

Research Review

SPEAKER SERIES

Practicing Evidence-Based Treatment of Schizophrenia: Now and Future
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About Research Review

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This publication is a summary of a recent presentation by Professor Herbert Meltzer, Bixler/May/Johnson Professor of Psychiatry and Professor of Pharmacology at the Vanderbilt University School of Medicine, USA. He spoke about evidence-based current and future treatment practices in schizophrenia in his address to mental health professionals at the RANZCP 2010 Congress, held recently in Auckland.

Development of somatic treatments for schizophrenia

The serendipitous discovery of chlorpromazine in the 1950s and the subsequent emergence of a number of other antipsychotics (haloperidol, fluphenazine, thioridazine, loxapine, perphenazine) helped to elucidate the neuropathology of schizophrenia, with the evidence suggesting that dopamine-receptor blockade is essential to clinical antipsychotic activity. The drugs that were developed were primarily dopamine (D₂)-receptor blockers (the typical antipsychotics) and proved to be highly effective for treating psychosis but carried a significant risk of severe extrapyramidal symptoms (EPS) and tardive dyskinesia (TD).

Clozapine was also discovered in the 1950s and demonstrated that it too could effectively treat psychosis, without causing EPS. Abandoned in the 1970s and 1980s because of its association with agranulocytosis, clozapine was reintroduced upon the results of a landmark trial in 1988 showing its efficacy in treatment-resistant schizophrenia¹, followed by pharmacological data suggesting that the efficacy of clozapine and its lower risk of EPS is due to its more potent 5-hydroxytryptamine (HT)_{2A} receptor-blockade in addition to the D₂ receptor-blockade.² This pharmacological model inspired a new category of drugs, the second-generation or atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole). This model persists as the backbone today of the latest antipsychotic agents – asenapine, paliperidone, and iloperidone.

Clinical advantages of long-acting formulations

Substantial clinical advantages offered by long-acting formulations of typicals introduced in the 1970s and atypicals in the 1990s and later (e.g. risperidone in 2003, with a long-acting formulation of paliperidone palmitate expected soon) include reduced dosing frequency (once-monthly) and greatly improved patient adherence. The long-acting injectable (LAI) formulation of risperidone (Risperdal[®] Consta[™]) does not require any elaborate preparations, which has made it very popular in the USA. Other somatic treatments that have been developed out of the serotonin-dopamine hypothesis include pimavanserin, a selective 5-HT_{2A} antagonist.

While these drugs are enormously helpful for a variety of individuals differing in genetic makeup, the medications achieve ideal results in only a small proportion of patients. "Rational" polypharmacy may be a way of augmenting receptor-binding properties of antipsychotics and thereby increasing their efficacy in greater numbers of patients. Exciting new potential approaches to augmentation treatment that show promise in animal models include agents that possess potent muscarinic anticholinergic properties (M₁ and M₂ agonists), α 7 nicotinic receptor agonists, 5-HT₆ and 5-HT₇ antagonists, mGluR2 and mGluR5 agonists, D₁ agonists and γ -aminobutyric acid (GABA)-enhanced antipsychotics, e.g. BL-1020.

Atypicals preferable

Considering side effect profiles (not just efficacy), using a typical antipsychotic cannot be justified over an atypical antipsychotic, in Professor Meltzer's opinion. Atypicals decrease the risk of acute and chronic EPS and TD, and show superior efficacy in neuroleptic-resistant patients, e.g. clozapine; high-dose olanzapine for up to 6 months may be as effective as clozapine – a possibility that is being examined with high-dose Risperdal Consta. Compared with typicals, atypicals produce superior improvement in some domains of cognition, are more effective for positive, negative, cognitive and mood symptoms; notably, clozapine decreases the risk for suicide by about 80% and seems to be associated with a substantially lower mortality than any other antipsychotics.³⁻⁶ Clozapine should be suggested as a treatment option to suicide survivors, to prevent future attempts, advises Professor Meltzer.

