Research Review
SPEAKER SERIES

Schizophrenia – Can We Modify the Course of Illness May 2010

Professor Rajiv Tandon, MD

Professor of Psychiatry at the University of Florida College of Medicine, USA

Rajiv Tandon, MD, is currently a Professor of Psychiatry at the University of Florida College of Medicine in Gainesville, Florida. He was previously a faculty member at the Department of Psychiatry in the University of Michigan Medical Center, Ann Arbor, where he was a tenured Professor of Psychiatry. Since 2000, he has been a member of the Scientific Council of the National Alliance for the Mentally Ill and on the Board of Directors of the National Schizophrenia Foundation (Chair 2002-2005). He was a member of the State of Florida Supreme Court Subcommittee on Criminal Justice and Mental Health, where he co-chaired the workgroup on Best-practice standards. He is a member of the State of Florida Blueprint Commission on Juvenile Justice and a member of the Advisory Council of the State of Florida Advocacy Center Council for the Protection and Advocacy of Individuals with Mental Illness (PAIMI). Professor Tandon has authored more than 250 scientific publications, and given over 600 national and international scientific presentations. He has received several awards for research and teaching in schizophrenia, including the American Psychiatric Association Young Psychiatrist of the Year award in 1993 and the 1997 FuturPsych award for outstanding achievement in schizophrenia research. He has been included in every edition of THE BEST DOCTORS IN AMERICA since 1995. He received the Exemplary Psychiatrist Award from the National Alliance for Mental Illness in 2009.

His major areas of clinical and research interest are the neuropharmacology of schizophrenia, differences between typical and atypical antipsychotic agents, dimensions of schizophrenic psychopathology (with a particular focus on negative symptoms), neuroendocrine and polysomnographic abnormalities in schizophrenia, and the evidence-based treatment of schizophrenia and other major mental disorders.

This publication is a summary of a recent presentation by Rajiv Tandon, Professor of Psychiatry, University of Florida College of Medicine, Gainesville, Florida, USA. He addressed psychiatrists, nurses and pharmacists in Auckland in May 2010 about the course of schizophrenia, the opportunities and challenges involved in modifying its course, antipsychotics and treatment adherence, and future possibilities.

Course of schizophrenia

Schizophrenia is a chronic, debilitating mental illness with significant functional impairment, affecting approximately 1% of the population.[1] The disease typically presents in late adolescence and persists throughout the patient's life, with males typically experiencing symptoms 5 to 7 years earlier than females.[1,2]

Schizophrenia has long been considered to be a unique disease entity, but in fact there is significant heterogeneity regarding the aetiopathology, symptomatology, and course of schizophrenia; the different psychopathological dimensions of schizophrenia vary in severity across patients and over the course of the illness, defying attempts to define this syndrome or its component entities as a single disease with a unitary aetiology or pathogenetic process.[2]

A new approach to understanding the phenotypic heterogeneity of schizophrenia proposes that we deconstruct the illness into its multiple component parts and reconfigure them in a more meaningful way, by adopting a dimensional approach to psychopathology and a staging approach to illness evolution and course.[2]

This dimensional approach identifies distinct psychopathological dimensions (positive symptoms, negative symptoms, disorganisation of thinking and behaviour, cognitive deficits, mood symptoms, motor symptoms), which all impact on functional impairment and can vary in severity and relative proportions across patients and through the course of the illness.[2] The dimensional approach incorporates a clinical staging of schizophrenia that maps where the patient is at in the continuum of illness; differences in prognosis, optimal treatment, and pathology are putatively associated with a given location in the disease.[2]

Stages of schizophrenia

Whereas a comprehensive pathophysiological model of treatment-resistant schizophrenia hypothesises three evolutionary stages: 1) cortical pathology and deficient neuromodulatory capacity; 2) neurochemical sensitisation; and 3) neurotoxicity,[3] the dimensional approach extends this model by adding in neurobiological criteria and clarifying specific prognostic and treatment implications for six distinct stages; as illustrated in Figure 1.[2]

