

Lessons from the history of antipsychotic discovery: part 1 – initial insights

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Summary The recent introduction of the first non-dopaminergic antipsychotic marks a pivotal moment in psychopharmacology. This article revisits the development of chlorpromazine, the world's first licensed antipsychotic, and considers what its history reveals about innovation in psychiatric drug discovery. Chlorpromazine emerged in the early 1950s as a treatment for surgical shock. Its subsequent recognition as an antipsychotic transformed psychiatric care, ushering in the modern era of psychopharmacology. This article argues that chlorpromazine's success was not serendipitous: it depended on specific enabling conditions, including rigorous behavioural neuroscience, astute clinical observation across disciplines, close collaboration between clinicians and industry, and relatively agile regulatory frameworks. Understanding these factors is essential as psychiatry enters a new phase of drug development for the treatment of psychosis.

Keywords History of psychiatry; psychotic disorders/schizophrenia; antipsychotics; clinical trials; psychopharmacology.

More than 73 years have passed since chlorpromazine, the first antipsychotic drug, transformed psychiatric care. For 7 decades, all known effective antipsychotics have worked by acting on dopaminergic neurotransmission. Only within the past year has a new medication emerged in the USA with a genuinely different mechanism – one that targets muscarinic receptors instead of dopamine receptors. This landmark moment makes it timely to revisit how antipsychotics were first discovered and what their history can teach us about developing the next generation of treatments.

This three-part series will chart this journey: in the first article I will discuss the history of the discovery of chlorpromazine; in the second article I will review subsequent developments in the evolution of antipsychotic medications and the rise of dopamine-based drugs. Then in the final article I will discuss recent breakthroughs in muscarinic therapies and future new treatments. The goal is to identify the principles that drove past progress and how they can help drive success in a new era of discovery of medications for treating psychosis.

A poet with ideas

Henri Laborit was a handsome, at times anarchic, surgeon, scientist, philosopher and poet.¹ Born in Hanoi in 1914, at the age of 6 he saw his father die of tetanus, he survived tuberculosis aged 12, and later trained in the French Navy. Finding medicine too slow paced he turned to surgery. At the

start of the Second World War, Laborit was stationed on the naval destroyer *Siroco*, which was sunk by German torpedoes at Dunkirk with the loss of 666 lives. Laborit survived by throwing himself into the Channel, where he was rescued by a passing British ship. He went on to treat severely injured soldiers and civilians across North Africa and France, and was awarded the French Military Cross with Distinction for his bravery. By the age of 30, Henri Laborit had seen more of life, and of human frailty, than many do in a lifetime.¹

The search for 'central blockers' and the discovery of 4560 RP

One problem obsessed Laborit. He and his colleagues would often operate apparently successfully on injured patients, only for them to sink inexorably into surgical shock. Laborit was convinced that these deaths were not inevitable, but were driven by the body's excessive response to physical stress.^{1,2} He sought to identify drugs that could dampen down the body's responses, developing what came to be known as the 'Laborit cocktail'. In his desire to progress this treatment, Laborit encouraged the French pharmaceutical company Rhône-Poulenc to develop stronger 'central blockers' of chemicals produced in response to stress.^{1,2} In 1950, the chemist Paul Charpentier and behavioural neuroscientist Simone Courvoisier identified a compound, derived from dyes used in the clothing industry, which they showed had powerful actions in the central nervous system.² They knew

the drug was related to compounds with antihistaminergic properties, but were uncertain of the best use for this new drug. After testing it in animals they therefore sent samples to Laborit and other physicians across France for trials in different indications. The drug was initially known as 4560 RP, and later came to be known as chlorpromazine.

When Laborit administered chlorpromazine to his surgical patients he noticed an unexpected consequence – the drug produced a calmness even in the most distressed patients that he referred to as a ‘euphoric quietude’.^{1,2} Working at the Val-de-Grâce military hospital in Paris, Laborit tried to persuade his psychiatrist colleagues to try the new drug, telling them that it might help their patients. However, the psychiatrists were initially reluctant, having heard that a colleague, Cornelia Quarti, had fainted following an early experimental dose.^{2,3} Eventually, in 1952, Laborit persuaded Colonel Joseph Hamon, director of the neuro-psychiatric service at Val-de-Grâce, to try the new treatment on the agitated and psychotic soldier Jacques.² Jacques presented with a severe illness and in previous episodes had shown a poor recovery even with electroconvulsive and insulin coma therapy, so Hamon likely thought that there was little to lose. Remarkably, Jacques’s agitation settled with treatment with chlorpromazine combined with a few sedatives.² More remarkable still was that Jacques fully recovered after only a few weeks, without the need for electroshock or coma treatments.²

