

# Research Review

## SPEAKER SERIES

Optimal outcomes in treating schizophrenia  
– strategies for relapse prevention early in illness May 2009

This publication is a summary of a recent presentation in Auckland by Dr Robin Emsley from the University of Stellenbosch, Cape Town, South Africa on the management of schizophrenia, with particular focus on the use of long-acting injectable risperidone (Risperdal® Consta®; Janssen-Cilag) in achieving sustained remission in early disease.



### Robin Emsley

Robin Emsley is Professor and Chair of the Department of Psychiatry, University of Stellenbosch, Cape Town, South Africa. He obtained his medical degree at the University of Cape Town in 1974, and his psychiatry degree with distinctions at the University of Stellenbosch in 1981. He was awarded a Doctorate in Medicine in 1987, for studies on the neuro-endocrinology of schizophrenia and alcohol dependence and obtained the degree D.Sc. in 2007 for studies in the psychopathology, neurobiology and psychopharmacology of schizophrenia. He serves on several national and international professional and scientific committees and advisory boards, and is the recipient of various research grants and awards. His main area of interest is in the psychopharmacology of schizophrenia. His group has published extensively in this field. He is on the editorial board of several international journals, including *Schizophrenia Research*, *Early Intervention in Psychiatry*, *Psychiatry* 2008, the *Open Psychiatry Journal*, the *Open Clinical Trials Journal*, the *Open Neuropsychopharmacology Journal* and is the past Editor of the *South African Journal of Psychiatry*. He is involved in the development of mental health advocacy and support organisations.

**Publications: 182 articles in scientific journals; 17 letters to the editor; 14 Chapters; 3 Books**

## Management of early schizophrenia

Schizophrenia is an incapacitating brain disease with a diverse accumulation of psychological symptoms, and remains one of the main challenges facing modern medical science. How the diverse range of symptoms that are associated with the disease are able to exist simultaneously has not yet been ascertained. It is the most costly disease treated by psychiatrists,<sup>1</sup> with significant financial and social costs.<sup>2</sup> Estimated direct and indirect costs in the UK are £2 billion and £4.7 billion, respectively, with £615 million spent by families for informal and private care. Not only do patients and their families have to deal with these costs, they also have to deal with the fact that it is still a much stigmatised disease.

Chlorpromazine was the first major pharmacological breakthrough that changed the way patients with schizophrenia were managed in clinical practice. Many other agents have since been introduced, from the older conventional antipsychotics through to the new generation agents. The development of many of these new agents focussed on mechanisms of action involving glutamate, serotonin, etc, but it now appears that dopamine receptor-2 (D<sub>2</sub>) antagonism is fundamental to the antipsychotic effect, particularly for providing quick treatment of acute psychotic symptoms.

Contrary to beliefs commonly held some years ago, antipsychotic agents are very effective in the treatment of psychosis. They are also very quick acting, with very good evidence showing that the greatest reduction in core psychotic symptoms is seen within the first two weeks after treatment initiation.<sup>3</sup> This early onset of action has also been seen in early psychosis, which is the period of illness when patients are most likely to respond, with 80% of patients achieving response within the first 4 weeks of treatment (see figure 1).<sup>4</sup> Furthermore, the patients who did not respond within 4 weeks did achieve response as long as they continued to receive antipsychotic medication.

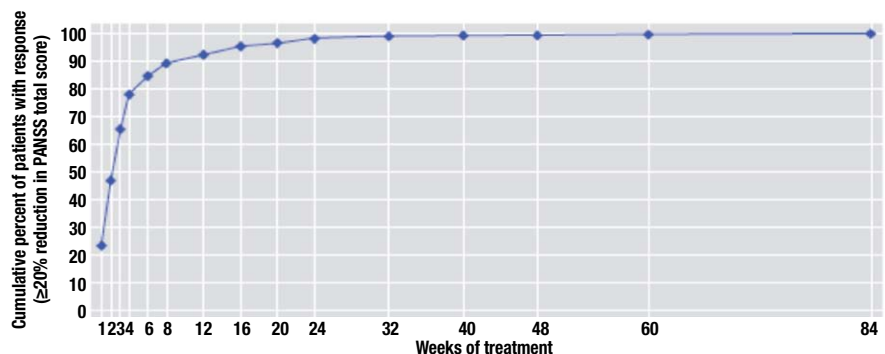


Figure 1: Time course for antipsychotic treatment response in first episode schizophrenia<sup>4</sup>