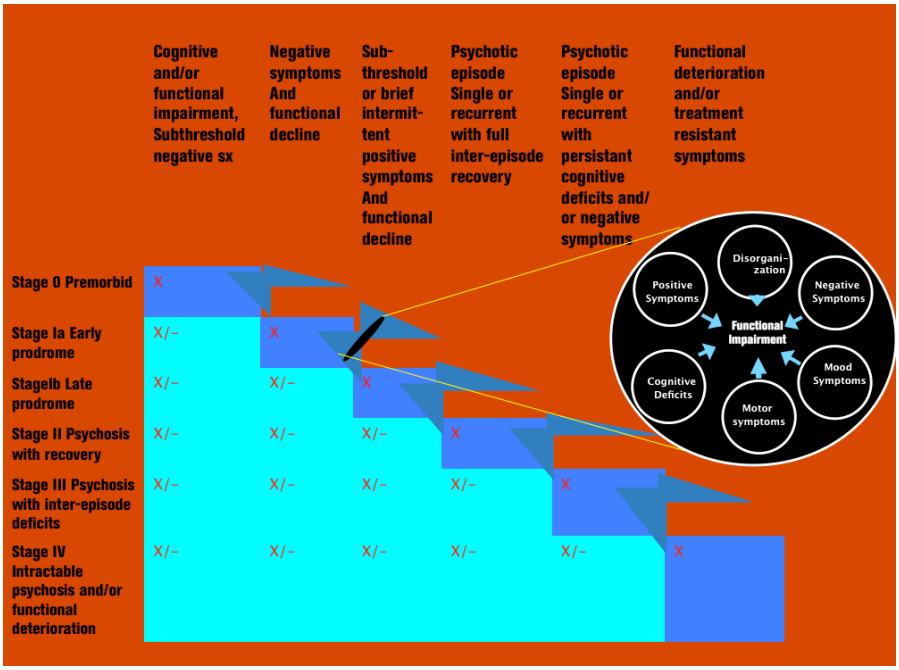

Figure 1: Stages of Schizophrenia

At the premorbid stage (Stage 0; Fig. 1) the degree of risk for developing schizophrenia varies according to genetic features, environmental exposures, behaviour, and social function, without any clinical evidence of schizophrenia itself. It is suggested that using targeted approaches to reduce other risk factors or enhance protective factors may lower the chances of developing schizophrenia in an individual identified as being at risk.

The prodrome phase incorporates Stages Ia and Ib (Fig. 1), which define how some of these risk factors are expressed clinically (Stage Ia) and how basic or sub-threshold psychotic symptoms are manifested (Stage Ib). This model supposes that a specified set of interventions may prevent the progression to psychosis. The prodrome is thus potentially a reversible stage in the early evolution of schizophrenia, with stage Ia (early prodrome) being less likely to devolve into schizophrenia than the later stage Ib (late prodrome). At this stage of the illness, interventions that may have efficacy include antidepressant medications, GABA-ergic agents, cognitive behaviour therapy, and low-dose antipsychotics in the late prodrome.

Stage II (Fig. 1) indicates that the threshold for psychosis has been crossed – at least one full psychotic episode has occurred, but the deterioration generally associated with schizophrenia has not occurred during remission.

In Stage III (Fig. 1), inter-episode deficits emerge with the psychosis. The reasoning holds that while some irreversible deficits associated with schizophrenia have occurred, additional potentially preventable deterioration can still occur; effective control of psychosis will limit such deterioration.

Stage IV (Fig. 1) implies substantial deterioration, with treatments being at best symptomatic and rehabilitative.

These six stages can be conceptualised as multiple declines, which also represent multiple opportunities for intervening with treatment to prevent that deterioration and reduce the manifestations of disease.