Key biological differences between typicals and atypicals

Atypical antipsychotics are a heterogeneous group of 5-HT_{2A}/D₂ antagonists with varying patterns of receptor affinities and dissociation.⁷ Except for risperidone and paliperidone, atypical antipsychotics do not cause the hyperprolactinaemia associated with all typical compounds.⁸ Atypical, but not typical antipsychotics, enhance cortical and hippocampal dopamine and acetylcholine efflux, both of which are thought to contribute to improved cognition in patients with schizophrenia, and in animal models the atypicals can reverse phencyclidine (PCP)-induced cognitive deficits, whereas typicals have no effect.^{9,10} Notably, preclinical data show that the atypical amisulpride is a potent competitive antagonist at 5-HT_{7A} receptors; it is proposed that the 5-HT₇ receptor antagonism, rather than D₂/D₃ receptor antagonism, underlies the atypical antipsychotic actions of amisulpride.¹¹

Serotonin_{2A}-dopamine ratio an important concept

Additional data about to be submitted for publication by Professor Meltzer and colleagues provide new evidence that the 5-HT_{2A}-D₂ ratio is a valuable concept to pursue. Significantly more of acutely psychotic patients with schizophrenia met the response criteria (20% improvement in PANSS) at 2 weeks when treated with combination risperidone 2 mg plus pimavanserin than those given risperidone 2 mg (low-dose) alone or risperidone 6 mg monotherapy (high-dose) [see Figure 1 on next page]. Whereas at 6 weeks the 6 mg dose showed comparable efficacy to the combination treatment arm, the 2 mg dose remained ineffective.

Notably, risperidone-induced side effects were dramatically reduced with combination treatment; \geq 7% weight gain was experienced by approximately 6% of patients in the combination treatment arm versus around 16% of patients receiving low-dose risperidone and 18% of those in the high-dose risperidone group ($p < 0.05$ for comparisons with combination treatment). Compared with all other treatment arms (including haloperidol alone and in combination with pimavanserin), combination treatment had the lowest rates of EPS and elevations in prolactin levels. Professor Meltzer observed that this type of potentiation has been seen in preclinical studies with other atypicals such as clozapine, olanzapine and aripiprazole.

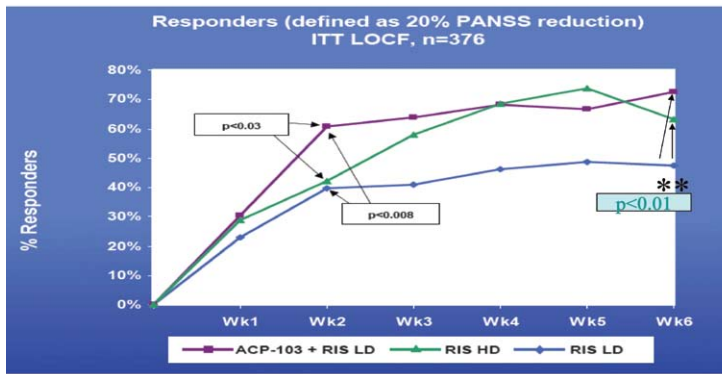


Figure 1. Response rates at 2 weeks for risperidone 2 mg/day + pimavanserin, risperidone 2 mg/day + placebo, and risperidone 6 mg/day

trials are needed to establish treatment resistance. This information is critical for informing whether or not to instigate clozapine or potentially some high-dose strategy (not involving atypicals, which do not operate on this basis). An adequate trial entails the patient taking the medication for at least 6 weeks and at adequate doses. Professor Meltzer notes that physicians frequently consider that the patient has had an adequate trial, when the patient has actually not adhered to treatment. In this early phase of determining treatment-resistance, LAI atypicals are not appropriate for a non-adherent patient. If the patient fails to respond after two adequate trials, the IPAP algorithm recommends clozapine.

RANZCP guidelines for treating relapses

The IPAP algorithm is largely concurrent with the Royal Australian and New Zealand College of Psychiatrists guidelines for antipsychotic drug management of relapse. Areas that could be improved upon include the statements shown in Figure 3 on next page.