Available from URL: <http://ajp.psychiatryonline.org/cgi/content/full/163/4/743>

## Relapse rates in schizophrenia

Although data show that antipsychotic treatment can achieve a rapid response, schizophrenia is a chronic, relapsing disease. The reality for the majority of patients in clinical practice is characterised by relapses and hospitalisations, persistent symptoms, cognitive and psychosocial function deficits, and high rates of unemployment, homelessness and suicide.<sup>5-7</sup> Robinson and colleagues published data in 1999 indicating that the relapse rate 24 months after a first schizophrenia episode (n=104) under ideal circumstances was 54%, and this increased to 82% at 5 years.<sup>8</sup> Also, among patients who recovered after a first relapse, 78% experienced further relapse(s). Moreover, the strongest predictor for relapse was discontinuation of antipsychotic therapy, and this reflects the common scenario seen in clinical practice of 'revolving door' patients.

## About Research Review

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## Toxic psychosis hypothesis

Schizophrenia relapse is an issue that needs to be addressed, as it is now known that relapses can have serious consequences, and a stepwise deterioration after each relapse is often observed. Evidence suggests that schizophrenia is a progressive encephalopathy. It has been hypothesised that as long as active psychotic symptoms are present, the disease progresses and the patient deteriorates further. This 'toxic psychosis' hypothesis is supported in brain imaging studies showing that grey matter loss increases over time in patients with schizophrenia, and that patients who have experienced the longest durations of psychosis, due to either longer duration of untreated psychosis or frequent relapses, have the greatest loss of grey matter. Regardless of whether or not this hypothesis is correct, the psychosocial consequences of relapses can be devastating, particularly in the early stages of the disease as they are often young patients who are prone to become withdrawn as a result. It is therefore important that the healthcare workers treating these patients are doing everything they can to prevent relapse.

## Early years of psychosis

Early psychosis is the critical period when the illness appears to be at its most aggressive, and what happens following prodrome and a first episode of psychosis is important. Typically, a patient's first episode is treated and they respond, after which there is pressure to discharge them. From this point, there are many possible outcomes, which can be broadly categorised into one of three groups (see figure 2).<sup>9,10</sup> There seems to be a critical period of around 4–5 years during which patients experience multiple relapses requiring treatment, but each relapse is associated with further deterioration in their functioning level. In the chronic stable phase, these patients continue to experience further relapses. Such patients are considered to be 'chronic relapsing', and they make up the majority of patients. Another undesirable outcome is that the patient improves, but not to a desirable extent, and continues to have ongoing symptoms without relapsing or achieving remission or relapse. Such patients are referred to as 'partial responders' and are representative of most of the patients seen in the outpatient setting. There is a close association between partial response and partial medication adherence. Missing even a few days of treatment can greatly increase the risk of rehospitalisation and breakthrough symptoms. In the ideal world, patients would continue their medication and improve, and achieve a state of sustained remission, thereby increasing their chance of a relatively normal life.

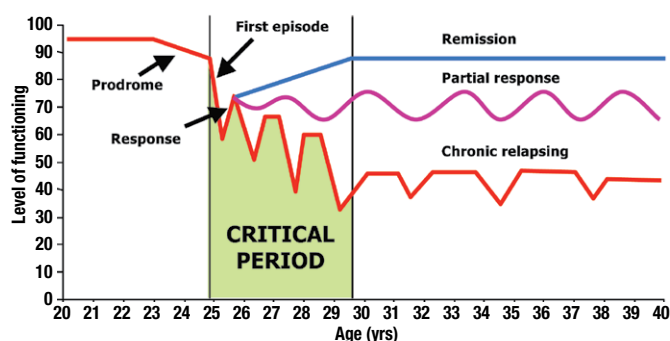


Figure 2: Possible outcomes after acute treatment response in first-episode schizophrenia<sup>9,10</sup>

## Discontinuation rates with oral antipsychotics

The use of oral antipsychotics in first episode psychosis has been well studied. The CAFÉ study is a typical example of such a study that reported the effectiveness, as assessed by any-cause discontinuation, associated with oral olanzapine (mean modal dosage 11.7 mg/day), quetiapine (506 mg/day) and risperidone (2.5 mg/day).<sup>11</sup> The rates of any-cause discontinuation during the first treatment year with these three drugs were similar and around 70%. This rate is consistent with other long-term studies and clinical practice, suggesting that current treatment of first episodes of psychosis is inadequate.

## Remission as a treatment goal

The goal of treatment should be sustained remission, rather than just a partial response. An expert group from the US recently published a definition of remission in schizophrenia that comprises two parts.<sup>7</sup>

1. The patient should have become asymptomatic in the core symptoms, or at least exhibit only mild symptoms; score of  $\leq 3$  on eight PANSS items.
2. The patient should remain asymptomatic for  $\geq 6$  months.

