Antipsychotics

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What's new?

- Ziprasidone is now available in many settings, and sertindole is poised for re-release

- Weight gain and metabolic disturbances continue to be issues of notable clinical interest

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and International Psychopharmacology Algorithm Project (IPAP) inform clinical practice

Abstract

The discovery of the antipsychotic chlorpromazine made the *British Medical Journal*'s recent 15-item shortlist of the most important medical milestones since 1840. Serendipity has played an important role in the development of antipsychotic therapies, in combination with clinical observation and progressive pharmacological refinement. The progress from low-potency typical antipsychotics to high-potency agents, atypicals and beyond shaped the emergent discipline of psychopharmacology and prompted a fundamental change in our approach to patients with psychotic illnesses, from one of paternalistic guardianship to patient-led community-based care. Additional progress is still needed, as the current medication options are not yet ideal. Issues such as QTc prolongation, metabolic disturbances, suboptimal effectiveness and limited data supporting real-life prescribing algorithms are key areas to explore. This contribution reviews these issues in their historical context, pointing out current limitations and suggesting future therapy directions.

Keywords antipsychotics; atypical; metabolic; psychopharmacology; weight

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Serendipity has played a surprisingly important role in the discovery of modern medications, and the history of antipsychotic development is no exception. Fruitful accident, astute clinical observation, empirical trial and sequential refinement underlie the remarkable progress in antipsychotic treatments seen in the last half century. This contribution uses a chronological perspective to explore the development of antipsychotics and discuss current topics of interest.

Phases of antipsychotic development

Phase 1: discovery (antihistamines, chlorpromazine)

The discovery in 1947 of phenothiazine antihistamines such as promethazine occurred as a by-product of research into tropical infections. Almost all modern antidepressants and antipsychotics are derived from these antihistamines, and the later differentiation of H_1 and H_2 receptors led to the synthesis of H_2 antagonist anti-ulcer therapies.

A chlorinated antihistamine, chlorpromazine, was produced in 1951 and was found to exhibit anticholinergic and anti-emetic effects. It was for the latter indication that the drug was first licensed – even though psychotropic effects were soon observed – as there was no antipsychotic market at that time. The dramatic effects of chlorpromazine on psychotic patients in asylums worldwide, and the demonstration of its ability to reverse lysergic acid diethylamide (LSD)-induced psychosis, heralded a new era of psychiatric practice.

At around the same time, researchers in the West rediscovered the antipsychotic effects of the rauwolfia herb (*Rauwolfia serpentina*), which had been used in India since ancient times. Rauwolfia, and its active ingredient reserpine, were introduced as antihypertensive agents and were significantly less expensive than chlorpromazine. There was initially little understanding of the neurochemical basis of chlorpromazine action, although we now know that chlorpromazine blocks H_1 histamine, α_1-adrenergic, muscarinic and dopamine receptors. In contrast, the gradual revelation of reserpine's action as a monoamine-depleting agent was pivotal to the growing science of psychopharmacology and to the development of both the monoamine hypothesis of depressive illness and the dopamine hypothesis of schizophrenia.

Phase 2: refinement (D_2 antagonists, haloperidol)

In 1958, Janssen produced a new butyrophenone compound, haloperidol, in the process of trying to refine the analgesic effect

of pethidine. This was soon found to have a potent antipsychotic effect as well as efficacy in patients with Tourette's syndrome, in doses far lower than were needed for chlorpromazine. This high-potency neuroleptic was also observed to be more likely to cause extrapyramidal side effects (EPS), but less likely to cause anticholinergic effects than chlorpromazine.

Other drugs followed; these first antipsychotics were referred to as major tranquillizers (due to their significant sedative actions) and neuroleptics (due to their potential to cause EPS). These typical, or 'classical', antipsychotics have class-specific side effects, including:
- acute and chronic movement disorders (acute and chronic akathisia, acute and tardive dystonia, tardive dyskinesia, drug-induced Parkinsonism)
- hyperprolactinaemia
- neuroleptic malignant syndrome.

Drug-specific side effects include:
- anticholinergic symptoms (dry mouth, constipation, blurred vision, confusion)
- weight gain
- sedation
- postural hypotension
- reduced seizure threshold.