Impressed, Hamon and his colleagues presented the findings to the Paris Société Médico-Psychologique 1 month later, suggesting chlorpromazine might represent a new class of agents capable of ‘enriching psychiatric therapy’.⁴ However, these findings were based on one single patient, treated with other drugs at the same time, leaving key questions unanswered: Would chlorpromazine work on its own? Which patients would benefit? Was chlorpromazine more effective than simple sedation?

A trick that works

Jean Delay was head of the psychiatry department at the vast Sainte-Anne Psychiatric Hospital in Paris and the leading French psychiatrist of his generation. Austere and authoritative, Delay was the complete opposite of Laborit.³ One of the youngest professors of medicine in France, he was a pillar of the establishment, who had examined Rudolph Hess at the trials of Nuremberg. Delay firmly believed that conditions of the mind could and would be managed with medications if only the right treatments could be found.³ He had conducted systematic research on a range of compounds that altered mental states, including barbiturates, and saw that drugs could produce profound effects on the mind,³ yet none affected the delusions and hallucinations characteristic of psychosis. In the early 1950s, the only options for treating patients with these symptoms were to sedate them with drugs like barbiturates or subject them to physical therapies like electroconvulsive shock treatment, insulin coma therapy or invasive brain surgery.

Chlorpromazine: from surgery to psychiatry

Delay’s chief assistant, Pierre Deniker, was an astute clinician and former hero of the French Resistance. Deniker had heard

of Laborit’s work and its calming effects through his surgeon brother-in-law. Surrounded as he was at Sainte-Anne’s by patients who were agitated, disturbed and psychotic, Deniker immediately recognised the potential benefit of chlorpromazine. Delay and Deniker were aware that other groups across France had also been sent the new drug, and pressed forward with urgency to test the treatment in a range of patients at Sainte-Anne’s. Critically, having seen that other treatments failed to work for many of their patients, they chose to investigate the effects of chlorpromazine given alone.^{2,3} Deniker and Delay were impatient to see whether the new treatment could work where so many others failed. Was this the medical treatment they had been seeking? At Sainte-Anne’s they were able to rapidly select a suitable group of patients on whom to try the new medication.⁵ The eight patients they chose to treat were all agitated and currently psychotic, similar to the patient Jacques whom Hamon treated. Having little information to guide the dose of chlorpromazine to give, they took a chance on a relatively high dose, given either as an injection into the muscle or as a tablet.^{2,3,5}

The results of treatment of these patients with chlorpromazine were spectacular.⁵ The drug calmed the patients and helped them sleep better, working even when the patients were not sedated. Better still, chlorpromazine began to progressively treat the psychotic symptoms that no other medication could touch at that time.^{2,3} The nurses looking after the patients asked in excitement ‘What is this new drug?’⁵ Delay and Deniker realised the importance of these findings, and presented them as soon as they could at the Société Médico-Psychologique and subsequently the French Congress of Psychiatry and Neurology in 1952.^{6,7} They continued giving chlorpromazine to more patients, presenting their results in a number of reports.^{2,8} The results, and those from other groups, supported their original findings – chlorpromazine was particularly effective in agitated patients with psychosis, many of whom would now be diagnosed with either schizophrenia or bipolar disorder. Chlorpromazine was also of some benefit in severe anxiety, but it did not appear to work for patients with depression.²

Deniker noted a number of other key features of the new drug.^{2,3} First, while it dampened down the psychotic symptoms, such that they faded into the background, they did not immediately disappear completely – they just became less preoccupying and disturbing. Second, although some patients appeared to recover, most relapsed when treatment stopped. Together, these findings suggested that chlorpromazine was not a permanent cure for psychosis, but that it decreased psychotic symptoms and agitation. In testing chlorpromazine and finding that it could reverse the symptoms of psychosis, Delay and Deniker had opened the door to a new world of rational, medical treatment in psychiatry.