"Snowball effect"

The pathophysiology of schizophrenia is theorised to be regulated by a cascade of sequential, cumulative events, promoted by environmental signals and genetic susceptibility (see Figure 2). This cumulative process has been likened to a "snowball effect", a progressive downhill course in which the premorbid deficits can be aggravated by negative family and societal responses, thereby helping the problem develop into the prodromal stage of schizophrenia. Psychotic and negative symptoms can appear at this stage, compounding the negativity from family and society. Stresses of adolescence can worsen the prodromal symptoms, which may be worsened in the patient by fear, denial, and stigma. Left untreated, these feelings and symptoms influence neurotoxic consequences, then subsequently the first psychotic episode and secondary negative symptoms, with eventual relapse. Side effects of treatment, poor insight and cognitive impairment are factors implicated in noncompliance with the medication, which in turn leads to relapse.

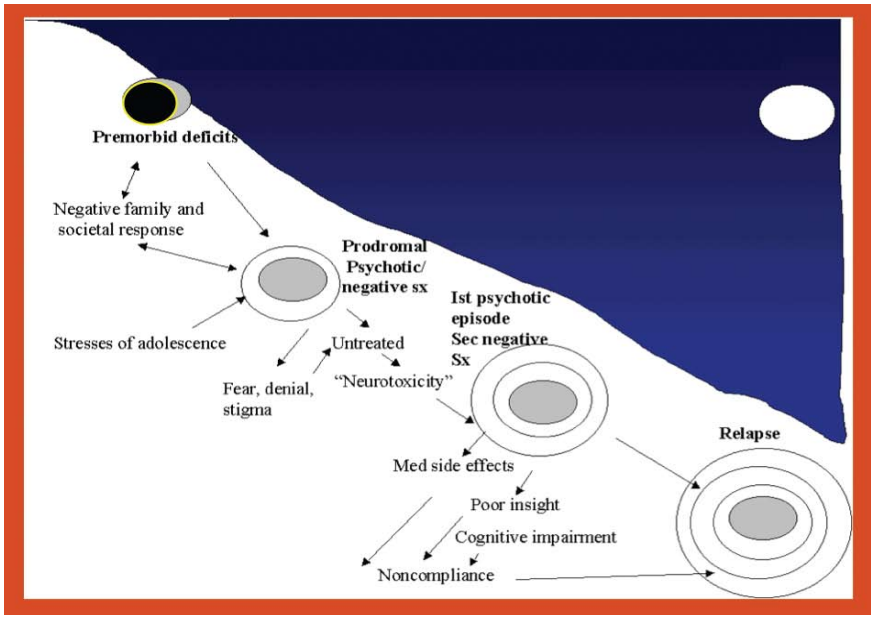

Figure 2: The "snowballing effect" in the course of schizophrenia

Can the risk for psychosis be predicted?

A recently published North American study involving 291 clinical high-risk (prodromal) patients reported that five clinical features improved the prediction of psychosis: a genetic risk for schizophrenia with recent deterioration in functioning, higher severity of unusual thought content, suspicion/paranoia, greater social impairment, and a history of substance abuse.[4] The cohort of treatment-seeking patients met Structured Interview for Prodromal Syndromes criteria and the study also enrolled 134 demographically comparable normal control subjects. The risk of conversion to psychosis was 35%; the rate of transition progressively slowed during the 2½-year follow-up. Notably, combining 2 or 3 of the five clinical features in prediction algorithms dramatically increased the positive predictive power (i.e., 68%-80%) compared with the prodromal criteria alone. Thus, this study has shown that it is possible to predict which individuals will convert to psychosis, with a level of predictive accuracy comparable to that in other areas of preventive medicine.

Introduce a "Psychosis High-Risk Syndrome" in DSM-V?

A Task Force is actively debating the appropriateness of including a Psychosis High-Risk Syndrome in DSM-V. Those in favour of this maintain that it would allow early targeting of illness to prevent deterioration and better outcomes. Further, they argue that we have the treatment tools to better define such high-risk conditions.