Professor Emsley and colleagues investigated how these criteria for remission measured up in a group of 462 patients with a first episode of psychosis treated with oral antipsychotics.<sup>12</sup> While symptomatic remission was initially seen in 70% of patients, only 24% (approximately one in three responders) met the full remission criteria by remaining asymptomatic after 6 months.

## Medication nonadherence in schizophrenia

It is likely that nonadherence to medication is a major factor in poor maintenance of remission, as it is a big problem in psychiatry as well as in general medicine. There are many devices available that are designed to help compliance, and in general they are useful for reminding patients with chronic illnesses that it is time to take their medications. However, patients with schizophrenia also exhibit impaired insight, and 50–80% of patients do not believe they have an illness, or that they need long-term treatment.<sup>13</sup> This lack of insight is not limited to schizophrenia, and is an example of anosognosia (neurological deficit characterised by unawareness of an impairment). There are other conditions in which anosognosia occurs (e.g. stroke, Alzheimer's disease, cortical blindness), and it is typically due to damage to the areas of the brain required for awareness of the disease. Studies have shown that frontal and parietal brain areas are important for insight, particularly the dorsolateral prefrontal cortex, which is also very important in schizophrenia. Therefore, lack of insight in patients with schizophrenia means that devices reminding patients it is time to take their antipsychotic medication are of limited value, as noncompliance is often not just due to forgetfulness as it is in many other chronic diseases.

There are several important measures that can be adopted to help improve compliance with treatment in patients with schizophrenia. Measures that engage the patient and their family include psychosocial education, family involvement, a good doctor-patient relationship and 'compliance therapy'.

Treatment-related factors also play an important role in patient compliance. Reducing adverse effects helps to improve adherence, as does achieving remission.

## Oral versus IM administration

More recently, the route of antipsychotic administration, specifically oral versus intramuscular (IM), has been receiving attention as a contributor to patient adherence. Conventional depot IM antipsychotics were developed in the 1960s to address poor medication adherence, and were subsequently used extensively for this purpose and were very effective. However, they are typically used only for difficult to manage patients who have been nonadherent with frequent relapses, and as a result they have acquired a reputation of being a punitive measure for patients who will not take their oral medication. Consequently, IM depot antipsychotics have usually only been used in the chronic stage of illness. However, referring back to figure 2, it is clear this is not the most appropriate approach, as the IM formulations were developed specifically to address adherence and prevent relapse, and by the time most patients receive such treatment, the disease has progressed and the patient has already entered the chronic relapsing or partial response phase. It is much smarter to use these formulations to treat early disease and prevent relapse, as is extensively practiced in other morbidities (e.g. malignancies).

## Long-acting injectable risperidone in the treatment of subjects with recent-onset psychosis

Professor Emsley and colleagues conducted a study to assess whether or not long-acting injectable risperidone can be used to effectively manage early psychosis without relapse occurring.<sup>14</sup> In this open-label study, 50 patients with newly diagnosed schizophrenia or schizophreniform disorder received long-acting risperidone 25–50mg every 2 weeks for 2 years. The all-cause discontinuation rate was 28%, with participants discontinuing due to consent withdrawal (n=5), insufficient response (3), relocation (3), loss to follow-up (2) and relapse (1). The data from the 72% of the participants who completed the study were compared with those from 47 participants who received oral risperidone or haloperidol in a trial with an otherwise identical protocol.<sup>15</sup> The comparison showed that while response was similar in the early weeks of treatment, mean PANSS score was greater with the injectable preparation than with the oral treatment from about 40 weeks onwards (see figure 3). The difference at the end of treatment was approximately 14 points on the PANSS scale, which represents a clinically significant difference. Of note, the difference is probably due to discontinuation or skipping doses of the oral antipsychotics, rather than any difference in potency of the formulations.

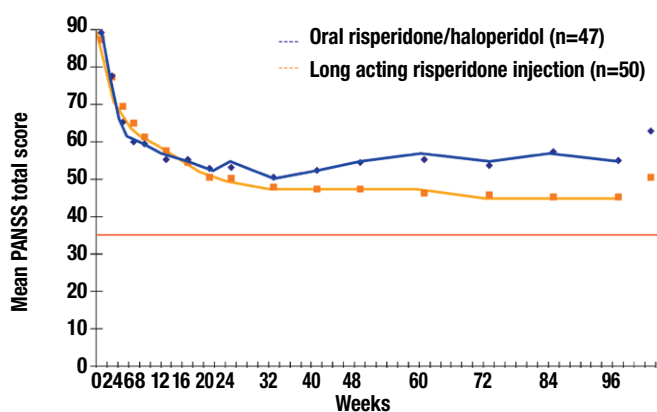


Figure 3. Shift in PANSS total scores for oral antipsychotics and long-acting injectable risperidone<sup>15</sup>