- The recommendation to restart a relapsed patient on a typical is a more positive statement about the use of typical antipsychotic drugs than Professor Meltzer would personally endorse.
- The apparently negative attitude towards LAIs is unfortunate – Professor Meltzer advises that it would be more helpful to identify whether the patient is treatment-resistant. In proven cases of treatment resistance, the suitability of clozapine can be re-examined.
- Instead of considering a depot as a last resort, it should be an option physicians feel comfortable using in a first-episode schizophrenic patient, says Professor Meltzer. Ten percent of all first-episode schizophrenic patients are treatment-resistant – these patients must be given clozapine and early on. If clozapine is only thought of as a treatment for someone who has been ill for 5 or 10 years, a valuable opportunity is being lost.
- If any of those first-episode patients are not responding, if they stop their oral medication and relapse, the way to ensure that they get their medication is by using long-acting depot/injectable, with some patients needing 75 mg of Consta and others only 25 mg; doses below 12.5 mg are not advisable, advises Professor Meltzer.

Guidelines for carers and patients with schizophrenia

Professor Meltzer praises the Australian and New Zealand guidelines for emphasising every principle that he uses in his practice, in regard to finding the *right type and dosage* of atypical to treat symptoms with the fewest side effects, and he agrees with the advice that the *older drugs produce more side effects*, especially if used in high doses. It is especially true, in Professor Meltzer's experience, that *it can take time* to find the most effective medication and dosage – he advises giving the medication a chance to work, before switching to an alternative. The guidelines emphasise the importance of taking an atypical, in view of the risk of EPS associated with older typical antipsychotics. The guidelines greatly underestimate the risk of TD (5%) associated with typical antipsychotics; it is more like 20–25%. The risk of TD increases by 2% per annum, and in postmenopausal females and for older patients, the risk can increase by 50–100% per annum. Patients should know that they do not have to risk developing TD if they take an atypical. The single failure of the guidelines is their *failure to discuss adherence and nonadherence and the bland discussion of LAI medication formulations*; Professor Meltzer would like the guidelines to highlight for patients the relationship between adherence and relapse.

Antipsychotic use in Australasia

Between 1995 and 2001, drug utilisation data for oral conventional, depot and atypical antipsychotic medications in Australian States and Territories reveal a marked increase in oral atypicals (from around 20% comprising risperidone and clozapine in 1995 to nearly 80% in 2001), a decrease in use of conventional first-generation oral agents (from 40% to less than 10%) and a reduction in the use of depot formulations (from 40% to about 12%).¹²

The uptake of atypicals was slower in New Zealand, with oral conventionals accounting for around 50% of prescribing in 2000, depot formulations around 20%, and atypicals about 30%.¹³ Risperidone depot became available in New Zealand in 2003. By 2004, prescribing patterns for atypicals showed they were the preferred treatments for outpatients with psychotic illness; 82.5% of all antipsychotics were atypicals: oral risperidone (30.9%), olanzapine (30.3%), quetiapine (17.1%), clozapine (26.3%), and depot risperidone (0.4%).¹⁴ The clozapine data are exciting for Professor Meltzer, who surmises that this cohort represents most of the treatment-resistant patients and some suicidal individuals. Professor Meltzer notes that the use of long-acting risperidone has increased since then to around 7%. He questions if this is sufficient, with evidence suggesting that up to 50% of patients with schizophrenia discontinue their oral medication within 6 months of an acute episode. The rate of treatment discontinuation is probably higher, advises Professor Meltzer.

Delayed response in treatment-resistant patients

While the study by Kane et al. demonstrated the superiority of clozapine over haloperidol in treatment-resistant schizophrenia, only 30% of patients had responded within 6 weeks of starting clozapine.¹ Around half of treatment-resistant patients who respond will do so by about 6 weeks, the other half take up to 6 months. In a long-term follow-up study in which 36 of 51 treatment-resistant patients had responded to clozapine at 6 months, 16 patients did so within 6 weeks, with another 12 between weeks 6 and 13, then 8 more responded between weeks 13 and 52.¹⁵ Evidence from several studies since then suggests that other serotonin-dopamine antagonists used in a similar manner produce this clozapine-like effect, indicating that the duration of an adequate clozapine trial is 9 months or longer for identifying the majority of possible responders.

