

Schizophrenia Management: An Update

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Schizophrenia is the most disabling psychiatric disorder and one of the world's top ten causes of long-term disability, affecting 1% of the population worldwide. Traditional or typical antipsychotics appear to act principally on dopamine(D2) receptors and they relieve mainly the positive symptoms in approximately 75% of the patients and produce much less improvement in negative symptoms. Unfortunately, all of them produce extra-pyramidal side effects(EPS) to a varying degree. Newer antipsychotics (second generation or atypical) appear to have additional blocking action on serotonin receptors, are more likely to relieve negative symptoms and are relatively free from EPS seen with typical/first generation neuroleptics. In this review, the efficacy of the novel atypical antipsychotics on the resistant schizophrenia is discussed with an emphasis on the future medication which are claimed to be more effective in the management of schizophrenia. These medicines are still in the various stages of clinical testing and development.

Key Words: medications, resistant management, schizophrenia, update

Schizophrenia is the most common (approximately 1% of the world's population) and chronic debilitating mental disorder, characterized by loss of contact with reality. An illness like schizophrenia has been variously described over the years. Falvet in 1851, called it folie circulaire, Hecker in 1871, called it Hebephrenia. Kraeplin in 1878 pulled the various concepts together into one disease entity, which he termed Dementia Praecox. Bleuler first used the term schizophrenia.

Schizophrenia is more common among the lower socioeconomic classes in urban areas. It has an incidence of 18-20 cases per 100,000 per year.⁷⁶ The average age of onset for men is 20-25 and the average age on onset for women is 25-30. Most of the studies demonstrate, male to female ratio 1.5-2:1. Schizophrenia is uncommon in children under the age of 12. However child born into a family with one or more family members affected by schizophrenia has a greater chance of developing schizophrenia than a child born into a family with no history of schizophrenia. Risk of developing schizophrenia in first-degree relatives of people is approximately 10 percent.¹⁰ If both the parents have schizophrenia, the risk is as high as 40 percent.¹⁰

Pathophysiology

Neuroimaging studies have demonstrated anatomical abnormalities in patients with schizophrenia,

ventriculomegaly and decreased brain volume exists in medial temporal areas such as hippocampus, amygdale.⁵¹ Indeed neuropsychological studies show impaired information processing in patients of schizophrenia because of anatomical abnormalities in the Interneuronal network of neocortical and limbic regions.⁷³ Abnormalities in release of neurotransmitters also play a very important role in the pathophysiology of schizophrenia.²⁴ Excessive dopaminergic activity may induce a schizophreniform psychosis. Other neurotransmitters involved in the pathogenesis of schizophrenia are glutamate and serotonin.²³ The brains of people with schizophrenia have elevated dopamine and serotonin activity.

Causes

There is no known single cause responsible for schizophrenia. It is believed that a chemical imbalance in the brain, an inherited factor, which is necessary for schizophrenia to develop. However it is likely that many factors – genetic, behavioral and environmental play a role in the development of this condition.

Symptoms and Signs

The symptoms of schizophrenia are often classified as :

- Positive symptoms – including psychotic symptom such as hallucination, delusions and disorganized speech and behavior.

- Negative symptoms – Include a decrease in emotional range, flat affect, poverty of speech and social withdrawal
- Cognitive symptoms - Include deficits in attention and executive functions.

Symptoms usually follow a waxing and waning course. Some schizophrenia patients may become violent. The symptoms of schizophrenia in adolescents are similar to adults, however adolescents, more often (in 80% of the diagnosed cases), experience auditory hallucinations and typically do not experience delusions or formal thought disorders until mid adolescents or older. In children with schizophrenia, behavior change may occur slowly, over time or onset. The child gradually becomes more shy and withdrawn. They may begin to talk about bizarre ideas or fears and begin to cling more to parents.

Diagnosis

According to the American psychiatric Association's Diagnostic Manual of Mental Disorder (DSM-IV),^{5,6,7} the patient must have experienced at least two of the following characteristics for at least one month to establish the diagnosis of schizophrenia:

- Delusions
- Hallucinations
- Disorganized speech
- Catatonic or disorganized behavior
- Negative symptoms, such as blunting of affect.

Treatment

A combination of therapies is often necessary to meet the individualized needs of the child or adolescent with schizophrenia. Treatment is aimed at reducing the symptoms of schizophrenia; specific treatment should be based upon :

- Age, overall health, medical history
- Severity of the condition
- Type of schizophrenia
- Tolerance to the drug therapies or medication.