In 1963, Carlsson and Lindqvist proposed that dopamine antagonism explained the antipsychotic effects of chlorpromazine, haloperidol and reserpine. Antagonism of dopamine D_2 receptors became a defining feature of the antipsychotic class. Affinity for dopamine receptors and clinical potency of classical antipsychotics are very highly correlated (see Figure 1). Thus, it has been suggested that the key deficit in schizophrenia is increased dopaminergic activity, with over-stimulation in limbic areas responsible for positive symptoms, and decreased dopaminergic activity in the prefrontal cortex, inducing negative symptoms.

The dopamine theory of schizophrenia also posits that blockade of mesolimbic dopamine receptors mediates antipsychotic efficacy, with blockade in the tuberoinfundibular, nigrostriatal and mesocortical pathways mediating the side effects of hyperprolactinaemia, EPS and worsening of negative symptoms respectively.

Phase 3: atypical agents (clozapine-like drugs)

Clozapine, the most successful of the tricyclic antipsychotics, was originally synthesized in 1958 but withdrawn from most markets because of the risk of lethal agranulocytosis. It took the pivotal results of a seminal study of clozapine in treatment-resistant schizophrenia 30 years later for it to gain approval from the US Food and Drug Administration (FDA) and subsequent wide use.[1] Clozapine has an extremely complex binding profile, including $D_{1,4} > D_{2,3}$ antagonism, $5\text{-}HT_{2A/2C,3,6,7}$ antagonism, potent muscarinic (M_4) agonism, as well as H_1 histaminergic and $\alpha_{1,2}$ binding actions. This abundance of psychopharmacological actions has complicated the search for clozapine-like antipsychotics, which became known as second-generation or atypical antipsychotics.

There is no uniform definition of atypicality, but the cardinal feature is a similar psychopharmacological profile to clozapine. This is variously interpreted, and a host of clinical features and associated pharmacological criteria have been proposed to account for the atypical action of these drugs (see Table 1). Most authors suggest that atypicals have three essential features:
- efficacy in treating positive symptoms
- low incidence of EPS
- $5\text{-}HT_2$ as well as D_2 antagonism.

The revelation that clozapine has a higher affinity for $5\text{-}HT_{2A}$ receptors than for D_2 receptors prompted a wider investigation of the role of 5-HT in the mechanism of action of antipsychotic drugs. Observations that several $5\text{-}HT_{2A}$ receptor agonists such as
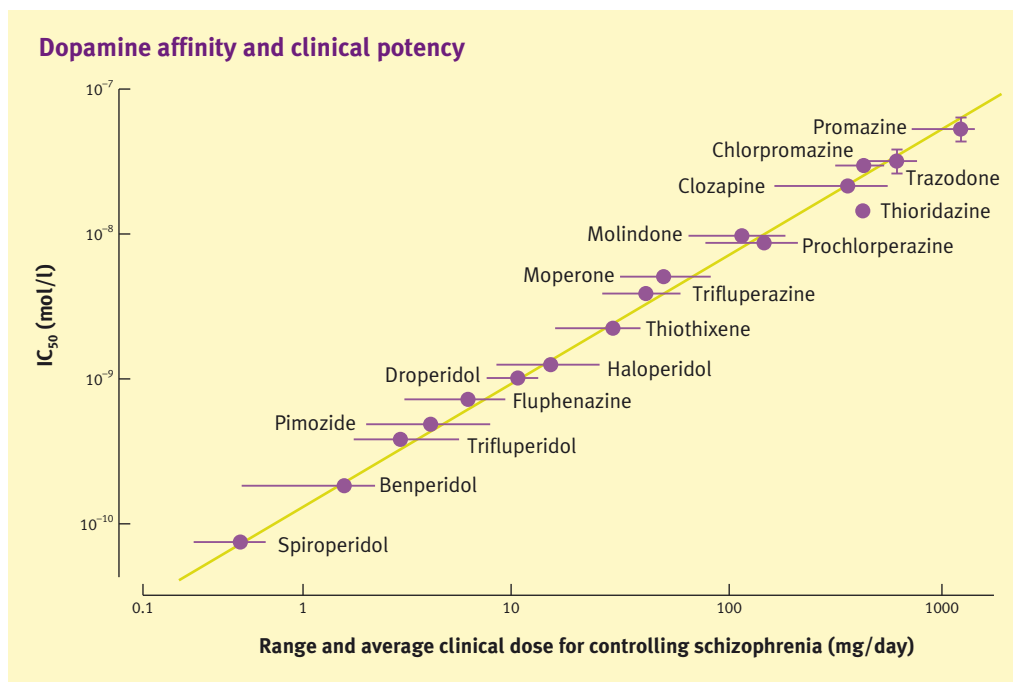