Those against introducing such a syndrome question whether we do have the tools to safely/effectively modify the course of schizophrenia; existing interventions for preventing that progression are not completely safe. These dissenters also query the negative consequences of false positive diagnoses; what effects will occur and what opportunities will a child receive when diagnosed as being at a 30-fold higher risk of developing schizophrenia?

Recovery in schizophrenia

What does recovery mean and does it happen in schizophrenia? Professor Tandon explains that, as with any other chronic disease that lacks a definitive cure, the individual's service/recovery plan must include treatment interventions intended to reduce symptoms and prevent relapse (antipsychotics, cognitive behavioural therapy), rehabilitative strategies that enhance adaptive skills (social skills training), and social support mobilisation (supported housing, supportive employment) that optimises function and quality of life.[5] This multidimensional approach should promote recovery, a state of health and wellness, in which the person can undertake vocational and/or educational functioning, live independently, be physically healthy, develop instrumental competence and integrate socially, and enjoy a good quality of life. Professor Tandon emphasises that all of this must be accompanied by the least possible burden of treatment (costs and unintended adverse consequences of treatment, including side effects, related health risks, fiscal costs, and discrimination). Providing optimal individualised treatment for schizophrenia can enable recovery, with an individual able to lead a maximally productive and personally meaningful life, says Professor Tandon.

Options for antipsychotic therapies

Following the discovery of chlorpromazine in 1952, a number of conventional or typical antipsychotics emerged: haloperidol, fluphenazine, thioridazine, loxapine, perphenazine, trifluoperazine, thiothixene, and molindone. These first-generation antipsychotics (FGAs) proved to be highly effective for treating psychosis but carried a significant risk of severe extrapyramidal symptoms (EPS) and tardive dsykinesia (TD). In the 1980s, although clozapine proved to be another highly effective treatment for psychosis, without causing EPS, it was abandoned because of its associations with agranulocytosis then reintroduced after publication of data from a landmark trial in 1988 demonstrating the efficacy of clozapine in treatment-resistant schizophrenia.[6]

The pharmacological model of clozapine led to the development of a new category of drugs – the second-generation antipsychotics (SGAs) or atypical antipsychotics: risperidone, olanzapine, quetiapine, and ziprasidone, all of which decrease the risk of acute and chronic EPS and TD. This pharmacological model has persisted, inspiring the latest antischizophrenic agents: aripiprazole, paliperidone, iloperidone, and asenapine.

Translating data to guide best practice

Deciding on which antipsychotic to prescribe involves the clinical aspects of dose and duration of treatment, besides the specific circumstances of the patient (diagnosis, stage of illness, and consideration of any previous antischizophrenic medications) and the desired treatment outcome. Further, the choice of antipsychotic must allow for their heterogeneity (e.g. differing side effect profiles between typical and atypical antipsychotics, and the varying patterns of receptor affinities and dissociation amongst atypical antipsychotics).

Considering CATIE and real-world interventions

How relevant to clinical practice are the controversial results of CATIE (Clinical Antipsychotic Trial of Intervention Effectiveness), which raise questions about the relative effectiveness of newer atypicals over older antipsychotics?[7] Despite its controversy, its independence of industry render the results as unbiased and more believable. It is the largest single study to date comparing antipsychotics in schizophrenia, and it is universally referred to.

Findings of CATIE include:

1. Olanzapine was the most effective in terms of discontinuation rates; the likelihood of remaining on olanzapine throughout the 18-month study was 36%, versus 18%–26% of remaining on the other medications (quetiapine, risperidone, perphenazine, or ziprasidone).
2. The typical antipsychotic perphenazine showed similar efficacy to the newer antipsychotics quetiapine, risperidone, and ziprasidone.
3. Significant metabolic side effects occurred during olanzapine treatment.

In response to all clinical study findings, Professor Tandon seeks to discover what the study really found and whether those findings are applicable to any of his own patients; the results will only apply to those patients who are similar to those in the study.

A recently published paper, co-authored by Professor Tandon, helps to elucidate how we may make sense of CATIE and offers guidance as to how to correctly interpret and apply study findings relevant to a clinical question needing to be answered and transformed into a treatment decision.[8] The paper discusses the threats to validity approach, with regard to CATIE in particular.