Types of the treatment may include:

- Medication (also called as psychopharmacological management to reduce the symptoms of schizophrenia) include:
 - 1) Antipsychotic medications
 - a) Conventional / Typical/ First generation
 - b) Atypical / second generation.
 - 2) Alternative therapies
- Individual and family psychotherapy (including supportive, cognitive and behavioral therapy)
- Specialized educational and / or structured activity program (i.e. social skill training, vocational training, speech and language therapy)
- Self help and support group
- Assertive community treatment (ACT)

Conventional neuroleptic agents have since the mid 1950s, proven to be the most consistently effective compounds in the treatment of acute and chronic schizophrenia patients. This efficacy though, comes at the

cost of a number of untoward neurological side effects. Prominent among these are disturbance of extra pyramidal system, including dystonia, tremors, akinesia, bradykinesia, rigidity, akathisia and variety of tardive dyskinesic (TD) syndrome. These side effects account for the notorious patient noncompliance and iatrogenic morbidity over the ensuing 40 years. Several classes of compounds with antipsychotic activity have been developed, but until the recent development of new class of antipsychotic medications none have been shown to possess superior antipsychotic activity.

In fact there is growing evidence that most of the new medications can offer some advantages over typical or first generation or conventional antipsychotic drugs such as greater improvement in negative symptoms and cognitive impairments, relapse prevention, functional capacity and quality of life with fewer extra pyramidal symptoms and less tardive dyskinesia. Accordingly many clinicians are prescribing these new antipsychotic as first line of agents for acute and maintenance therapy for schizophrenia. However these advantages thus far have been regarded as incremental and not necessarily substantial. In addition concerns about side effects such as extra pyramidal side effects (EPS) have been replaced by other distressing side effects including weight gain, hyperglycemia and dyslipidemia. At present we are still in the process of defining fully the clinical profiles of new agents in terms of the extent of their therapeutics efficacy and adverse effects on a variety of other outcome including cognition, affect, suicide, subjective response, social and vocational functions, cost effectiveness etc.

Resistant Schizophrenia

Resistant schizophrenia could be defined as the presence of persistent positive psychotic symptoms such as hallucinations, delusions, bizarre behavior or formal thought disorder and / or enduring negative symptoms such as affective flattening, alogia (poverty of speech, poverty of content of speech, blocking or latency of response), anhedonia (lack of pleasure in normal interests) and asociality (impaired intimacy and few relationships with friends/ peers) despite adequate treatment with antipsychotic medications.

The precise incidence of poor treatment response in schizophrenia is not easy to determine. Data from the National Institute of Mental health psychopharmacology Research Branch multicenter, controlled trials of newly admitted patients who received antipsychotic treatment, found that about 10% of the patients demonstrated “no change” or “were worse” and approximately 20% of patients were considered only “minimally improved”.^{21,25,33} Kane et al concluded from these studies that 10-20% of patients derive little benefit from typical antipsychotic medications (Kane 1989).⁴⁷

Management of the patient with an inadequate response after a four week treatment course with conventional / typical antipsychotic course includes five options –

- 1) Continuing the same regimen for a longer duration
- 2) Increasing the dose of current antipsychotic
- 3) Switching to different class within the typical antipsychotics (e.g. butyrophenone (haloperidol) to a phenothiazine (thioridazine).

- 4) Adding a second drug to the current antipsychotic (ie, adjunctive treatment) or
- 5) Switching to a newer agent such as risperidone or clozapine.^{46,48,73}

Although most individuals with psychosis show a moderate to substantial reduction in their positive symptoms after treatment with a conventional antipsychotic drug. About 30% of the patients do not respond to psychopharmacology. The negative symptoms of schizophrenia are ever less responsive to the traditional drug treatment. Christoph U., Correll et al (2003) examined the relationship between changes in Brief Psychiatric Rating scale (BPRS) total score and each factor score following 1 week of treatment. These data suggest that the patients with minimal improvement in positive symptoms during first week of the treatment with typical antipsychotics are unlikely to respond to 4 weeks trial and require the confirmation and extension of the treatment with second generation antipsychotic drugs.²² Several new antipsychotic drugs have been introduced recently. It has been claimed that the new antipsychotics have statistically significant advantages on various measures of clinical outcome, when compared with traditional antipsychotics.^{50, 58} There is evidence to suggest that patients on the new antipsychotic drugs have superior performance on neurocognitive measures (e.g. working memory) compared with patients on traditional antipsychotics.⁶⁰ Randomized controlled trials comparing new generation antipsychotic drugs with placebo and/or conventional antipsychotics were identified. The analysis of six placebo comparisons involving a total of 983 patients clearly demonstrated that new generation antipsychotics are effective for relapse prevention.⁵⁹ Classical antipsychotics unspecifically block mesolimbic and nigrostriatal dopaminergic pathways resulting in unwanted EPS, tardive dyskinesia, neurocognitive deficits.¹⁷ The blockage of the dopamine receptors in the infundibulum results in prolactin elevation, sexual dysfunctions, inadequate efficacy, resistance to the treatment, and little effect on negative symptoms.²⁷