Figure 1

Atypicality criteria, grouped by clinical features and pharmacology

Clinical feature	Presumed pharmacological mechanism	Importance to atypicality classification	Drug examples
'Clozapine-like'	Clinical profile similar to clozapine	Essential	All (to varying degrees, none as good)
Improves positive symptoms	Occupancy of at least 60% of mesolimbic D_2 receptors	Essential	All (although clozapine is effective at less than 60% occupancy)
Low EPS after acute dosing	Less than 80% occupancy of striatal D_2 receptors	Essential	All
			Ziprasidone, risperidone, amisulpride and olanzapine all show dose-related increase in EPS incidence
Improves negative symptoms	$?5\text{-}HT_{2A} > D_2$	High	Clozapine, ziprasidone, aripiprazole, risperidone, olanzapine, quetiapine amisulpride, sertindole
No elevation of prolactin	Low selectivity for tuberoinfundibular D_2 receptors	High	Most, except risperidone, zotepine, amisulpride
Improves cognitive symptoms	Low EPS → low anticholinergic use Low intrinsic anticholinergic effect ? $5\text{-}HT_{2A}$ antagonism	Moderate	Quetiapine, clozapine, risperidone, sertindole, ziprasidone, olanzapine
Improves mood	? $5\text{-}HT_{1A} > D_2$ 5-HT, noradrenaline reuptake inhibition, a_2 antagonism	Low	Ziprasidone, risperidone, olanzapine, aripiprazole, amisulpride
More beneficial than typical antipsychotics in treatment-resistant patients	?	Low	Best demonstrated for clozapine
	α_2 antagonism	Moderate	Clozapine, risperidone, quetiapine
	Low affinity and fast dissociation from D_2 receptors	Unclear	Clozapine, quetiapine
	Low occupancy of striatal D_2 receptors	High	Clozapine
	$5\text{-}HT_6$ blockade	Low	Clozapine, olanzapine, sertindole, ziprasidone

Table 1

LSD and mescaline produce hallucinations in humans, and post-mortem evidence of high cortical density of $5\text{-}HT_2$-like receptors in schizophrenic patients, support a serotonin hypothesis of schizophrenia. Co-administration of the $5\text{-}HT_{2A}$ antagonist ritanserin with the typical antipsychotic haloperidol resulted in improvement of negative symptoms and diminished EPS. Additionally, $5\text{-}HT_{2A}$ receptors are highly localized to cortical layer V pyramidal neurons, making them well positioned to mediate the cognitive and perceptual integrative functions of antipsychotic drugs.

In spite of these promising findings, drugs such as cyproheptadine have $5\text{-}HT_2$ antagonist properties but negligible antipsychotic effect, and agents such as chlorpromazine and thioridazine also have high $5\text{-}HT_2$ affinity but are not considered atypical in their action. The serotonin hypothesis thus proposes that both serotonin and dopamine antagonism together (especially high $5\text{-}HT_2$:D_2 ratios) are needed for atypical antipsychotic action.

An exception to this is the benzamide antipsychotic amisulpride, which has antagonistic effects at dopamine D_2 and D_3 receptors, negligible $5\text{-}HT_2$ antagonism and yet has effective antipsychotic effects with low extrapyramidal side effects. This observation is explicable by a proposal that the defining feature of atypicality is not simply due to dual $5\text{-}HT_2$:D_2 receptor antagonism but by a drug having a low affinity for the D_2 receptor, which is ultimately determined by a fast dissociation from the D_2 receptor.[2] Clozapine, the protypical atypical, demonstrates a far shorter occupancy rate of striatal D_2 receptors than that of haloperidol, for example. Amisulpride and quetiapine both exhibit this fast dissociation property.

