How chlorpromazine improved the treatment of schizophrenic patients

In *The Journal*'s latest article on landmark drugs, Jenny Bryan takes a look at the discovery of chlorpromazine and how its use has revolutionised the care of patients with schizophrenia

Psychiatric practice was revolutionised by chlorpromazine — and, soon after, haloperidol — because they allowed people's behaviour to be controlled and treated in an effective way without the need for straitjackets and other restraints (Kevin Curtis/Science Photo Library)

Few landmark drugs in this series have so dramatically changed the way that a disease is managed as the first antipsychotic agent chlorpromazine. From the day in January 1952 that it was used to calm a young, severely agitated male patient in a Paris hospital, contributing to his release 20 days later,[1] interest in chlorpromazine spread rapidly through Europe and North America. In less than a year, it was available on prescription in France as Largactil — a brand name reflecting its "large action."

"Before the introduction of chlorpromazine — and, soon after, haloperidol — schizophrenic patients were hospitalised for life in Victorian asylums. The new drugs revolutionised psychiatric practice because they allowed people's behaviour to be controlled and treated in an effective way without the need for straitjackets and other restraints. The atmosphere of asylums was improved and patients could be discharged — something that was previously unthinkable," explains Stephen Lawrie, professor of psychiatry and neuro-imaging and honorary consultant psychiatrist at the Royal Edinburgh Hospital.

From anaesthetic to antipsychotic

Chlorpromazine is a phenothiazine derivative made by chemists at the French pharmaceutical company Rhône-Poulenc (now part of Sanofi-aventis) in 1950. Three years earlier, the company had synthesised promethazine as part of an ongoing research programme into new antihistamines. But the compound had useful sedating properties and the chemists' search for more stable substances with minimal peripheral actions led them to chlorpromazine.

French surgeon Henri Laborit pioneered the use of chlorpromazine in a cocktail to sedate surgical patients and reduce shock without sending them to sleep and persuaded psychiatrist colleagues to experiment with it.[1] After the first tests, promising results were described with chlorpromazine in a series of 38 psychotic patients[2] and, before long, reports were accumulating from Canada,[3] the UK[4] and the US[5] of recovery and significant improvement in large numbers of institutionalised patients with schizophrenia or mania.

In an early British study, psychiatrists described subtle improvements in the behaviour of the most agitated and overactive patients on their wards, which were often only appreciated once the effects wore off when chlorpromazine was stopped.[4] "The patients in the definitely and slightly improved groups

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became quieter and more amenable to suggestion and guidance by the nursing staff, and could carry out simple ward tasks," wrote the researchers.[4]

Subsequent research into the mode of action of chlorpromazine and later agents has shown that their primary antipsychotic activity is through blockade of dopamine (D_2) receptors in the mesolimbic pathway of the brain, overactivity of which is understood to be responsible for the positive symptoms of schizophrenia (eg, delusions, hallucinations and disorganised speech).

However, there is little or no effect on the negative symptoms of schizophrenia (eg, lack of emotion and apathy). The dopamine-blocking effects of antipsychotic agents on other neurological pathways, such as the nigrostriatal pathway, and their effects on other neurotransmitter systems, such as serotonin, acetylcholine and histamine, impact on the nature and severity of their side effects.

Haloperidol: an early rival

Within a few years of chlorpromazine's arrival in psychiatric hospitals, Paul Janssen and colleagues at the Belgian pharmaceutical company, Janssen Laboratories (now part of Johnson & Johnson), discovered haloperidol, one of the butyrophenone class of antipsychotic compounds. Like chlorpromazine, haloperidol was the result of a research programme that was not looking for antipsychotic agents — in this case for pethidine-like central analgesics. But after haloperidol was shown to have neuroleptic actions without morphine-like effects, it went into clinical trials in France, where its efficacy in the treatment of acute and chronic paranoid psychosis, mania and chronic treatment-resistant schizophrenia was soon demonstrated.[6]

Haloperidol was quickly approved and marketed in Europe, but it was not approved in the US until the late 1960s, seemingly because of safety concerns. Ironically, however, haloperidol was to prove the antipsychotic drug of choice in the US while chlorpromazine became first-line therapy in the UK.