Clozapine

Clozapine was the first effective drug used in resistant schizophrenia (launched in the world market in 1990) with significant improvement in both positive and negative psychotic symptoms with fewer side effects like EPS, tardive dyskinesia, neuroleptic malignant Syndrome.⁴⁸ Chakos M.M.D., et al (2001) conducted a review and meta analysis of studies that compared the efficacy and tolerability of typical and second generation antipsychotics for patients with treatment resistant schizophrenia. The meta analysis confirmed that treatment-resistant schizophrenia patients have more favorable outcome when treated with clozapine rather than typical antipsychotic as reflected by BPRS total score, categorical response rate, scale for the assessment of negative symptom score, Simpson-Angus Rating Scale Score and compliance rate. In the aggregate Clozapine exhibits superiority over typical antipsychotics in terms of both efficacy and safety.¹⁹ It has got ten fold higher affinities for D4 compared to D2 or D3 receptors. In addition, to dopaminergic blocking property,

it is also an antagonist of adrenergic, cholinergic, histaminergic and serotonergic receptors. Clozapine is more effective than typical antipsychotic in producing clinical improvement including a significant delay in relapse rate.⁸¹ Major side effects with clozapine are weight gain, sedation, akathisia, orthostatic hypotension and agranulocytosis. Despite the superior clinical effectiveness and EPS profile of clozapine its clinical utility is restricted by the propensity to cause agranulocytosis and mandatory hematological monitoring of the patients.^{3,4,11,12} It is available in both 25 and 100 mg tablets. The starting dose should preferably low 12.5 mg at bedtime and gradually increase to therapeutic dose of 300-450 mg/day, over 2-3 weeks. Maximum dose is 900 mg per day. One should not forget to perform WBC count before starting clozapine therapy. Then after starting clozapine, it is mandatory to do WBC count every week for the first six months, then fortnightly for the duration of therapy. The risk of agranulocytosis has made its use highly regulated over the last decade.³ However close monitoring of WBC efficiently decreases the risk of granulocytopenia.^{3,11} Clozapine should be contraindicated in a patient of documented hypersensitivity, when WBC count is less than 3500 cells/cubic mm before or during therapy.

Concurrent treatment with lithium may precipitate neuroleptic malignant syndrome. Epinephrine and Phenytoin may decrease the effect. Tricyclic antidepressants, neuroleptics, CNS depressants valproic acid, can increase the effect.¹²

Any drug known to induce bone marrow suppression should be avoided with clozapine like carbamazepine.

Risperidone and olanzapine

They were the first new atypical antipsychotics. Olanzapine was introduced in the US market in 1996. It has high binding ratio of 5HT₂ to D₂ receptors. Like clozapine, olanzapine is an antagonist of dopamine receptors D₁ to D₄ and 5HT₂ receptors. It also possesses anticholinergic, antihistaminic and alpha₁ adrenergic blocking action. It is as effective as haloperidol against the positive symptoms of schizophrenia and more effective against negative symptoms with significantly fewer EPS. Olanzapine seems to be as effective as clozapine in the treatment of refractory schizophrenia. Few long term studies compared the acute and long term effectiveness of haloperidol with that of Olanzapine in patients with first episode psychosis. Two hundred sixty three patients were randomly assigned under double-blind conditions to receive Haloperidol or Olanzapine and were followed up to 104 weeks. At the end of study period Olanzapine treated subjects had greater decrease in the symptom severity as measured by positive and negative syndrome scale total score and negative and General scales and by the Montgomery -Asberg Depression Rating scale, with lower rate of treatment emergent parkinsonism and akathisia as compared to Haloperidol treated patients.⁴⁴ Available data suggests that olanzapine may be considered as first line treatment for the patient in an acute episode of schizophrenia.^{26,44} It is valuable in treating mood disorders and has been approved by FDA for the treatment of acute mania.^{69,12,26} Olanzapine is associated with excess weight