What did CATIE find? The study cohort comprised 1460 patients with schizophrenia who were randomly assigned to five antipsychotic medications. They had been ill with schizophrenia on average for 16 years and had been receiving an antipsychotic on average for 14 years. Seventy-two percent were on antipsychotic medication at study entry, at which point they were randomised or switched to one of the study antipsychotics. They were moderately stable (with an overall CGI severity score of 4.0 and PANSS total score of 75.7). What happened to those who were switched to another antipsychotic?

At study randomisation, many more of the CATIE cohort were receiving olanzapine than any other antipsychotic (23% on olanzapine, 18% on risperidone, and 1%–4% on perphenazine, quetiapine, or ziprasidone; other antipsychotics were also being taken). There was thus a significant bias in favour of olanzapine, for those patients who continued to receive olanzapine in CATIE.

The study authors later controlled for this bias by evaluating the extent to which continuing to take the antipsychotic prescribed before the study, versus switching to that medication, influenced the outcome of that drug treatment.[9] In a comparison of the "stayers" and "switchers", the rates of treatment discontinuation were lower for the "stayers." This advantage was strongest for olanzapine, whereas patients who stayed with quetiapine did less well than those who were switched from quetiapine to olanzapine or risperidone. While this distinction between "switchers" and "stayers" attenuated the overall CATIE phase 1 results, they were essentially unaltered (this analysis confirms the absence of any difference in efficacy outcomes between the five antipsychotics). An important aspect of this finding is the fact that, in general, even though the patients were not doing very well on the medication that they were receiving at study entry, those who stayed on it did better than those who switched to another antipsychotic. According to CATIE, switching is risky. It is preferable to augment with medications; worldwide, 20% of patients with schizophrenia are on 2 or more antipsychotics.

Another important aspect to the CATIE findings concerns the patient population. To whom do the CATIE results apply? A total of 231 patients in CATIE had TD and could only be assigned to an atypical, to prevent the worsening of TD. Thus, for the purposes of perphenazine efficacy comparisons, CATIE yields a total of 1229 patients who had received an antipsychotic for 14 years who did not have TD, no history of akathesia, dystonia, or significant EPS.

After 18 months treatment in CATIE, EPS rates were not significantly different between treatments, ranging from 4% to 8%. Professor Tandon notes that clinical practices observe much higher rates of EPS. This is because CATIE recruited patients who were at low risk for EPS. How to make sense of such data, when wanting to understand their clinical implications for our practice?

Which antipsychotic?

The recent World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia is intended to clarify clinical practice.[10] The statement emphasises the importance of reducing positive symptoms by the greatest possible extent, while avoiding EPS or using anticholinergic medications. It notes this may be achieved with FGA treatment, but that it is more likely with SGA treatment.

Do atypical antipsychotics actually exist? Avoiding EPS is seen as the key to realising benefits with atypical antipsychotics. However, CATIE found no differences in various EPS ratings between patients treated with perphenazine or SGAs, which might explain why it also failed to observed FGA-SGA differences in overall effectiveness, cognition, negative symptoms, and TD.[9] Perhaps there are only relative differences in EPS risk between FGAs and SGAs (see Figure 3).[9]

In Figure 3, the six outer circles represent the potential advantages of atypical antipsychotics. CATIE failed to identify these advantages. Why? If a good antipsychotic effect is obtained without EPS and without using an anticholinergic, it does not matter which antipsychotic is prescribed – the patient obtains all of the benefits as detailed in the outer circles.

The difference between typical and atypical antipsychotics is that with the typical antipsychotics, there is a greater degree of separation between the doses at which an antipsychotic effect is obtained and the dose at which EPS occurs. With so-called atypicals, it is less difficult to obtain a good antipsychotic effect without EPS, without using an anticholinergic. These outcomes can be achieved with a typical antipsychotic in some patients; admittedly, with fewer patients and with greater difficulty than with atypicals, but it is possible.