Spreading the word

Because of Delay’s prominence as a psychiatrist in France and the group’s demonstration of chlorpromazine as a stand-alone treatment in psychiatric patients, Delay and Deniker’s findings quickly attracted attention across France and Europe. Rapid publication ensured their lasting association with chlorpromazine. However, wider international recognition

was slower, partly because their findings were predominantly published in French.

Rhône-Poulenc sought partners to enter the American market and eventually struck a deal to licence chlorpromazine to US drug company Smith, Kline & French. Laborit and Deniker toured the USA to demonstrate the new treatment. Although Laborit's use of chlorpromazine in surgery failed to impress, Deniker's psychiatric reports proved persuasive, leading Smith, Kline & French to market chlorpromazine in the USA for psychiatric use.

Cracking the North American market: Heinz Lehmann

The American market proved hard to crack, as much of psychiatry in the USA at that time was dominated by private practitioners influenced by Freud. They believed psychosis derived solely from early childhood relations that could be treated only by extensive psychoanalysis. Patients who did not respond to these psychodynamic therapies, or who could not pay, ended up in an array of vast public 'asylums'. These asylums were considered a backwater of the medical profession, avoided by many of the best doctors and ignored by much of society.⁹ The outcomes for patients in such establishments, many of whom were suffering from psychosis, were often poor. Sedation, restraint and physical treatments like electroconvulsive therapy, insulin coma treatment and psychosurgery ('frontal lobotomy') were the main approaches employed in these industrial-scale psychiatric institutions.⁹ Optimism and interest about the potential of any new treatment was low.

Chlorpromazine needed a champion in North America, and that champion was found in Heinz Lehmann.^{2,3} Lehmann was a German-born Canadian psychiatrist working as Director of the Verdun Protestant Hospital in Montreal. Lehmann had a scientific mind and, being fluent in both French and German, played a major role in the introduction of new therapies and ideas from Europe into North America. Lehmann was out of his office when the representative of Smith, Kline & French first called to give him information on chlorpromazine.³ When Lehmann's secretary offered to arrange another appointment, the company representative said it would not be necessary as the material would speak for itself.

Lehmann initially ignored the papers. However later, apparently while taking a Sunday bath, he decided to read the pack, which included reports from Laborit, Delay, Deniker and others.³ He immediately recognised the potential importance of chlorpromazine and requested samples for trials in his hospital. Lehmann carried out large-scale clinical trials of chlorpromazine in his hospital and was impressed by what he saw.^{2,3,10} What struck him the most was the ability of the drug to affect patients with psychosis who had never responded to any treatments before, relieving their psychotic symptoms without being overly sedating. He published his work and presented his findings at scientific meetings across America, having a major impact on the adoption of chlorpromazine in the USA.^{2,3,10} Here at last was a psychiatric medication that could have a transformative effect on patients with psychosis in the vast American asylums and could bring psychiatry into the realms of modern medicine. This laid the ground for the eventual enthusiastic uptake of

chlorpromazine (under the brand name Thorazine), with over 2 million prescriptions written in the first 8 months.²

From asylums to out-patients: a revolutionary shift in psychiatric care begins

The introduction of chlorpromazine undoubtedly had a huge impact on psychiatry and on the treatment of people with psychosis in mental institutions around the world. Within 10 years of its entry onto the market, the population of US asylums decreased by 30%.² A similar pattern was seen in other countries, including the UK. The discovery of chlorpromazine was undoubtedly a major contributor to this trend. Patients who had been psychotic for years could now be treated with a tablet, often given in an out-patient service or at home. Severe mental health illness was seen as a medical condition that could potentially be treated, rather than an inevitable legacy of early-life trauma or the family environment.^{2,5} Chlorpromazine was a major reason for this change, although not all patients responded to the treatment as well as the majority.^{2,3} Both Rhône-Poulenc and Smith, Kline & French made vast fortunes from the sale of the drug.^{2,3} This in turn attracted other companies to invest in mental health research and helped usher in the first era of what became known as psychopharmacology.