Phase 4: beyond D_2 antagonism (partial D_2 agonism, aripiprazole)

Current research is beginning to challenge the axiom that D_2 antagonism is essential for antipsychotic effect. Aripiprazole, now licensed in Australia, the UK, the USA and other countries, is the first antipsychotic that is not a D_2 antagonist. It is a quinolinone derivative with a unique mechanism of action: it exhibits partial agonist activity at D_2 and $5\text{-}HT_{1A}$ receptors and antagonist activity at $5\text{-}HT_{2A}$ receptors.

Preclinical and early clinical data support functional antagonism in dopaminergic hyperactivity states as well as functional agonism in states of dopaminergic hypoactivity without concomitant significant undesirable extrapyramidal side effects. This effect is sometimes referred to as 'dopamine stabilization'. Thus, aripiprazole is a potentially effective treatment of both positive and negative symptoms of schizophrenia. Early clinical data confirm that it is more efficacious than haloperidol with respect to negative symptoms, and is comparable to haloperidol and risperidone in the treatment of positive symptoms. It appears to be very well tolerated, with minimal evidence of significant EPS, hyperprolactinaemia, weight gain, metabolic disturbance or QTc prolongation, although it can cause nausea, proving a degree of dopamine agonism.[3–5]

Current issues

Problems with atypical antipsychotics

The atypical antipsychotics, while representing a substantial improvement over the classical antipsychotics in many respects, are not without their own problems. Both clinicians and patients have become increasingly less tolerant of antipsychotic adverse effects over recent decades as treatment has moved out of the asylum and into the community. Maximizing antipsychotic effect while minimizing unwanted side effects is a major goal of current research. Two significant adverse events are QT interval prolongation and metabolic disturbance.

QT interval prolongation

The QT interval is the time from the earliest Q wave onset to the latest T wave offset. It is assessed in the same lead (usually limb lead II) on serial ECGs and is most commonly corrected for heart rate by Bazett's formula (which may be expressed as $QTc = QT/RR^{1/2}$). This formula is less accurate at very high and very low heart rates, when direct comparison of absolute QT duration at similar heart rates can be more reliable. Prolongation of the QT interval is a recognized side effect of many commonly used medications. This effect is most pronounced in the antipsychotic group for thioridazine, followed by pimozide. QT prolongation concerns prompted restrictions on the use of these two drugs, both of which are in the process of being withdrawn from the market, as droperidol was.

QT prolongation predisposes to the development of ventricular tachyarrhythmias such as torsade de pointes and can lead to syncope, cardiac arrest or sudden cardiac death.

There is evidence of gradations of risk among the current atypical antipsychotics. Sertindole carries a significantly higher risk of QTc prolongation than ziprasidone, clozapine, quetiapine, risperidone or olanzapine, which in turn carry a greater risk than haloperidol, sulpiride, amisulpride and aripiprazole. The clinical relevance of this hierarchy is unclear, as no increase in rates of either torsade de pointes or cardiac death has been found with any of these agents.

Sertindole had been withdrawn in 1998 following early concerns but the European Commission recommended lifting marketing restriction in 2005, after population studies did not reveal any increase in overall or cardiac mortality. Nevertheless, routine ECG monitoring with the clinical use of sertindole is strongly recommended.

Multiple factors are usually required to cause drug-induced QT prolongation, including:
- female sex
- older age
- bradycardia
- congestive heart failure
- drug interactions
- hypomagnesaemia
- hypokalaemia
- familial long QT syndrome (LQTS).

Although there is no absolute threshold for drug-induced QTc prolongation, most authors agree that QTc is less than 410 milliseconds (ms) and a increase of QTc of less than 30 ms represents a low risk. Prolonged QTc should be considered at QTc greater than 450 ms or a drug-induced increase of QTc of greater than 60 ms. In this case, serial ECGs, monitoring of potassium and magnesium levels, and careful review of risk factors should be performed. In cases where QTc is greater than 500 ms, the drug should be ceased and a cardiologist's opinion obtained. Most reported cases of drug-induced torsade de pointes occur in women with a QTc greater than 500 ms.[6]