International Psychopharmacology Algorithm Project

In 1996, the IPAP Scientific Advisory Board And Technical Group developed an algorithm for use of antipsychotics in treatment-resistant schizophrenia [see Figure 2]. Professor Meltzer emphasises that the core regimens of two

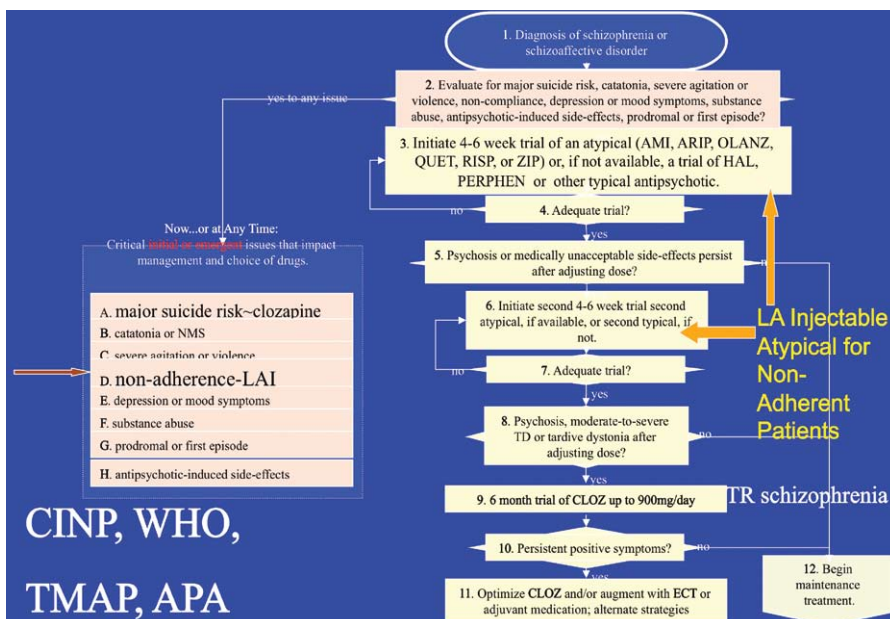


Figure 2. IPAP algorithm for treatment-resistant schizophrenia (available on www.ipap.org)

The skeptics

Critics contend that atypical antipsychotics do not represent the advance in drug therapy that we have been led to believe. Nobel laureate Dr. Eric Kandel proclaimed in 2008 there have been no advances in drug treatment of schizophrenia since the discovery of chlorpromazine in the early 1950s. In 2009, Peter Tyrer and Tim Kendall from Imperial College London claimed in a Lancet editorial that doctors and psychiatrists have been manipulated by the drug industry into prescribing second-generation antipsychotics that are no more efficacious or safe than the earlier antipsychotics, fail to improve specific symptoms, and are less cost-effective.¹⁶ Tyrer and Kendall go on to say that the atypicals are only a spurious invention, “cleverly manipulated by the drug industry for marketing purposes and only now being exposed”. They conclude that “first-generation drugs, if carefully prescribed, are as good as most second-generation drugs in many if not most patients with established schizophrenia”.

Professor Meltzer notes that while practicing US-based physicians have largely ignored Tyrer and Kendall, policymakers have not, which has led to increasing difficulty in accessing atypical drugs in the USA. In Professor Meltzer’s view, the editorial by Tyrer and Kendall is a spurious attack on the pharmaceutical industry.

CATIE and CUTLASS implications

That editorial was produced in response to the controversial CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) outcomes, which give the impression that newer atypicals are not superior to older antipsychotics.¹⁷ The findings of the CUTLASS (Commentary on Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) study add to the questions raised by CATIE about the relative effectiveness of second-generation antipsychotics and first-generation antipsychotics.¹⁸ Such data indicate that the most effective antipsychotic treatments have yet to be discovered for patients with schizophrenia.