gain and sedation. Side effects also include somnolence. It should be given in a dose of 10-15mg /day, (not to exceed 20 mg/day), preferably at bedtime. There is no reported agranulocytosis with olanzapine, Minor elevation of hepatic transaminase, may occur but no serious hepatic problems has been reported with olanzapine like clozapine. Olanzapine also produces α -adrenergic blocking action, resulting in increased orthostatic and dizziness. Because of its liability to induce orthostatic hypotension, it should be started at 1.25-2.5 mg, and increased up to 5 mg in the first week, which could be, raised up to 10mg/day. (Do not exceed beyond 20 mg/day).

Risperidone was the first atypical antipsychotic agent introduced after clozapine. Drug exerts more D2 and D1 antagonistic effects. Although it has 5HT2 receptors blocking action as well, which is likely to be associated with low EPS liability compared to haloperidol,³⁴ but risperidone at higher doses produces EPS, indicating high levels of D2 antagonists can not be completely ameliorated by even maximal 5HT2A receptor antagonism. Risperidone appears more likely to raise prolactin level than does olanzapine.⁵³ Side effects are orthostatic hypotension and agitation over sedation. However, compared to clozapine risperidone doesn't cause agranulocytosis but caused increased incidence of malignant syndrome in addition to EPS.²⁷

Orthostatic hypotension can result in syncope and fainting, so dose should be raised slowly and one should also keep in mind about the pharmacokinetic interaction with other drugs like SSRI, which may enhance the orthostatic side effects, adults dose is 4-8 mg/day in two divided dose (Do not exceed 16mg/day).

Volavka Jan, Czobor Pal et al (2002) compared the efficacy and safety of three atypical antipsychotics (Clozapine, Olanzapine, risperidone) with one another and with haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Clozapine, risperidone and olanzapine (but not haloperidol) resulted in statistically significant improvement in total scores of positive and negative syndrome scale.⁸⁰⁵

Quetiapine (seroquel)

This was released in USA in 1998. Like clozapine, it has low affinity for D1 and D2 receptors, but relatively high affinity for D4 receptors.¹² It also appears to have high affinity for 5HT2 receptors with no significant anticholinergic or antihistaminic effects. But it blocks α -adrenergic receptor to some extent. It is more antipsychotic drug with proven efficacy in schizophrenia with positive, negative as well as cognitive functions, making it well suited as first line therapy.^{2, 35,77} Dose is 300-450 mg/day

Side effects are orthostatic hypotension, tachycardia, syncope, neuroleptic malignant syndrome, tardive dysfunction, dry mouth sedation with minimal or no risk for EPS or hyperprolactinemia. Associated weight gain with Quetiapine is less than what one observes with clozapine and olanzapine but more than that associated with ziprasidone.⁷⁷

Ziprasidone (Geodon)

This atypical neuroleptic introduced to US market in the year 2000. It has high affinity for 5HT1A, 5HT1D, 5HT2 and

D2 receptors and moderate inhibition of serotonin and noradrenalin reuptake.⁷³ Ziprasidone significantly increases dopamine release in the prefrontal cortex, without increasing the levels in striatum. This property may be beneficial for the amelioration of negative symptoms improving cognitive functioning with low liability for inducing EPS. In addition to have antipsychotic property, it also possesses antidepressant and Anxiolytic qualities.¹²

Ziprasidone appears to be well tolerated. Most notable feature is that it is not associated with significant weight gain as observed in most of the other antipsychotics.² The most common side effects observed with Ziprasidone are drowsiness, dyspepsia, dizziness, constipation nausea. However Biswas et al (2003) recently reported a case of cardiac arrhythmia without fatality, yet requiring aggressive cardiac monitoring in 17 year old adolescent, who overdosed with Ziprasidone and Bupropion combination.¹⁴ The initial dose should be 5 mg/day, increased in steps of 5 mg up to 40 mg/d as maximal dose.