Weight gain and other metabolic disturbances

Weight gain was originally noted with typical antipsychotics and is often a reason why patients wish to discontinue treatment. Some atypical antipsychotics are nevertheless associated with significantly more weight gain than typical agents. This is believed to occur via increased appetite and food intake, which is mediated by central histaminergic H_1-antagonism, with 5-HT_{2C} antagonism having a synergistic effect. The increase in fat is accompanied by increased levels of the adipocyte regulatory hormone leptin. This weight gain is not clearly dose-dependent and substantial individual variation occurs.[7,8]

The American Diabetes Association concluded that of the six available atypicals in the USA, clozapine and olanzapine have the most potent effects on weight gain, with risperidone and quetiapine having an intermediate effect and ziprasidone having negligible effect.[9] In addition to the weight gain, the safety advantages of the atypical antipsychotics have been challenged because of their propensity to alter glucose and lipid metabolism. This is of particular concern since clinicians do not want to subject a population with substantial physical morbidity and mortality to the increased risk of developing metabolic complications such as the metabolic syndrome (truncal obesity, atherogenic dyslipidaemia, hypertension, insulin resistance). Interestingly, these metabolic abnormalities do not appear to be necessarily related to the weight gain. Behavioural treatment of antipsychotic-induced weight gain and metabolic disturbance has met with limited success to date.

Some clinicians recommend that patients with persistent dyslipidaemia should be considered for lipid-lowering agents or even switched to atypicals with less deleterious metabolic effects. Ziprasidone, aripiprazole and possibly risperidone are considered to have a lower risk for hyperlipidaemia.[10]

Choice of antipsychotic

The decision to choose a typical or an atypical antipsychotic is often dictated by factors beyond the psychopharmacology of these agents, such as local prescribing guidelines and cost considerations. Despite substantial debate in this area, there is

a general consensus that clozapine is the only atypical clearly more effective than conventional agents for treatment-resistant schizophrenia.

New research is focusing on the comparable effectiveness of the atypicals as well as on their short- and long-term side-effect profiles. There is some evidence that there are differences in effectiveness between the atypicals.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigated the continuation rate, effectiveness and tolerability of four atypicals (olanzapine, ziprasidone, risperidone and quetiapine) with a typical antipsychotic (perphenazine) in 1493 patients with schizophrenia.[11,12] Olanzapine had a significant advantage of over risperidone, quetiapine and perphenazine, but not ziprasidone, as measured by time to discontinuation due to a lack of efficacy. Those patients on olanzapine, however, developed significantly more dyslipidaemia and weight gain than with the other drugs.

Whilst these results are welcome, clinicians are seeking more information about comparative efficacy of medications in both the short and long term, and how such data translate into real-life effectiveness and quality-of-life outcomes. Side effects play a major role in antipsychotic non-adherence and thus a case-by-case consideration of how the proposed antipsychotic medication will be tolerated is essential (Table 1). The prescribing of medication is a dynamic and ongoing process given the chronic, fluctuating nature of schizophrenia. It needs to incorporate the option of medication 'switching' (how and when?) in response to the potentially changing health status of the patient, as well as consideration of balancing long-term treatment stability versus risk of treatment-related side effects.

Guidelines from the National Institute for Clinical Excellence specify that atypical antipsychotics should be considered as first-line treatment for new patients, for patients experiencing unacceptable adverse effects caused by typical agents and for relapsing patients. The guidelines also recommend that the early use of clozapine is an essential consideration in treatment-resistant schizophrenia.[13] An update of these guidelines is pending.

Other guidelines are now available, such as the excellent International Psychopharmacology Algorithm Project (IPAP) Schizophrenia Algorithm (see http://www.ipap.org/schiz). These interactive guidelines discuss switching options and include supporting documentation relating to incorporating CATIE Phase I results into clinical decision-making, amongst other useful contributions.

Future directions

Although medications that act on the positive symptoms of schizophrenia are called antipsychotics, activity in other areas, including negative symptoms, cognition and mood have been observed. Our expectations of an antipsychotic are thus widening into broader anti-schizophrenia-type action and beyond, as these medications are finding a niche in other areas such as anxiety, behavioural disturbance, mania, depressive disorders and sleep.

There has been continuing development of antipsychotics that appear to utilize dual 5-HT$_{2A}$ and D$_2$ receptor antagonist properties. In the wake of aripiprazole may follow another partial agonist of D$_2$ and 5-HT1$_A$, called bifeprunox. Also in the pipeline are drugs such as asenapine, iloperidone and perospirone, the latter already available in Japan.

Hypotheses of antipsychotic action involving other neurotransmitter systems are starting to emerge. The glutamate hypothesis states that glutamate hypofunction is responsible for some of the symptoms of schizophrenia. This is supported by observations that blockade of NMDA receptors by ketamine or phencyclidine leads to schizophrenic-like symptoms. Clozapine has been shown to reduce the densities of some NMDA-receptor subtypes. Direct NMDA agonism is limited by excitotoxic effects; however, there is a great deal of recent interest in drugs that inhibit the uptake of the NMDA co-agonist glycine and metabotropic glutamate receptor modulators.

There has also been a greater emphasis on treating the various symptom domains of schizophrenia with their putative associated neuronal circuitry, such as negative symptoms and cognition.

Atypical antipsychotics have a much greater relative affinity for α_2-adrenoceptors than do classical antipsychotics. Underactivity of the cortical noradrenergic reward system may account for negative and cognitive deficits in schizophrenia. Preclinical and clinical work with α_2-adrenoceptor antagonists such as idazoxan supports this theory.

A theoretically attractive area of research involves the hypothetical use of α_7 nicotinic cholinergic agonists. The α_7 nicotinic cholinergic receptor has been implicated in sensory gating deficits in schizophrenia, which could underpin cognitive vulnerabilities to the development of delusional thinking. There are now approaches to target this receptor system to improve cognitive functioning and possibly attenuate the nicotine dependence so prevalent in schizophrenia, albeit without current success.

Dopamine in the dorsolateral prefrontal cortex (DLPFC) of the brain has been implicated in the cognitive deficits seen in schizophrenia such as working memory function. The catabolic enzyme catechol-O-methyltransferase (COMT) has an integral role in the modulation of dopamine activity in the DLPFC. A hypothetical approach posits that improving dopamine neurotransmission in the DLPFC by inhibiting COMT may improve cognitive dysfunction without necessarily increasing dopamine activity in the limbic areas and thus destabilizing positive symptoms.

The psychopharmacological profile of an ideal antipsychotic might be an agent that exhibited significantly greater antagonism at 5-HT$_{2A}$ than D$_2$ or D$_1$ receptors, had low affinity and fast dissociation from D$_2$ receptors (especially in the striatum and tuberoinfundibular regions) and negligible affinity for muscarinic or histaminergic receptors. A degree of D$_3$, D$_4$ and α_2 antagonism could be of benefit in targeting negative symptoms and cognitive deficits, and a low impact on the QT$_c$ interval and weight would improve tolerance. A half-life allowing daily dosing, the availability of oral and intramuscular formulations, and even an intrinsic antidepressant activity mediated via 5-HT$_{1A}$ affinity of 5-HT reuptake inhibition, would all be of additional benefit. Unfortunately, such drugs do not currently exist, yet it is encouraging to reflect on the progress made in this area with currently available atypical agents. ◆

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Practice points

- All antipsychotic medications are antagonists at dopamine D_2 receptors. Aripiprazole, a novel antipsychotic that exhibits partial antagonist activity at dopamine D_2 receptors under hyperdopaminergic condition, also acts as a D_2 agonist under hypodopaminergic conditions
- There is no consistent definition of an atypical antipsychotic; however, efficacy in treating positive symptoms of schizophrenia, low incidence of EPS, and a combination of $5\text{-}HT_2$ antagonism and D_2 antagonism are core features
- QT interval prolongation is common with atypical antipsychotics although more than one factor (e.g. drug interactions) is usually required for clinical significance. A QTc of less than 410 ms and a prolongation of less than 30 ms are thought to represent a low relative risk
- The 2002 NICE guidelines for schizophrenia support the use of atypical antipsychotics as first-line agents for new patients and patients troubled by side effects. More recent guidelines, such as the International Psychopharmacology Algorithm Project (IPAP) Schizophrenia Algorithm (http://www.ipap.org/schiz) are useful to the practising clinician