Importantly, a careful appraisal of the CATIE study by the leading clinical trial statistician, Helena Kraemer, contends that its design and methods have been misinterpreted – the study goals, statistics, and inadequate power do not support appropriate clinical interpretation of the conclusions.¹⁹

Professor Meltzer highlighted the importance of the Finnish epidemiological study (Tiihonen et al., 2006), which involved 2230 patients and analysed the same endpoints as in the CATIE study – time to discontinuation and relapse.²⁰ Perphenazine depot performed outstandingly compared to every other drug, except clozapine, which did as well as the depot formulation of perphenazine. These two medications were superior to all others in terms of patient adherence, willingness to stay on medication, while oral perphenazine was amongst the worst performers for these outcomes. In regard to rehospitalisation rates, perphenazine depot users were at lowest risk, while oral perphenazine was significantly less effective. Professor Meltzer pointed out that it is not the molecule that matters, but rather, the route of administration: the continuous medication associated with a depot formulation assures better outcomes. Risperdal Consta was not available at the time of this study – Professor Meltzer predicts that it would have been even better than perphenazine depot.

The impact of medication nonadherence

Many reasons exist as to why patients discontinue their medication, including level of subjective distress, side effects attributed to the medication, with the

- *If patient has been in remission with good quality of life and has no tolerability problems, restart or continue the typical*
- *If relapse occurs on depot/injectable, review need for it within psychoeducational framework.*
- *Switch to typical depot represents last resort*
- *If depot/injectable really needed, consider lowest dose possible and maximum dosing interval*

Figure 3. RANZCP CPG Team for Treatment of Schizophrenia

burden varying between patients.²¹ Nonadherence to antipsychotic medication regimens increases symptom severity, increases relapse rates, increases rates of hospitalisation and suicide, and negatively impacts on functioning and course of illness.

Professor Meltzer noted that a major disadvantage with oral medication regimens is the fact that physicians cannot readily assess whether patients are adherent – nonadherence can be mistaken for efficacy problems and consequently, an incorrect treatment plan is put in place: medication may be discontinued when it was or would have been effective; excessive dosage may be prescribed and taken intermittently; and polypharmacy may be inappropriately prescribed.

Discontinuing medication has been documented to be the most powerful predictor of first-episode relapse.^{22,23} In a cohort of 104 patients with schizophrenia who responded to treatment with oral typical antipsychotics for their index episode and were at risk for relapse, discontinuing treatment increased the risk of relapse by almost 5 times (HR for an initial relapse, 4.89; HR for a second relapse, 4.57). It is suggested that enhancing medication adherence among first-episode patients may substantially improve long-term outcomes.

Patients can do better

The concept of using LAIs and in particular, atypicals, as the basis of antipsychotic treatment has a number of advantages, says Professor Meltzer. He does not necessarily advise using them for every patient, but he does advise that physicians should have a high degree of suspicion that patients are not adhering to treatment when they fail to improve on their medication. Potential advantages with LAI antipsychotics include the following:

- Reduce dosage deviations²⁴
- Eliminate guessing about adherence status^{25,26}
- Show start date of nonadherence^{25,26}
- Help disentangle reasons for poor response to medication²⁶
- Eliminates need for the patient to remember to take a pill daily²⁴
- Result in predictable and stable plasma levels²⁴
- Many patients prefer them, especially if already receiving them.²⁷

Risperdal Consta is being used in Professor Meltzer’s practice in doses of up to 100 mg every 2 weeks. The response of the patients to receiving their medication by injection has been highly positive. Similar findings have been reported by various reviews, as with that by Walburn et al., which found that approximately 60% of patients receiving LAI antipsychotics strongly preferred them over oral typical antipsychotic formulations.²⁸

When prescribing an LAI formulation, physicians should be prescribing an atypical, advises Professor Meltzer. In New Zealand, the only funded LAI atypical formulation is Risperdal Consta. This should not deter clinicians from prescribing Consta, simply because it is the only one available, notes Professor Meltzer. More choice will be available with several new long-acting injectable depot formulations of existing atypical antipsychotics (e.g. aripiprazole, paliperidone palmitate, iloperidone) expected to be launched worldwide within the next two years.

Potential obstacles to LAI antipsychotics

Initiating LAI programmes requires support from a good infrastructure, which Professor Meltzer acknowledges is difficult for busy, underfunded, understaffed medical centres to achieve.^{24,26} Other potential obstacles include:

- Need to refrigerate (risperidone)
- Overburdened public agencies
- Frequency of injections and consequent inconvenience for staff and patients
- Need to take concomitant medications orally
- Anti-shot sentiment, particularly in the USA
- Image problem, arguably perpetuated by manufacturers of oral atypical antipsychotics, and exacerbated by the predominant use of these medications as a ‘last resort’ often for the most stigmatised individuals.²⁹

Cost is an issue. However, a cost-effective analysis favours the LAI over other formulations; Professor Meltzer states that in the USA, the cost of every relapse equates to the cost of 12 patients prescribed Consta.

