The evolution of antipsychotic medication: a long-acting, injectable formulation of a second-generation antipsychotic

Schizophrenia remains one of the most devastating illnesses known to man: not only does it commonly strike young people at the threshold of their productive life, but its deteriorating, relapsing course over many years results in great emotional and financial cost to patients, carers and society at large. The introduction of the first antipsychotics raised hopes that we would be able to cure this terrible disorder; however, time has shown that, although effective against the positive symptoms of the disorder, the first-generation antipsychotics do very little to relieve other symptoms of schizophrenia and often exacerbate some of them. Furthermore, these medications produce a range of side-effects that are not only uncomfortable for the patient but also potentially dangerous, certainly stigmatising, and often resulting in non-compliance with treatment.[1]

It should be self-evident to anyone who has worked with patients who suffer from schizophrenia that the treatment of this illness is a complex, multimodal endeavour that is unlikely ever to consist of a single type of intervention, whether pharmacological or otherwise. They will also know that addressing the positive, negative and cognitive symptoms of the disorder as well as the treatment resistance that occurs in many patients requires the concerted effort of a number of different health professionals and allied health professionals. Nonetheless, pharmacological treatment remains the cornerstone of treatment without which the rest of the interventions will largely be in vain. Therefore, before we can address all the other issues involved in the treatment of schizophrenia, we must first ensure optimal pharmacological treatment.

In the past two decades, psychiatrists have become progressively more aware of the importance of early, effective and sustained intervention in the treatment of schizophrenia.[2] There is good evidence today to show that intervention in the early phases of schizophrenia will prevent further functional deterioration and that a majority of patients will achieve good outcome, at least in the short term. Over the longer term, the picture is considerably less encouraging – almost all patients will relapse within 5 years, and the principal reason for this will be non-compliance with pharmacological treatment. There are many reasons for poor compliance with treatment, but side-effects of the medication and poor insight into the importance of ongoing treatment are two important ones.

Treatment compliance and symptom remission have become increasingly important issues in the treatment of schizophrenia. Previously, much emphasis was placed on short-term efficacy and tolerability of antipsychotic medications, and results were often measured and reported as percentages of improvement in symptoms over 4 - 6 weeks. More recently, however, researchers and clinicians alike have been focusing more on functional outcomes, such as quality of life for patients and carers and social and vocational re-integration into society. This has again put into sharp focus the relative failure of current treatments to prevent the cycle of medication discontinuation, symptom relapse and incomplete response to subsequent treatment, often again accompanied by overt or covert non-compliance or partial compliance with progressively poorer functional outcomes.

The advent of the second generation of antipsychotic medications again raised hopes that, because of the improved side-effect profile and the improved effect on aspects of schizophrenia other than the positive symptoms, these medications would offer patients treatment options vastly superior to and better tolerated than the first generation of treatments. The second generation of medications did indeed prove to be better tolerated than their predecessors, and they also improved aspects of the disorder that could not be addressed adequately before. However, the vast improvement in compliance that was expected did not materialise – although compliance with second-generation antipsychotics certainly is better than it was with the first-generation medications, there is still a high rate of treatment recidivism, with the result that medication discontinuation still occurs at an unacceptably high rate.[3] There is therefore the risk that the clinical advantages that may be attained with the second-generation antipsychotics will be negated by poor compliance. Simply put, the medication cannot work if the patient does not take it.

One of the strategies to improve treatment compliance – and therefore functional outcome – has been the use of depot formulations of antipsychotic medications. Although depot formulations of first-generation antipsychotics have been available for many years they have found only limited application, mainly because of the side-effect profile and also to some extent the stigma of taking the control of the medication out of the hands of the patient and the perceived impact thereof on individual freedom. The literature on depot antipsychotics strongly suggests

that they do improve outcome, as shown in the Cochrane review of trials with depot fluphenazine.[4] Although they continue to be used in the public sector, their use in the private sector has been very limited as doctors and patients alike have opted for the greater efficacy and tolerability of the second-generation antipsychotics.

With the introduction of a long-acting, intramuscular formulation of risperidone (Risperdal Consta), psychiatrists and their patients now for the first time have available a compound that combines the advantages of assured medication delivery with the improved tolerability profile of a second-generation antipsychotic. Patients need only have a single injection every fortnight to ensure adequate levels of risperidone for the treatment of schizophrenia. Absolute medication compliance has therefore become a more realistic goal for many patients.

Risperidone long-acting injection (RLAI) has been proven to be effective and safe in a number of studies in subjects with recurrent schizophrenia;[5,6] however, a most significant development has been the use of this compound in subjects with first episodes of psychosis.[7] The use of a long-acting, intramuscular formulation of an antipsychotic medication in subjects with first onset of psychosis seems counter-intuitive, but when we stop to evaluate the arguments surrounding the issue, I believe that the prejudice against such a treatment modality can be overcome.

Many clinicians who have worked with psychiatric disorders over long periods still seem to fail to recognise the fact that patients with schizophrenia, and in particular those in the early phases of the disease, face many obstacles to compliance: they are often bewildered and paranoid, and may have been admitted and treated against their will. They do not understand why they had to come to hospital and why they had to get treatment. Furthermore, they are often discharged from hospital long before the illness is in remission and may therefore still have active delusional thinking when they are discharged. Patient psycho-education programmes in this country – as in many others – are very limited and often not particularly effective in patients who are in the active phase of the illness. Disorganisation is an integral part of many patients' disorder – when you are not yet able to organise your thoughts properly, how can you be expected to understand a complex brain disease and, even more importantly, remember to take your medication? Insight into the nature and treatment of psychiatric illness is something that does not develop overnight. It takes many months and even years for healthy individuals to come to understand the complexities of psychiatric disorders – in fact many so-called healthy people and societies never reach that goal – yet we expect our patients to attain it during the brief and chaotic time of their first admission to hospital. We expect them to use their logical brain to integrate all the information, yet it is this very logical brain that is dysfunctional during the psychotic illness! Furthermore, families are often divided in their level of insight and commitment, and it is not uncommon for family members to be ambivalent about treatment. Also, family members often harbour anger towards and fear of the patient, due to sometimes traumatic months and years that precede the first admission, and are therefore either afraid to put pressure on the subject or unwilling to because of resentment. Because they do not have the privilege of years of experience like we do, they find it difficult to grasp the importance of sustained treatment over long periods of time.

We now have robust evidence that untreated psychosis is detrimental to the brain and to the long-term outcome of schizophrenia. We also know that poor compliance is a very real problem in this patient population. No effort should therefore be spared to improve compliance and thereby prevent the 'toxic' effects of psychosis on the brain. A long-acting, injectable formulation of an atypical antipsychotic is probably one of the best pharmacological tools that we have available at this point. At the very least it will provide patients and doctors with an additional treatment option to those currently available, but in the ideal situation a patient in the early phases of illness will start on this medication and, if effective, maintain treatment for the full prescribed period, ensuring the best possible outcome that modern psychiatry can provide. Long-acting, injectable risperidone is clearly a step forward in the evolution of antipsychotic medications.

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