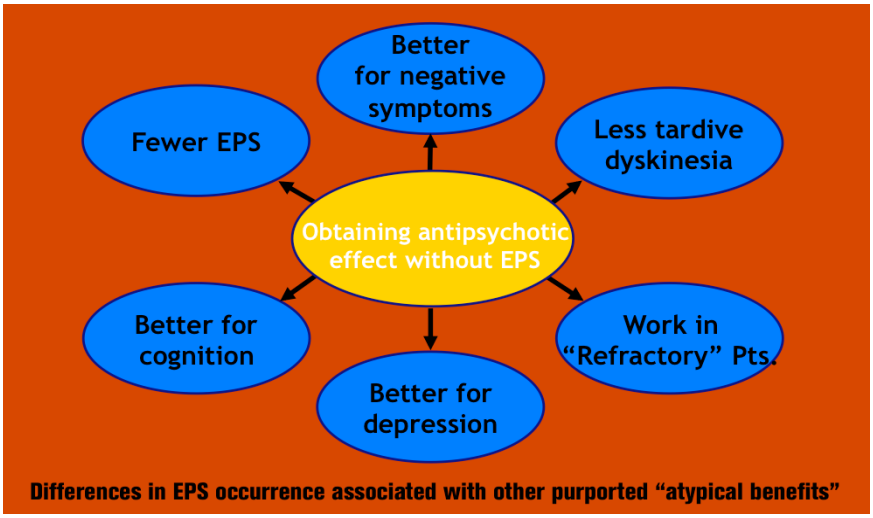

Figure 3: THERE IS NO ATYPICAL. Only relative differences in EPS risk

Two important clinical implications arise out of this. Ultimately, what we want for our patients is:

a. A good antipsychotic effect (without EPS or having to add an anticholinergic) with all of the associated clinical benefits.

b. The right dose, with almost continuous treatment.

Antipsychotics in the treatment of schizophrenia: Facts and Fiction

As detailed by the WPA Pharmacopsychiatry Section statement, compelling clinical data support the efficacy of clozapine over all 63 existing FGAs and SGAs in regard to otherwise neuroleptic-refractory schizophrenia; none of the other agents have proven to be clozapine-like in this aspect.[10]

Varying degrees of EPS and metabolic side effect risks exist *within* both classes; while SGAs are generally less likely than FGAs to cause EPS, there is substantial variation within each class in regard to how easily and consistently an adequate antipsychotic effect can be achieved without EPS.[10] Although SGAs are generally associated with metabolic adverse effects to a greater extent than FGAs, variation exists within each class with regard to their liability to cause these side effects.[10]

EPS avoidance is the key to benefits of treatment with SGAs, such as better cognition, less dysphoria, lower negative symptom burden, and lower risk of TD.[10]

Minimising metabolic side effects (weight gain, dyslipidaemia, diabetes mellitus) is critical to reducing risk of cardiovascular disease and mortality.[10] Although SGAs are generally associated with metabolic adverse effects to a greater extent than FGAs, variations exist among both classes as to their liability to cause these side effects.[10]

FGAs and SGAs: a meaningless dichotomy

Some favour abandoning the dichotomy between FGAs and SGAs, arguing that not only is it not useful, but it also misinforms. Supporters of this view point out that there are no consistent differences in efficacy across agents, except for clozapine, which is superior to other antipsychotic agents in treatment-refractory schizophrenia patients (specifically those with antipsychotic-refractory positive symptoms).[10] Within both antipsychotic classes, there are varying degrees of risk of EPS, metabolic side effects and other adverse effects, as well as varying degrees of ease of optimal dosing across agents. The challenge is that different agents at different dosages may provide the best outcomes for individual patients, and the optimal agent and/or dosage (i.e. to achieve high efficacy with low side effects) can vary in the same patient at different stages of the illness.[11]

Managing schizophrenia

Critical aspects of antipsychotic management for schizophrenia include:

- Dosing strategies (key to accomplishing an adequate antipsychotic effect without EPS)
- Duration of antipsychotic treatment before considering it a treatment failure (an adequate duration is a medication regimen that lasts for at least 6 weeks)
- Sequencing of alternative medication treatment options
- Monitoring: tracking benefits and risks
- Outcomes: benefits and adverse effects.