Despite these obstacles, Professor Meltzer contends it is worth persevering with LAIs. Contrary to what some people maintain, oral atypical medications have not solved the issue of nonadherence. In an analysis of pharmacy refill records, compliant fill rates at 12 months were only moderately higher in outpatient veterans who received oral atypical antipsychotics than in those who received oral typical agents (54.9% vs 50.1%).³⁰

Cognition data

Some evidence suggests that the cognitive impairment in first-episode psychosis differs from that in chronic schizophrenia only in terms of degree of severity³¹ and a number of studies attest to the fact that cognitive deficits are the best predictor of functional status across a number of outcome domains and patient characteristics.³² Improving cognition is therefore obviously a priority in schizophrenia. In Professor Meltzer's opinion, the conventional antipsychotics have never shown consistent improvement in attention, vigilance, working memory, storage memory, or executive function.³³⁻³⁵ The effects are worsened if anticholinergics are added.³⁶ Cognitive and motor performance are adversely affected by EPS and sedation. Notably, a recent analysis of data from the CATIE study has found that the effects of olanzapine, quetiapine and risperidone on neurocognitive function were not significantly different from those of perphenazine during treatment periods lasting less than 18 months.³⁷

Data published in 1993 were the first to report on the ability of clozapine to improve cognitive function in patients with treatment-refractory schizophrenia; 36 such patients experienced significant improvements in various measures of cognitive function after 6 months' treatment.³⁸

Cognitive change on antipsychotic therapy

In 2001, a review of all previously published research addressing cognitive enhancement in patients with schizophrenia following novel antipsychotic treatment discussed the impact of various methodological and conceptual issues on the results of those studies.³⁹ The reviewers suggest ways in which readers can examine the improvement of cognitive function in patients with schizophrenia, in order to better evaluate and understand the implications of future study outcomes for the treatment of schizophrenia.

More recently, two meta-analyses examined the available clinical evidence supporting cognitive improvement with atypical antipsychotics.⁴⁰ The analyses revealed that atypicals are superior to typicals at improving overall cognitive function and that specific atypicals have differential effects within certain cognitive domains.

Patients vary markedly as to how much cognitive improvement they experience on antipsychotic treatment. When using a Cognitive Factor 2 score comprised mostly of attention and verbal fluency (Digit symbol substitution test; Controlled word association; Category Instance Generation), an improvement of half a standard deviation (SD) is considered to be a clinically noticeable difference that physicians and family members can detect in a patient. Outcomes from a study currently being prepared for publication by Professor Meltzer show that after 6 months' treatment, nearly 30% of clozapine recipients (36/127) were improved from baseline by ≥ 0.5 SD and a further 20% (24/127) had an improvement of ≥ 0.8 SD; corresponding values for the 61 patients given typical neuroleptic drugs were approximately 8% (5/61) and 3% (2/61), respectively. Data such as these indicate that atypicals have an important therapeutic role in the treatment of schizophrenia.

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Conclusions – Professor Meltzer

- There have been major advances in the treatment of schizophrenia since chlorpromazine, despite what Eric Kandel, CATIE and CULASS state but do not prove.
- These are the atypical antipsychotics which are far from a panacea but have advantages in EPS and tardive dyskinesia, which make them the first-line choice for long-term treatment or prevention.
- Differences in efficacy and tolerability issues among the atypicals must be appreciated. Shared advantages for cognition and negative symptoms in some patients are efficacy reasons for preferring them.
- Dosage and duration of trials with atypicals must be attended to, in order to achieve maximum benefits.
- Nonadherence is a fact of life when treating schizophrenia.
- Many patients are nonadherent deliberately or accidentally and it is difficult for clinicians to assess this.
- Long-acting atypical antipsychotic drugs should not be the last resort treatment.
- Long-acting injectable atypicals should be considered for all patients, including first-episode patients.



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