Editorial

Antipsychotic therapy over half a century:
A tale of discovery from chlorpromazine
to aripiprazole

Schizophrenia affects about 1% of the world’s population and is diagnosed primarily on the presentation of psychotic symptoms (hallucinations and delusions); and patients suffering from schizophrenia often present themselves with concomitant negative symptoms (e.g. apathy, anhedonia) and cognitive dysfunction. The illness has been known and the symptoms documented since antiquity: some of the earlier treatments, based largely on ill-founded theories, have ranged from spiritual ministrations to barbaric interventions. Even in the late 19th century, confining patients to tranquilizing chairs, bleeding and purging patients were recommended as standard treatments. In the early 20th century, insulin therapy was proposed on the belief that schizophrenia was caused by high blood sugar. In the 1930s, two treatments, electroconvulsive therapy (ECT) and brain surgery known as lobotomy, gained widespread use. Although, ECT is still appropriately useful in selected patients, the others have been abandoned for good.

The era of modern medical treatment of schizophrenia began in the 1950s. A French anaesthesiologist, Henri Laborit, found that promethazine, an antihistamine, reduced the need for anaesthesia in his patients. Its analogue chlorpromazine induced a state of ‘artificial hibernation’ in his patients and as they could withstand the stress of surgical trauma much better, Laborit recommended it to Hamon and Delay’s group in Paris who were the first to experiment with chlorpromazine for hyperactive behaviour, and their results were promising. In 1952, Rhone-Poulenc marketed chlorpromazine under the trade name Largactil® and by the 1990s, more than 40 antipsychotic drugs were introduced. These drugs revolutionized the care of the mentally ill and, from terminal and custodial disorders, they became community-based and manageable chronic illnesses. However, side-effects including extrapyramidal motor effects, hyperprolactaemia and tardive dyskinesia linked to this class of drugs have limited their success and acceptance by patients and families.

Understanding the mechanism: A classic case of reverse engineering

Modern drug discovery is supposed to proceed from mechanism to molecule to medication. In the case of schizophrenia, it happened the other way round. The medications came first, followed by the discovery of the responsible neurotransmitter (dopamine), then its receptors (dopamine D2) and finally genes associated with the receptors. Two convergent streams of discovery led to the understanding that the monoaminergic ‘dopamine system’ was involved in its actions. Nobel laureate Arvid Carlsson, in the late 1950s, used reserpine to deplete monoamines which led to hypoactivity in animals and by reversing it with L-dopa, a precursor of dopamine, the role played by dopamine in motor functions was discovered. Around the same time, the observation that amphetamine abusers presented themselves with the most elaborate psychotic symptoms which were blocked by haloperidol, linked the role of dopamine to psychosis. These two streams of observations and the discovery that...
antipsychotic potency correlated with the drug’s affinity to the dopamine D2 receptors and motor side-effects led to the understanding that antipsychotics blocked dopamine transmission in order to be clinically efficacious.8

With the advent of brain imaging it became possible to directly observe the state of the dopamine system in schizophrenia. Using single-photon emission computed tomography (SPECT) and positron emission tomography (PET), researchers have been able to confirm that patients with schizophrenia show increased presynaptic dopamine synthesis, increased dopamine release and increased synaptic levels of dopamine with a largely unchanged postsynaptic dopamine receptor density.9 While ‘subcortical’ increase in dopamine transmission is linked to positive and psychotic symptoms, evidence has also emerged about hypodopaminergia in the ‘prefrontal regions’ which is linked to cognitive and negative symptoms of the disorder.10 So the presence of concomitant cortical hypodopaminergia along with subcortical hyperdopaminergia in schizophrenia helped us to understand the success (against positive symptoms) and limitations (limited effect on negative and cognitive symptoms) of antipsychotic medication.

Refining the mechanism: Second-generation antipsychotics

As our understanding of the mechanism of antipsychotic action grew, so was the search for newer antipsychotics without the side-effects that were seen with the first-generation antipsychotics. Clozapine, introduced in the 1960s, was recognized for its benefit in treatment-resistant patients.11 However, the discovery that life-threatening agranulocytosis was associated with clozapine treatment dampened its use. In the 1990s it was reintroduced in the USA12 and since clozapine had affinity to a number of receptors, it led to the introduction of a number of antipsychotics that had affinity to receptors other than dopamine D2 (5-HT2A, 5-HT1A and alpha adrenergic alpha-1). As a result, most antipsychotics introduced in the market (olanzapine, risperidone, quetiapine, ziprasidone to name some) in the past decade have affinity to multiple receptors, even though there is little evidence that they are more efficacious than the first-generation antipsychotics, sans for their propensity to cause extrapyramidal symptoms (EPS).13

While the previous antipsychotics were all D2 antagonists, the introduction in the past decade of aripiprazole, a partial dopamine D2 agonist, presented clinicians with a new treatment option.14 The idea of a partial agonist was mooted by Arvid Carlsson way back in the 1980s when he observed that agonists had preference for the autoreceptor and could decrease dopamine synthesis presynaptically.15 Although it is not clear if aripiprazole’s actions are driven by its presynaptic actions, postsynaptically it can lower dopamine signalling as its intrinsic activity is less than that of dopamine. A number of partial agonists have failed in the clinic (e.g. preclamol, terguride, OPC-4392 and bifeprunox) and aripiprazole’s success lies in its finding the fine balance of blocking D2 receptors (and hence preventing endogenous dopamine transmission) and providing only low partial agonist stimulation.16 Antagonist or partial agonist, all clinically available antipsychotics engage the first mechanism of blocking dopamine transmission via dopamine D2 receptors. While the newer generation of drugs has fewer motor side-effects, this has been replaced with newer side-effects of weight gain, diabetes and dyslipidaemia associated with the multireceptor profile of the new medications, and thus the clinical gains made are limited.17

Antipsychotic therapy: Beyond first mechanisms and hope for the future

It has been possible to get patients out of asylums and, to a large extent, rehabilitate them back into the community, but it has not been possible to restore them to their rightful place in society. Too many stay unemployed, too many stay symptomatic, and too many fail to establish their own families and form meaningful social networks. This will require a new and different approach to drug discovery. It is recognized that the next generation of medications must go beyond addressing ‘psychosis’ but must address the cognitive and negative symptoms. A number of such initiatives have been undertaken: a public–industry partnership called ‘MATRICS’ is one such enterprise.
It focuses on developing consensus on issues such as how cognition should be measured. It also streamlines pharmacological approaches, addresses challenges in clinical trials and aims to guide regulatory approaches for treating sub-domains of this illness. Rather than hoping for a single medication with multiple mechanisms to find the ‘silver bullet’, the field is reconciling to mechanism-based add-ons. As we write this, phase 2/3 trials are testing new approaches beyond monoaminergic mechanisms: mGLU II/III especially for refractory positive symptoms; Glycine transporter-1 for negative symptoms; and Nicotinic alpha-7 for cognitive symptoms. The journey from chlorpromazine to aripiprazole has highlighted the progress made and the persisting unmet needs. We hope the coming generation of newer medications will help patients overcome the social and cognitive deficits that hold them back and claim their rightful and valued place in society.

Conflict of interest: Professor Shitij Kapur has received grant support from AstraZeneca and GlaxoSmithKline and has served as consultant and/or speaker for AstraZeneca, Bioline, BMS-Otsuka, Eli Lilly, Janssen (J&J), Lundbeck, NeuroSearch, Pfizer, Roche, Servier, and Solvay Wyeth in the past three years.

REFERENCES