

Lessons from the history of antipsychotic discovery: part 2 – dopaminergic diversification

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Summary This article examines the development of antipsychotic medications in the period following the discovery of chlorpromazine in the mid-1950s up to the early 21st century. This era is defined by the identification of dopamine modulation as the central mechanism for treating psychosis, and by the development of a diversity of treatments around this mechanism. This strategy yielded a broad range of effective treatments and transformed clinical care; however, with the notable exception of clozapine, it failed to produce substantial gains in overall efficacy. Newer agents primarily differed in tolerability rather than therapeutic impact. Partial dopamine agonists refined, rather than replaced, this approach. As a result, the dopaminergic era offers a cautionary lesson for psychiatric drug development and underscores the need to move beyond dopamine-based models *per se*.

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

In the first of this short series of articles I reviewed the history of the development of the first commercially available antipsychotic – chlorpromazine – and its implications.¹ In this second article I will discuss the development of antipsychotics between the mid-1950s and the early 21st century, and the advances in mechanistic understanding that were achieved during this era. This period is characterised by the identification of a single dominant mode of action and the subsequent remarkable diversification of treatments acting on this pathway.² I will conclude by considering lessons that can be learned from this period of diversification of dopaminergic treatments.

From ‘speed’ to Haldol

There was a lot of amphetamine available in Japan after the Second World War.² Amphetamine (‘speed’) and its more potent relative methamphetamine (‘meth’) had been used by troops in both Allied and Axis countries for their stimulant effects. Methamphetamine was used extensively by Japanese troops to enhance vigilance and performance during periods of combat. At the end of the Second World War, a large amount of manufactured methamphetamine was available in Japan. It found a ready market among young Japanese workers who were ‘moonlighting’ in second jobs to supplement meagre wages: the meth helped them stay awake.

However, by the 1950s, Japanese psychiatrists noticed that an increasing number of people were being admitted to their hospitals with paranoid psychotic symptoms. A common feature of these patients was that they had consumed considerable quantities of amphetamines. In parallel, Philip Henry Connell at Maudsley Hospital, London, had noticed a similar phenomenon in the UK and formally described a series of cases of ‘amphetamine psychosis’.^{3,4} By the late 1950s it began to be generally recognised that stimulants such as speed and meth could trigger psychotic episodes similar to those seen in schizophrenia.² Meanwhile, in Belgium a young chemist named Paul Janssen decided to increase research activity in his small family-run pharmaceutical company.^{2,5} He hoped to discover novel compounds to the stage where they could be developed and licensed to large drug companies. His initial interest was in pain control, and his team started modifying opiate drugs to determine whether these could make more effective painkillers.² When testing the new drugs on mice, they noticed that these drugs produced behavioural changes similar to those seen with the recently discovered antipsychotic chlorpromazine.⁵ Furthermore, some of these compounds could block the effects of amphetamines. Rodents given amphetamine showed increased movement and Janssen’s new drugs could block these effects – a property they shared with chlorpromazine. Janssen felt that these compounds could have clinical use and sought to modify the molecules to maximise their

amphetamine-blocking and ‘neuroleptic’ (literally ‘nerve-seizing’) capabilities. By 1958, Janssen’s team had produced the molecule R1625, later named haloperidol (trade name Haldol), that was highly effective at blocking the effects of amphetamine in rodents. At this stage, Janssen did not know haloperidol’s optimal dose or clinical indication. Undeterred, he guessed that it might be useful in psychiatry and sent supplies of 5 mg vials of haloperidol to his contacts at the large nearby Liege psychiatric hospital to try on their patients.⁵

The drug was apparently first tried on the son of one of the doctors at the hospital, who was admitted overnight with a sudden-onset agitated psychotic episode.² In an effort to control these symptoms, and probably feeling under some pressure to act decisively, the duty resident decided to administer a whole 5 mg vial of haloperidol by injection. The drug had a remarkable effect in calming the young man, who rapidly became less disturbed.² He remained well into the next morning when the boy’s father, other senior doctors in the hospital and Janssen himself reviewed him and were amazed at the effectiveness of the new compound. Following review, the decision was made to continue treating the boy with haloperidol at the lower dose of 1 mg per day, initially given in liquid form with his morning coffee. The patient remained well on this treatment and was discharged home a few weeks later, when he continued to take the medication. He completed college, got married and had children, all while still taking the medication.² Eventually after 7 years the decision was taken to determine whether it was now safe to stop the treatment. Three weeks after discontinuing the medication the young man was readmitted to hospital in an acute psychotic state. Clearly haloperidol could dampen the symptoms of psychosis, as was confirmed in subsequent clinical studies in Liege and beyond.⁵ However, like chlorpromazine, haloperidol did not produce a permanent cure. Haloperidol and chlorpromazine could both treat acute psychosis, but how they worked in the brain remained unknown.

Clues from India

Studies of the effects of a tropical shrub found in sub-Himalayan India would eventually pave the way to understanding of the action of these antipsychotic agents. The plant *Rauwolfia serpentina* has for centuries been known to have medicinal properties.⁶ Preparations of the plant (especially the dried root) have been used traditionally in India for the treatment of a range of ills including fever, vomiting and difficulties with labour. *Rauwolfia* was also known to have a calming effect and was used to help with meditation and to settle patients suffering with poor mental health. Portuguese explorers who found the plant in use when they landed in Goa in the west of India recognised its uses and referred to *Rauwolfia* as ‘*premium et laudatissimum remedium*’ (‘best and most highly praised remedy’).⁷ In the 1930s, Indian researchers began to report the effects of *Rauwolfia* preparations in lowering blood pressure. At this time the adverse effects of hypertension were being increasingly recognised by Western doctors, and the effects of *Rauwolfia* on blood pressure were brought to the attention of major drug company Ciba Pharmaceuticals. Subsequently

the biochemist Hugo Bein at Ciba isolated the key active ingredient in *Rauwolfia*, which was named reserpine.⁷

Psychiatrist Nathan Kline in New York had heard about the medicinal effects of *Rauwolfia* through a *New York Times* article.⁸ The report noted that a Dr Hakim had been awarded a gold medal in Ahmabad, India, for his presentation of a paper on the treatment of schizophrenia with a compound used by Ayurvedic practitioners.⁸ The main ingredient of the compound was *Rauwolfia serpentina*. Kline obtained samples of the plant extract and of reserpine from Ciba. He initially tried these on himself ‘for several weeks each’ before trying them on his colleagues.⁸ Satisfied that they were safe, he commenced a trial on over 400 patients in Rockland State Hospital, New York.⁸ Klein’s work and that of later studies confirmed that reserpine was effective in calming agitated patients with psychoses and related conditions, in a manner very similar to that seen with chlorpromazine and haloperidol.^{2,8} Now there were three effective treatments for agitated psychoses, but still no explanation as to how any of them worked.

From treatment to target

Many new biological molecules were being identified in the 1950s, one of which was serotonin, found in high concentrations in the brain as well as in the gut and blood. Intriguingly, serotonin was noted to be very similar in structure to lysergic acid diethylamide (LSD), which can induce symptoms of psychosis such as hallucinations. In 1955, Bernard ‘Steve’ Brodie at the National Institutes of Health in Bethesda, USA, hypothesised that reserpine might act in the brain to alter serotonin levels. He showed that rabbits treated with reserpine became sedated, which was accompanied by a dramatic lowering of serotonin levels in the brain.⁹ Furthermore, when brain transmitters returned to normal levels following treatment, the sedation abated.⁹ It seemed that reserpine was exerting its sedative and calming effects by lowering brain serotonin levels. This neat explanation of the actions of reserpine apparently linked the effects of a drug, for the first time, to a specific brain chemical.

However, Arvid Carlsson, a young Swedish researcher who had visited Brodie’s laboratory in 1955, was aware that reserpine was lowering the levels of other chemicals in the brain as well as serotonin, including both dopamine and noradrenaline. This raised a critical question: which of these molecules was actually responsible for the calming effects of reserpine? In an ingenious series of experiments, Carlsson showed that the effects of reserpine could be reversed by restoring dopamine levels, but not by restoring the levels of serotonin or noradrenaline.^{9,10} Dopamine, and not serotonin, was therefore the key chemical in the brain on which reserpine was acting.

So, if reserpine was exerting its antipsychotic effects by decreasing brain dopamine levels, what about chlorpromazine and haloperidol? Researchers quickly tested whether these drugs could also decrease dopamine levels but found that they did not. Were chlorpromazine and haloperidol acting through a completely different mechanism? A range of possible mechanisms for the actions of these drugs were considered. However, no resolution was found until Carlsson

and van Rossum suggested that these drugs might be working by blocking a receptor for dopamine.^{11,12} This hypothesis was to prove correct, although it was not definitively proven until the 1970s when Philip Seeman in Toronto was able to show that the antipsychotic efficacy of drugs like chlorpromazine and haloperidol was related to how well they bound to and blocked dopamine D2 receptors.¹³

Finally, a clear picture was emerging. Antipsychotic drugs acted by inhibiting the dopamine system – either by depleting dopamine levels (reserpine) or by blocking the binding of dopamine to its D2 receptors (chlorpromazine and haloperidol). This also explained their action in opposing the effects of amphetamines, because amphetamines increase dopamine levels in synapses in the brain. In the space of just a couple of decades, from the discovery of the first antipsychotics, their action had been linked to a specific molecular target in the brain – dopamine and, specifically, D2 receptors.

Dopamine drawbacks

Almost as soon as chlorpromazine entered clinical practice, clinicians noted that patients treated with the drug could develop strange movements.² Patients became stiff and walked rigidly without the normal swaying of their arms. At higher doses some patients developed dramatic spasms of their neck or back, even becoming ‘twisted like a pretzel’ (dystonia). Some patients also developed a persistent state of restlessness (akathisia). Most of these symptoms abated if the medication was stopped but some movement symptoms, such as repetitive oro-facial movements, persisted even after treatment ceased (tardive dyskinesia).

Haloperidol and reserpine were even more likely than chlorpromazine to cause these motor symptoms, which came to be termed ‘extrapyramidal side-effects’. With hindsight it is not surprising that these motor effects developed, because Carlsson had shown that dopamine plays a critical role in the motor system and that loss of dopamine signalling is the cause of Parkinson’s disease, work for which he was later awarded the Nobel Prize.¹⁴ Initially some clinicians saw these Parkinsonian extrapyramidal symptoms as a positive sign that the drug was working, even advocating treating patients with doses sufficient to produce side-effects. However, extrapyramidal symptoms are often highly distressing and stigmatising for patients. Furthermore, drug companies became concerned about the potential for litigation, especially in regard to the irreversible features of tardive dyskinesia.² The hunt was now on for antipsychotic medications that produced fewer extrapyramidal side-effects.

‘Atypical’ antipsychotics

In the late 1950s the pharmacologist Gunther Stille, working at the Wander company, was screening a series of new compounds for potential antipsychotic effects, using an animal-testing approach similar to that adopted by Janssen.^{2,15} He identified a series of promising compounds that acted on animals similarly to haloperidol and chlorpromazine but that did not induce severe movement symptoms (catalepsy), even at high doses.^{2,15} Perhaps they would be antipsychotic with fewer motor side-effects? The most promising of these compounds, later named clozapine,

was sent to various groups for testing, including Pierre Deniker at St Anne’s hospital in Paris. It was found to be an antipsychotic with actions similar to chlorpromazine.¹⁵ Furthermore, from the earliest trials, clozapine was noted to produce fewer motor side-effects.¹⁶ However, although this was encouraging, clozapine unfortunately had significant side-effects of its own. It made patients drool with excess saliva, at high doses it could cause seizures and, worse still, when Deniker gave clozapine to 19 patients at St Anne’s hospital, 4 died from side-effects including overheating and loss of a specific class of immune cells in the blood.² Deaths caused by blood changes (specifically agranulocytosis) were also seen in patients treated with clozapine in Finland.^{2,15,16}

