, initially as a pharmacologic tool, but later also as a therapeutic agent.[9] The turning point in the history of clozapine came in 1988 with the publication of 2 landmark comparative trials demonstrating the efficacy of

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clozapine in a significant proportion of treatment-resistant patients.[1,10]

1988–1998: REDISCOVERY OF CLOZAPINE—FROM WALLFLOWER TO GOLD STANDARD

In the United States, clozapine was approved by the Food and Drug Administration (FDA) for treatment-resistant schizophrenia in 1990 and was subsequently reintroduced into clinical practice in many countries. Comparative studies have since demonstrated the superiority of clozapine over chlorpromazine, fluphenazine, haloperidol, and placebo in treatment-resistant patients in terms of both the positive and negative symptoms of psychosis.[11–13] Over the past 10 years, clozapine has become the "gold standard" for the development of new antipsychotics, demonstrating marked advantages in terms of reduced EPS, in particular tardive dyskinesia.[14] Further advantages include improvement in cognitive function and symptoms of disorganization,[15] lack of effect on serum prolactin,[16] improved quality of life,[17] improved compliance, reduction in suicidality,[18–20] reduced aggression,[21,22] absence of depressive effects, and continued efficacy in long-term treatment.[23] The risk of agranulocytosis with clozapine therapy can be minimized with regular blood monitoring.[24]

The ability of clozapine to restore function in even the most refractory of schizophrenia patients, its low propensity to cause tardive dyskinesia, and efficacy in patients with negative symptoms have changed the management of schizophrenia. Clozapine is, by any definition, an atypical neuroleptic. The most appropriate definition of atypicality, however, is controversial. Should it be broad or narrow? The most distinctive feature that separates clozapine from standard antipsychotics is the absence of EPS, in particular tardive dyskinesia, and this should be the benchmark by which future atypical antipsychotics should be judged.

In conclusion, the fortunes of clozapine have changed dramatically over the past decade, and the indications for clozapine are expected to widen in future years. However, the mechanism of action underlying the atypical profile of clozapine remains an enigma and has become a major goal in antipsychotic drug development. Subsequent articles in this supplement will review the accomplishments of clozapine in more detail and consider its future role in psychiatry.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril, Leponex), fluphenazine (Prolixin), haloperidol (Haldol and others), levomepromazine (Levoprome).

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