Aripiprazole

This is another atypical antipsychotic partial dopamine agonist with high affinity for D2 and D3 receptors. It acts on both presynaptic autoreceptors and postsynaptic D2 receptors. In addition it displays 5HT1A partial agonism and 5HT2A antagonism. It also has a very modest affinity for alpha adrenergic, histamine (H1), 5HT6 and 5HT7 receptor, no appreciable affinity for D1, histaminergic or cholinergic muscarinic receptors. It has long half-life about 50-80 hrs and steady state therefore achieved after 2 weeks. Therapeutic adult dose is 15-30 mg/day. All the short and long term studies have shown that aripiprazole has a favorable safety and tolerating profile with low liability for EPS, tardive dyskinesia, weight gain, sedation hyperprolactinemia, prolongation of QT interval, no effects on glucose and lipid metabolism.^{15,54} Aripiprazole appears to improve negative symptoms, cognitive function, and prevents relapses, disease progression and improves the quality of life.³²

Sertindole

It has high affinity for 5HT2 receptors, D2 receptors and alpha1-adrenoceptors. The affinity for D1, alpha-2 receptors are low. There is no affinity for 5HT1A, muscarinic cholinergic receptors. Binding experiments indicate limbic preference vs. striatal D2 receptors.⁴² Many trials showed that sertindole was as effective as haloperidol in controlling positive symptoms, and was superior to placebo in reducing negative symptoms, whereas haloperidol was not.³⁹ In a recent single photon emission computerized tomography (SPECT) study, Sertindole treated patients demonstrated significantly lower levels of striatal D2 binding compared to those treated with haloperidol and risperidone but significantly higher levels compared to clozapine.⁵² Sertindole was not associated with EPS at dose of 12-24 mg/day. The highest dose 24 mg might induce EPS. Slight prolongation of QT interval (1.7% of pts) was seen with sertindole in early clinical trials and its use is contra-indicated in patients suffering from cardiac diseases.

Zotepine

Zotepine, a tricyclic compound structurally similar to clozapine, was as a broad-spectrum antipsychotic drug with high affinity for D1 and D2 receptors as well as for 5 HT₂, 5HT₆, and 5HT₇ receptors.⁴⁰ A unique feature of this drug was claimed to be its noradrenalin reuptake inhibition, which could have clinical relevance for the treatment of co morbid affective states. Zotepine was reported to elevate enkephaline; mRNA levels in the limbic area, a property suggested to be relevant to its neuroleptic property.⁶¹ Somnolence and weight gain were the most frequent side effects. An average dose of zotepine is 50-100 mg thrice a day.

Alternative Treatments

Chritson et al (1991),²⁰ and Meltzer (1992),⁶⁴ have extensively reviewed alternative pharmacological treatments for schizophrenia. According to them schizophrenia patients (resistant to conventional antipsychotic) could be benefited by alternative medications.

Benzodiazepines (BZD)

BZDs are known to facilitate gamma-amino butyric acid (GABA) transmission in the CNS. GABA is an inhibitory neurotransmitter that modulates the CNS release of serotonin, norepinephrin and dopamine in the nigrostriatal and possibly the mesolimbic brain region via a negative feedback loop, as there is decreased GABA activity in schizophrenia patients and BZD may reverse this biochemical deficits. Many studies were made to investigate the efficacy of BZD in patients resistant to the treatment with conventional antipsychotic. There was a significant improvement in the schizophrenic symptoms, when added to the stable dose of antipsychotic and was subsequently crossed over in a double blind fashion for comparison with placebo.^{20, 74}

Various studies suggested that those patients with higher baseline anxiety and psychosis may show the greatest improvement.^{55, 59} Side effects associated with BZD are social disinhibition, aggression sedation and ataxia.⁴⁹

Carbamazepine (CBZ)

Several small open studies have suggested that CBZ may be useful as an adjunct to antipsychotic in resistant schizophrenia.^{13, 38} Carbamazepine should not be added to clozapine, because of its potential to suppress bone marrow function and increased the risk of clozapine – induced agranulocytosis. Carbamazepine appears to be potentially useful adjunctive agent in the treatment of resistant schizophrenia with history of EEG abnormalities, manic like symptoms, excitement and hyperactivity.

Valproate

Several anecdotal reports and uncontrolled studies have suggested that valproate may be useful in treating resistant schizophrenia patients when added to conventional antipsychotics.^{37, 56}

Lithium

The addition of lithium to conventional antipsychotic has resulted in improvement in some treatment of resistant

patients. Several double blind controlled crossover trials (so far) showed lithium to be superior to placebo for hallucination, delusion, negative symptoms, irritability and excitement. The result suggest that 33-50% of treatment, resistant patients will show some improvement within four weeks when lithium is added to antipsychotic.^{18, 36} Dose of lithium should be adequate to achieve plasma concentrations of 0.8-1.2 mg/l. Notably there have been reports of neurotoxicity when lithium has been combined with antipsychotic, so patients must be monitored closely for changes in cognition and neurological functions.