Clozapine could clearly be extremely dangerous and, normally, would have been removed from practice. However, a number of clinicians found that it could produce a response in patients who had not got better with any other antipsychotic treatment.¹⁷ It could also reverse some of the impacts of the feared long-term motor symptom tardive dyskinesia. Doctors petitioned for the drug to continue to be made available. Sandoz, who had bought the Wander company that made clozapine, initiated a large trial in the USA that compared clozapine with high doses of chlorpromazine in severely ill, treatment-resistant patients.^{17,18} Strikingly, in this double-blind, randomised trial many patients, who were among the most severely ill of all psychiatric patients, responded to clozapine even after failing to respond to chlorpromazine and other treatments.^{17,18} Sandoz decided to continue to market clozapine, with blood monitoring for all patients. Clozapine continues to be used in severely ill, treatment-resistant patients, although its dangers remain a concern and its use is accompanied by careful monitoring.

The ‘holy grail’ of antipsychotic drug development then became the development of a drug with the benefits of clozapine but without the side-effects. Any company that could produce such a drug would find a ready market. But what was it about clozapine that meant that it did not produce motor side-effects? Why was it effective in patients who were resistant to other treatments? Clozapine acted on the dopamine system like other antipsychotics, but did so more weakly than other effective antipsychotics. Clozapine was also known to have actions at a range of receptors beyond dopamine, including serotonin receptors. Perhaps its effects on the serotonin system were central to its special properties? In the 1980s, Janssen set about trying to identify compounds that blocked both dopamine and serotonin receptors.² His company succeeded in making such a drug, producing the effective antipsychotic risperidone in the early 1990s.²

The company Lilly took a different approach, aiming to produce molecules similar in structure to clozapine, hoping they could hit the ‘sweet spot of efficacy’ without side-effects. This led to the development of olanzapine, which entered the market in 1996 and, like risperidone, acted on both dopamine and serotonin receptors.² Both risperidone and olanzapine showed particularly strong antagonism of serotonin 5-HT_{2A} receptors, agonism of which is implicated in the psychogenic actions of drugs such as LSD and psilocybin, suggesting that this effect might contribute to their efficacy.² These drugs were very successfully marketed as ‘atypical antipsychotics’ (also referred to as ‘second-generation

antipsychotics’), and these soon came to dominate clinical practice.¹⁹

But were the atypicals really any better than the older drugs?¹⁹ By the early 2000s there was a sense that it was wrong, even cruel, to still prescribe older drugs such as chlorpromazine and haloperidol. After all, the assertions of the companies were backed up by clinical trials showing that drugs such as risperidone and olanzapine produced fewer extrapyramidal side-effects when compared with the older drugs such as haloperidol. However, trials of these drugs, which were often sponsored by the companies making the drugs, often compared the new drugs with very high doses of haloperidol or similar drugs, antipsychotics with a high tendency to produce extrapyramidal effects.¹⁹ When this was taken into account and they were compared instead with more moderate doses, the differences in tolerability between the new and old drugs became much less marked, although some benefit in terms of extrapyramidal side-effects remained.^{19,20} Furthermore, risperidone and olanzapine can indeed produce extrapyramidal side-effects in some patients, especially when given at higher doses. This is not surprising because they also block central dopamine receptors.

Furthermore, the new drugs were associated with other side-effects. Most prominent among these is increased appetite and weight gain – which can be 4 kg or more over the first couple of months of treatment in patients starting on olanzapine.²¹ This weight gain is associated with other metabolic changes such as dyslipidaemia and dysglycaemia, which put patients at long-term risk of complications such as diabetes and heart disease – contributing to the reduction in life expectancy seen in people with psychosis.²¹ Older drugs such as chlorpromazine can also cause weight gain, but usually to a lesser degree than is seen with atypicals such as olanzapine. Other side-effects seen in both atypical and ‘typical’ drugs include altered levels of hormones such as prolactin, as well as sedation and a lowering of the threshold for seizures. Overall, the side-effects of antipsychotics are related not only to their dopamine antagonist effects (e.g. extrapyramidal side-effect, hyperprolactinaemia) but also to their degree of antagonism at other receptors such as histaminergic (e.g. sedation and weight gain), adrenergic (e.g. hypotension), muscarinic (e.g. dry mouth) and serotonergic (elements of metabolic syndrome) receptors. Most disappointingly, there is no consistent evidence that these new drugs are actually more effective than the older examples, or have clozapine’s ability to produce antipsychotic benefit in treatment-resistant patients.^{19,20,22,23} The special efficacy of clozapine therefore largely remains a mystery. However, interestingly, clozapine has a particular agonist action at muscarinic receptors, a feature that is notable given the recent discovery that muscarinic agonism can itself have antipsychotic effects, discussed further in the third article in this series.²⁴