The missing Nobel Prize

The development of chlorpromazine was arguably one of the most impactful medical discoveries of the 20th century, but no one was awarded the Nobel Prize for its discovery.³ Laborit was one obvious candidate, but he was an outsider to the medical establishment. Never a conformist, he always felt undervalued by the orthodox medical profession and always felt that his contribution to the discovery of chlorpromazine was not sufficiently recognised. It is possible that Delay, who was on the Nobel committee, blocked Laborit's candidature.³ Delay and Deniker's work became that most associated with the introduction of chlorpromazine, as they published the first systematic results showing the action of chlorpromazine alone. However, they published all their findings in French and Delay travelled little outside the Francophone world. Lehmann paved the way to chlorpromazine's mass use in the USA. The work of Laborit, Deniker and Lehmann was eventually recognised by the award of the prestigious American Lasker medical prize, and Deniker and Laborit went on to become friends, partly through their shared tours of the USA.¹¹ Lehmann came to be known as the 'father of psychopharmacology' and played a role in the introduction and development of many of the major classes of treatment used in psychiatry. Delay was overlooked by the Lasker Prize committee but continued to be a highly influential figure in French medical society.^{3,5} He was eventually forced from office in the late 1960s, when he was targeted by student revolutionaries who saw him as representing the establishment inflicting a 'chemise chimique' (chemical straight-jacket) on his patients.³ In truth, the development of chlorpromazine, like so many important discoveries in science and medicine, relied on the contributions of all these individuals and many more besides, including Paul Charpentier and Simone Courvoisier at Rhône-Poulenc.

Was it all serendipity? Lessons from the discovery of chlorpromazine

The discovery of chlorpromazine as an antipsychotic is often said to have owed much to ‘serendipity’. Serendipity is defined by the Oxford English Dictionary as ‘the occurrence and development of events by chance in a happy or beneficial way’. There is no doubt that chance played a role in the discovery of the antipsychotic properties of chlorpromazine – after all, no one had even conceived of an ‘antipsychotic’ drug before the discovery of the actions of chlorpromazine. However, given that it has taken 72 years to identify a second fundamentally new mechanistic approach for the treatment of psychosis, it is worth considering whether the discovery was purely driven by chance, or whether there were particular features of the environment at that time that favoured innovation in psychopharmacology that are less prominent in the current era. Four in particular present themselves.

Research into behavioural neuroscience

One key factor in the discovery of chlorpromazine was the thorough behavioural neuroscience research conducted at Rhône-Poulenc by Simone Courvoisier.⁵ Although animal studies could not directly assess psychosis *per se*, they highlighted the compound’s neuroactive and behavioural effects. Behavioural neuroscience approaches have advanced considerably since the 1950s, including the development of tests more directly assessing neurocognitive processes relevant to psychosis.¹² However, there have been considerable pressures to reduce animal research in psychiatry. Continued advocacy and training in the appropriate use of animal models, such as that provided by the British Association of Psychopharmacology, remain critical for psychiatric drug development.

Astute clinical observation across disciplines

A second key factor was the astute clinical observations of clinicians from different specialties, such as Laborit and Deniker.¹ Supporting interdisciplinary training and interactions is key to finding new medications relevant to psychiatry, for example potential immunotherapies. Supporting open publication and dissemination of clinical observations will further maximise the impact of such new treatments, particularly during an era of rapid development of new treatment approaches.

Close collaboration between clinicians and industry

A third notable feature in the development of chlorpromazine was the close interaction between pharmaceutical companies and clinicians, supporting rapid innovation.² This appears to have been driven significantly by shared scientific and clinical objectives, rather than solely by direct financial rewards for the clinician-scientists involved. There was a network of clinicians ready to work closely with innovators to rapidly test new therapies.^{2,3} The fostering of open and close links between academics and industry, combined with new trial approaches, including ‘platform’ and ‘fast fail’, trials can help provide a similar environment,

while maintaining the necessary professional and regulatory governance.¹³ The UK Mental Health Translational Research Collaboration provides one initiative designed to help foster such links.

Increasingly agile regulatory frameworks

Fourth, compared with the mid-20th century, the modern regulatory environment for clinical trials is more time-consuming and costly, with implications for the pace of innovation. Although there is no desire to return to unregulated testing, recent experience during the COVID-19 pandemic shows that novel and repurposed treatments can be evaluated rapidly and at scale under streamlined but robust regulatory frameworks.

What of the future?

There are reasons to believe that psychiatry is entering a new phase of pharmacological discovery. Drawing on the lessons from the development of chlorpromazine is therefore critical for maximising progress in the treatment of complex psychiatric disorders such as schizophrenia.

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Declaration of interest

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