Propranolol

Propranolol (PPI), a beta-adrenergic blocking agent in high dose acts pharmacologically as an anticonvulsant, not as antipsychotic and suppresses temporal lobe abnormalities. This may explain the beneficial effect of propranolol in decreasing aggression in patients with head injuries. Thus a patient with schizophrenia that may actually be responsive to propranolol is the coarse/diffuse brain dysfunction as opposed to the psychosis per se.⁶⁰ Cardiopulmonary side effects of propranolol severely limits its utility in the treatment of resistant schizophrenia.²⁸

Antidepressants

Adjunctive specific serotonin reuptake inhibitors (SSRI) can be beneficial to schizophrenia patients. Also the addition of the 5HT_{1A} agonist buspirone has been of some benefit to the number of patients. Fluoxetine (or other SSRI) may result in dose regulation of post-synaptic serotonin receptors, causing the overall effect of the medication to be similar to serotonin blockade. Alternately (or perhaps additionally), it may work by increasing plasma levels of the neuroleptic through competitive metabolism. Patients with schizophrenia, who have obsessive-compulsive and depressive tendencies, may benefit more from trial of combined therapy with a conventional neuroleptics and SSRI.

Electroconvulsive Therapy (ECT)

Although ECT is not as effective as medication across the range of schizophrenia patients, it has been shown to be of some value, and its relative merits in refractory patients deserve further study. Those patients with illness duration of more than six month, significant affective symptoms or catatonia are the ones, likeliest to benefit from ECT.

Psychological Intervention

There is evidence of modest effects for skill training and supportive individual and group therapies. There is encouraging early evidence for the efficacy of cognitive behavioral therapy.⁵⁷

Family therapies, Assertive community treatments, Vocational rehabilitation have clear effects on the prevention of psychotic relapse and rehospitalization. Social skill training improves social skills. Assertive community training programs ought to be offered to patients with frequent relapses and hospitalizations, especially if they have limited family support.^{16, 57, 62}

New Schizophrenia Medication in Development

The field of neuroscience is booming, and the future of schizophrenia treatments is bright. Main goal should be how to treat the debilitating symptoms with minimum side effects. There is a list of possible future medications for schizophrenia in various stages of clinical testing and developments.

Schizophrenia Medications (currently in phase III trials)

1,8,30,33,41,42,43,45,63,65,70,77

- Asenapine (for positive and negative symptoms)
- Bifeprunox (positive, negative cognitive symptoms, also relieve side effects)
- Iloperidone /zomaril (positive, negative cognitive symptoms)
- Lamictal (adjunct therapy, may improve positive symptoms)
- Osanetant (for movement side effects cause by traditional neuroleptics)
- Paliperidone (for treatment of refractory patients)
- RG 1068 (for autistic type symptoms in schizophrenia patients)
- Seromycin/ d-cycloserine (adjunctive treatment for negative patients)

Schizophrenia Medications (currently in phase II trials)^{31,61,67,68,78}

- AMPAkinases/CX-516 (to enhance the therapeutics effects of current medications)
- Galantamine (for cognitive/negative symptoms and learning deficits)
- Memantine (for cognitive symptoms)
- Modafinil (for cognitive symptoms and working memory)
- Ocapiperidone (for positive symptoms with few side effects)
- Talnetant (for movement side effects, cognitive symptoms)
- Tolcapone (for cognitive symptoms)

Conclusions

The optimal goal of treatment must be the immediate, complete and sustained remission of all symptoms of psychosis in all individuals being treated for schizophrenia. Unfortunately each case represents with a unique symptom profile and needs different approach of treatment and thus a significant challenge for the clinicians. So the clinical approach should be one of determined simplicity with very careful and deliberate changes, made in non-reactive manner. The introduction of new antipsychotic drugs has alleviated many of the problems of side effects for people with psychoses and resulted in obvious improvements in their quality of life. Hopeful the use of new antipsychotic in combination with optimal education and community support will improve compliance with treatment and reduce the chance of relapse. Other medications (under phase II, III clinical trials) held promise for the improved outcome in this devastating illness. The increasing clinical availability of new and different antipsychotic drugs will undoubtedly fuel even greater advances along these fronts in the near

future. Although we are still a long way from achieving the goal, the new antipsychotic drugs have narrowed the gap between current and optimal practice.

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