Stabilising rather than blocking

In 1972, Arvid Carlsson correctly predicted that presynaptic dopamine receptors – so-called autoreceptors – exist on dopamine neurons and negatively regulate dopamine release.²⁵ Building on the dopamine hyperactivity theory for schizophrenia, the company Otsuka sought to develop novel

antipsychotic drugs that could diminish dopaminergic activity by acting as agonists at these presynaptic dopamine autoreceptors.²⁶ Trials of compounds acting primarily on such autoreceptors showed some efficacy against negative symptoms in schizophrenia, but no consistent benefits in terms of positive psychotic symptoms.²⁶ This led to the development of compounds that combined autoreceptor agonism with antagonism of postsynaptic D2 receptors, in the hope of gaining efficacy against both positive and negative symptoms.²⁶

This approach led Otsuka to the development of aripiprazole. Analysis of the mechanism of aripiprazole’s activity revealed that, in addition to acting as a presynaptic dopamine autoreceptor agonist it is a dopamine D2 receptor partial agonist with a relatively low level of intrinsic activity.^{26,27} This effectively means that aripiprazole acts to stabilise dopamine levels to a moderate range – diminishing but not completely blocking dopamine transmission in areas of high activity and increasing activity in areas of low transmission (as may be seen in mesocortical dopamine). Clinical trials have shown aripiprazole to be an effective antipsychotic, albeit with some evidence that it is slightly less effective than alternative D2-blocking drugs such as olanzapine.²⁶ Aripiprazole is associated with a lower incidence of side-effects, including extrapyramidal symptoms, metabolic disturbance and altered hormonal (e.g. prolactin) levels.^{26,27} This has led to its extensive use in psychiatry, despite reports of higher incidences of some side-effects such as restlessness, akathisia and insomnia.²⁶

Lessons from the era of dopaminergic innovation

All antipsychotic medications currently licensed in the UK modulate dopaminergic neurotransmission at D2 receptors. This therapeutic mechanism of action has yielded a diverse and highly effective range of medications. However, these drugs have limitations. First, they treat only a subset of symptoms – specifically positive psychotic symptoms. Second, a significant proportion of patients have symptoms that remain resistant to treatment with conventional antipsychotics. Although some of these patients will respond to clozapine, others do not respond to any currently available treatments. Third, all dopaminergic antipsychotic drugs are associated with significant side-effects, albeit with some variation in the exact side-effect profile among different medications.

Overall, with the exception of clozapine, the proliferation of newer dopaminergic antipsychotics has not resulted in significant advances in treatment efficacy. For a long period, antipsychotic development programmes were based on assays that predicted D2 receptor antagonist properties, driving circularity in drug discovery. This resulted in a lack of fundamental innovation. New treatments predominantly differed from older ones in terms of their side-effect profile, and were actively marketed on this basis. Although it is likely that there are still novel mechanisms in the dopaminergic system to be explored – such as TAAR1 agonism,²⁸ there is an urgent need to identify new non-dopaminergic targets for the treatment of psychosis. Allied to this is the requirement for better bioassays and biomarkers related to fundamental

disease mechanisms, facilitating the development of targeted treatment approaches that recognise the fundamental heterogeneity of patient populations.

In the final article in this series I will discuss the recent development of the first antipsychotic with a genuinely novel mode of action, and the potential for further therapeutic innovation in the coming years. This holds the promise of a diversification of treatments beyond dopamine, and the potential that effective treatments may be available for a broader range of patients, potentially with reduced side-effects.

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