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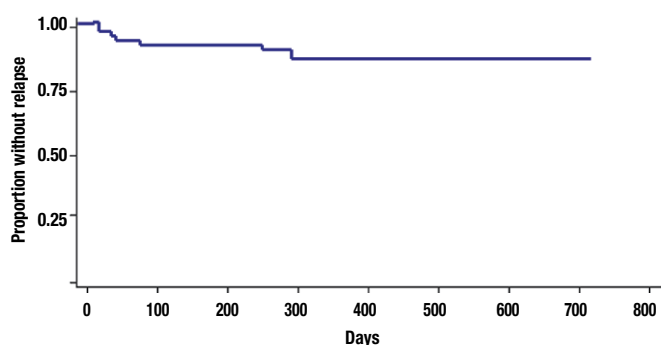


Figure 4. Relapse (according to broadly defined criteria) associated with long-acting injectable risperidone over 2 years<sup>14</sup>

Available from URL: <http://tinyurl.com/JClinPsychopharmacol-28-210>

### Effects on relapse rate and remission

The relapse rate over the 2-year study period among participants who responded was low, with only four participants relapsing, but notably none of these relapses occurred in the second 12-month period (see figure 4).<sup>14</sup> Using the remission criteria of Andreasen et al,

symptomatic remission was reported, as expected, in 70% the participants. However, this time, full remission was sustained for 6 months, according to the second part of the definition, in 64% of participants, and even on to the end of the study (24 months) in 62% (see figure 5).<sup>16</sup>

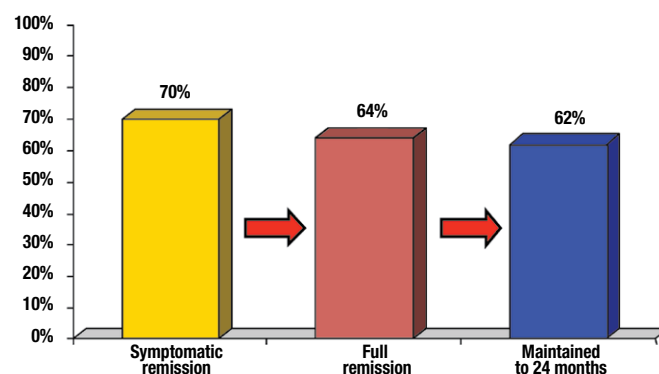


Figure 5. Remission rates for long-acting injectable risperidone over 2 years<sup>16</sup>

### Adverse effects

Overall, long-acting injectable risperidone was well tolerated.<sup>14</sup> Adverse events were typical for antipsychotics, and included extrapyramidal symptoms, bodyweight gain and hyperprolactinaemia. Hyperprolactinaemia is an important adverse effect associated with risperidone as many patients are young when they first experience symptoms, and sexual dysfunction associated with elevated prolactin levels is significant for them, and therefore may be an important reason for noncompliance. The prolactin-related adverse event profiles were similar between the oral and injectable risperidone trials. However, other studies investigating long-acting injectable risperidone have often shown lower prolactin levels and fewer prolactin-related adverse events than are typically seen with oral administration. This is thought to be due to the lower blood concentrations required to achieve steady state with the injectable form, thereby eliminating the peaks and troughs associated with oral administration, and it is the peaks that are typically associated with the emergence of adverse effects.

It must be remembered that the study was an open-label study with relatively few participants, so the findings need to be interpreted with caution. However, the results do suggest that long-acting injectable risperidone is effective, with high remission rates and low relapse rates, and is generally well tolerated. Additional larger comparative studies are warranted.

**Summary of results for patients with a first episode of psychosis treated with injectable long-acting risperidone compared with oral antipsychotics<sup>14,15</sup>**

- Low discontinuation rates
- High remission rates
- Few relapses
- Generally well tolerated

## Attitudes to injections versus tablets

An important issue that needs to be addressed is attitudes associated with patients receiving injections. Psychiatrists tend to believe that patients will prefer oral therapy to regular injections; however, this perception may not be accurate. A European survey questioned both patients and psychiatrists on their perceived preferences for oral and injection medication forms.<sup>17</sup> The results indicated that psychiatrists expected patients to see greater advantages with tablets, but they believe injections offer more benefits and assume patients will disagree (see figure 6). However, the patients thought that the advantages of injections outweighed the disadvantages. While the survey was quite small, the findings do suggest that psychiatrists' beliefs that patients do not prefer injections may not be consistent with what patients actually prefer.

