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

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, 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.

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. After the first tests, promising results were described with chlorpromazine in a series of 38 psychotic patients and, before long, reports were accumulating from Canada, the UK and the US 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. “The patients in the definitely and slightly improved groups...
“Antipsychotics made psychiatrists feel more like their colleagues in the rest of medicine, in that they had drugs that really did work”

became quieter and more amenable to suggestion and guidance by the nursing staff, and could carry out simple ward tasks,” wrote the researchers.6 Subsequent research into the mode of action of chlorpromazine and later agents has shown that their primary antipsychotic activity is through blockade of dopamine (D2) 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 neurolaptic 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 uses. Chlorpromazine became first-line therapy in the UK, and haloperidol was to prove the experience with chlorpromazine and the UK.

Chlorpromazine became first-line therapy in the UK and haloperidol in the US. A Cochrane review has supported chlorpromazine as a continued benchmark treatment for psychoses.6 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.7 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.”

References