Professor Lawrie explains that time and experience with chlorpromazine and haloperidol showed that each drug had its drawbacks. "As chlorpromazine was primarily a sedating drug, it could make patients rather drowsy. Haloperidol wasn't sedating but patients started to get striking extrapyramidal side effects, with parkinsonian-like symptoms, which made British psychiatrists wary of using it. However, haloperidol became the standard comparator drug for trials of other antipsychotics and for the next generation of agents," he says.

As is often the case with market-leading drugs, there were few head-to-head trials, and a recent Cochrane review found only 14 relevant studies, mostly of short duration, poorly reported and conducted in the 1970s, with fewer than 800 patients in total.[7] There was little to choose between the two drugs on efficacy, although haloperidol was associated with significantly fewer people leaving the studies early, and the outcome "no significant improvement" also tended to favour haloperidol.

Movement disorders were over twice as common in those taking haloperidol while chlorpromazine was more commonly linked to hypotension. The reviewers expressed surprise that, over 40 years after haloperidol and chlorpromazine were introduced, further, large, well designed, conducted and reported studies were needed to determine which was the better drug.

In the 1960s and 70s, more antipsychotics were introduced, including a number of new phenothiazines, which found their own niche uses. But, as Professor Lawrie points out, many were used in excessive doses. "They were undoubtedly over-prescribed and patients had a lot of side effects. Effective doses can vary markedly between patients. But there was no therapeutic drug monitoring, so doctors didn't know if patients were getting too much or too little drug. For example, with haloperidol, we would now use 0.5–1mg/day and, even in an emergency, only go up to 5–10mg, but in the early days it could be prescribed in doses up to 30mg."

Professor Lawrie adds that about a third of patients obtained no benefit from chlorpromazine or haloperidol.

The introduction of depot formulations of chlorpromazine and haloperidol was seen as a major advance, especially for patients who did not like taking tablets, and clinics sprang up where patients could go for maintenance injections. But use of excessive doses again resulted in unacceptable side effects, making many patients unwilling to continue treatment.

So there was a continuing need for more effective, better tolerated antipsychotics.

The arrival of the "atypicals"

A new generation of antipsychotic agents — the "atypicals" — appeared to be the answer to psychiatrists' prayers. They carried a much lower risk of extrapyramidal side effects and appeared to be more effective against the negative symptoms of schizophrenia than the first generation of antipsychotic drugs. But the first of these drugs, clozapine, launched in the UK in 1989, carried an increased risk of agranulocytosis and required regular blood tests. Subsequent drugs fared better and risperidone, launched in 1993, has become the first-line antipsychotic for many psychiatrists.

"Risperidone is a reasonable first choice as it can be used in low doses with few side effects. Olanzapine is slightly more effective and is probably somewhere between risperidone and clozapine in terms of efficacy. But patients tend to put on weight with olanzapine," says Professor Lawrie.

Chlorpromazine continues to play a significant role in schizophrenia treatment in the UK and haloperidol in the US. A Cochrane review has supported chlorpromazine as a continued benchmark treatment for psychoses.[8] But an equivalent analysis of haloperidol concluded that its role should be limited to potentially dangerous situations of untreated schizophrenia where other options are not available, and advised against its use as a control drug of choice for randomised trials of new antipsychotics.[9]

Today, about half of those with schizophrenia are treated by their GPs, and half are under the care of a psychiatrist. Admission to hospital is only required for severe, acute problems.

"Antipsychotic drugs revolutionised the care of schizophrenia, changing it from an incurable condition which required institutionalisation to one that could be treated in the community, with the potential for independent living and recovery," concludes Professor Lawrie. "Antipsychotics also made psychiatrists feel more like their colleagues in the rest of medicine, in that they had drugs that really did work."

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