### Choosing the route of administration

Choosing the route of administration for antipsychotic medications needs to be a shared decision-making process in which the patient is provided with as much information as possible. However, ultimately the patient will look to their healthcare professionals for guidance. How the options are offered to the patients is therefore critical. If patients are just asked if they would prefer tablets or injections, they tend to choose tablets. However, if patients are informed of the benefits of long-acting injections (e.g. patient doesn't have to remember to take the tablets or have someone check they have taken them, more likely to keep patient well and out of hospital), they tend to choose the injections. Moreover, patients who have chosen to receive long-acting injections also often prefer to continue with them in the long term.

## Considerations for long-acting injectable risperidone

Injections of long-acting risperidone are generally well tolerated and severe injection-site pain is quite unusual, but concern has been raised about severe injection pain in young patients, particularly Maori patients. While this needs to be further investigated, it was suggested that ensuring the injection is at room temperature and good administration techniques (including not showing the needle to the patient more than is necessary) may help reduce pain and improve patient co-operation.

The lag time between the administration of long-acting injectable risperidone and steady state blood concentration often results in a corresponding lag time to clinical improvement. Psychiatric healthcare professionals should also be aware that other substance abuse can result in re-emergence of symptoms in patients who had been stable on a therapeutic dose.

Unfortunately, NZ funding regulations do not currently allow the use of long-acting injectable risperidone for first-line treatment of early schizophrenia; however, the earlier such treatment can be started the better. There should also be no need to switch to oral therapy at a later stage, and long-acting injectable risperidone treatment should be regarded as life-long therapy, as the risk of nonadherence after switching to oral treatment continues, and the consequent potential deterioration can make ongoing management difficult.

### Managing adverse effects

For patients who do experience adverse effects, particularly hyperprolactinaemia, a dose reduction or increasing the dose interval to 4 weeks may help. Also, phosphodiesterase-5 inhibitors have been found to be an effective option for

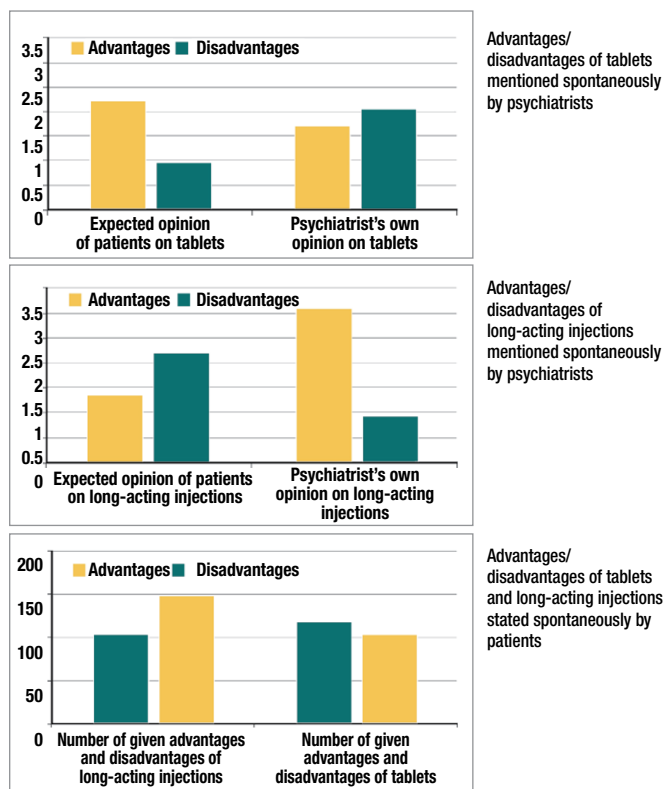


Figure 6. Attitudes of psychiatrists and patients towards long-acting injectable versus oral medications<sup>17</sup>

managing risperidone-associated erectile dysfunction in young men who are otherwise doing well on their treatment. While this is generally an expensive option in NZ as these drugs are not funded and many patients are receiving benefits, patients who are under section may be eligible to receive financial support from social services. Other treatment options need to be considered in patients with excessive adverse effects, as well as those who do not respond to risperidone.

### Take home messages

- Patients are more responsive to treatment during early psychosis.
- Risks for relapse and partial response are grave.
- Continued treatment promotes sustained remission and offers best chance of optimal outcomes.
- Long-acting injectable antipsychotic treatment appears to be a good choice for optimising outcomes (although further comparative studies are needed to confirm).
- Patients may not be as averse to receiving long-acting injections as psychiatrists believe.

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