Patient adherence to the antipsychotic regimen is another critical issue in the treatment of schizophrenia: vital for preventing relapse, limiting deterioration, promoting recovery, and improving outcomes.

Approaches that seek to enhance treatment adherence include psychosocial interventions, monitoring of adherence, the use of long-acting antipsychotic agents, and efforts to minimise adverse effects. Professor Tandon emphasises that long-acting antipsychotic formulations play a very important role and are significantly underutilised worldwide. Among a number of important benefits with such medications is that they improve adherence and they are associated with more constant, low blood drug levels, resulting in fewer side effects and a lower likelihood of treatment discontinuation.

Improving treatments for schizophrenia

- Can different treatments be useful at different stages of treatment?
- Can different treatments separately target different domains of psychopathology?
- Can treatment for different individuals be specifically individualised?

Developing better treatments for schizophrenia are driven by our understanding of the disease, which is informed by what we know about its aetiology (risk factors, protective factors, modifiers and interactions between the factors), pathophysiology (structural, functional and neurochemical alterations, pathogenesis, pathoplastic effects), disease course (predictable course, stages of illness, modifiers of course, defined outcome), as well as what we know about prevention and treatment. These findings inform each other, resulting in testable models that may generate new hypothesis-driven discovery and new treatments.[12]

Future trends in pharmacotherapy of schizophrenia

We have made a lot of progress in understanding the neurobiology of schizophrenia but there is more to learn and we need to utilise the information that we have, to help our patients. Otherwise, we are denying them the opportunity to recover. More effective antipsychotic treatments are needed for schizophrenia:

- New molecular targets – over 100 different molecules are being investigated as treatments for schizophrenia, or different symptom domains in schizophrenia
- Rational polypharmacy – there may be an opportunity to target different symptom domains with different medications, but probably not in the way that we currently practice
- Phase-specific treatments – in the future, there might be different treatments developed for different stages of the illness
- Better individualising of treatment – a number of different pharmacogenetic strategies are evolving, that are expected to enable clinicians to better individualise treatment.

References

1. Freedman R. Schizophrenia. N Engl J Med. 2003;349:1738-49.
2. Tandon R et al. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res. 2009;110(1-3):1-23.
3. Sheitman BB, Lieberman JA. The natural history and pathophysiology of treatment-resistant schizophrenia. J Psychiatr Res. 1998;32(3-4):143-50.
4. Cannon TD et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry. 2008;65(1):28-37.
5. Tandon R et al. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. J Psychiatr Pract. 2006;12(6):348-363.
6. Kane J et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45(9):789-96.
7. Lieberman JA et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12):1209-23.
8. Rankupalli B, Tandon R. Practicing evidence-based psychiatry: 1. Applying a study's findings: The threats to validity approach. Asian J Psychiatr. 2010;3(1):35-40.
9. Essock SM et al. Effectiveness of switching antipsychotic medications. Am J Psychiatry. 2006;163(12):2090-5.
10. Tandon R et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res. 2008;100(1-3):20-38.
11. Tandon R, Constantine RJ. Avoiding EPS is key to realizing 'atypical' benefits. J Fam Pract. 2006;5(11):35-45.
12. Tandon R et al. Schizophrenia, "Just the Facts": What we know in 2008. Part 1: Overview. Schizophr Res. 2008;100(1-3):4-19.

JANSSEN-CILAG

Professor Tandon reports no financial relationship with Janssen-Cilag Pty Limited, which supported the publication of this article with an educational grant. The content or opinions expressed in this publication may not reflect the views of Janssen-Cilag. Please consult all medication Data Sheets at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician.