

# Pharmacotherapy of Schizophrenia: Polypharmacy Approaches

Fatemeh Rahiminejad and Shahin Akhondzadeh\*

Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received: 30 May 2010; Accepted: 1 Jun. 2010

**Abstract-** Schizophrenia is a debilitating illness, rating as one of the leading causes of lost years of quality of life. The illness imposes a disproportionate burden on patients and their families, healthcare systems and society. Pharmacological management is the cornerstone of treatment of schizophrenia, and antipsychotics, both first generation of antipsychotics and second generation of antipsychotics, are efficacious in reducing levels of psychopathology in acute episodes of schizophrenia. Clearly a need for innovative treatment strategies in schizophrenia that will ensure increased effectiveness against negative symptoms and cognitive dysfunction. Therefore, in majority of cases polypharmacy is one of the effective approaches. This review focused on polypharmacy in the treatment of schizophrenia and in particular negative symptoms. © 2010 Tehran University of Medical Sciences. All rights reserved.

*Acta Medica Iranica* 2010; 48(4): 203-208.

**Key words:** Glutamates; serotonin; polypharmacy; schizophrenia

Schizophrenia is a relatively common form of mental illness and psychotic disorder (severe mental illness). Its lifetime prevalence is nearly 1%, its annual incidence is about 10-15 per 100000, and the average general practitioner cares for 10-20 schizophrenic patients depending on location and social surroundings of practice (1). It is a syndrome with various presentations and a variable, often relapsing, long-term course. No universally efficacious and tolerable treatment has yet been discovered for this chronic major illness, which typically has its onset in late adolescence or young adulthood. Between 25% and 50% of patients suffering from an acute episode attempt suicide and 10% of these attempts succeed a suicide mortality rate eight times that of the general population (2-4).

## What are diagnosis criteria for schizophrenia?

Criteria for diagnosis of schizophrenia dictate that at some stage of the illness patients have delusions, hallucinations, or certain characteristic disturbances in affect and the form of thought. However, the onset, time course, and nature of the disturbances in emotion, personality, cognition, and motor activity exhibited by patients with schizophrenia vary widely (2-4).

## DSM IV Criteria for schizophrenia

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

- 1- delusions
- 2- hallucinations
- 3- disorganized speech (eg, frequent derailment, incoherence)
4. grossly disorganized or catatonic behavior
5. negative symptoms (eg, affective flattening, alogia, avolition)

Note: Only one criteria A symptoms is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts or two or more voices conversing with each other

- B. Social/occupational dysfunction
- C. overall duration 6 months or more
- D. schizoaffective and mood disorder exclusion
- E. substance/general medical condition exclusion
- F. Relation to a pervasive development disorder

## Clinical features

Positive Symptoms (functions distorted):

These are essentially disordered versions of the normal brain functions of thinking, perceiving, formation of ideas, and sense of self. Patients with thought disorder may present with complaints of poor concentration or of their mind being blockade or emptied: a patient stopping in a perplexed fashion while in mid-speech and the interviewer having difficulty in following the speech are typical signs (2-4).

\*Corresponding Author: Shahin Akhondzadeh  
Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran  
Tel: +98 21 55412222, Fax: +98 21 55419113, E.-mail: s.akhond@neda.net

## Pharmacotherapy of schizophrenia

- \* hallucinations (perception)
- \* delusions (inferential thinking)
- \* disorganized speech (thought/language)
- \* disorganized (bizarre) behavior (behavioral monitoring/motor activity)

### Negative symptoms (functions diminished)

These involve loss of personal abilities such as initiative, interest in others, and the sense of enjoyment (anhedonia). Blunted or fatuous emotions (flat affect), limited speech, and much time spent doing nothing are typical behaviors (5).

- \* alogia (fluency of speech/thought)
- \* affective blunting (emotional expression)
- \* avolition (volition and drive)
- \* anhedonia/asociality (ability to feel pleasure, experience emotional attachments, and/or from relationships with others)
- \* attention impairment (focusing attention)

### Etiology

Despite a large effort to clarify the pathogenesis of schizophrenia, progress has been modest and definitive answers to the most pressing questions remain elusive (6).

### Dopamine hypothesis and schizophrenia

Scientists have noted the role of dopamine in schizophrenia since they uncovered the chemical reactions behind the first antipsychotics. However, the exact nature of its role has long been and remains in dispute. The first model of the role of dopamine in schizophrenia was the dopamine hyperactivity hypothesis. This asserts that hyperactivity of the brain's dopaminergic systems is directly responsible for the symptoms of schizophrenia. In the period since its inception, this hypothesis has been accepted, studied and supported by neuroscientists (7-10). One supportive observation involves the actions of drugs that enhance the activity of dopaminergic systems. Amphetamine is one such drug; when introduced in chronic amounts, amphetamines can induce symptoms virtually identical to those of a paranoid psychosis. The dopamine hypothesis was the first durable biological framework for understanding the etiology and treatment of schizophrenia; however, it failed to explain many aspects of schizophrenia, such as negative symptoms, cognitive deficits and other neurochemical and pathological findings. Interest in dopamine interactions with other neurotransmitter systems has contributed to the development of novel antipsychotics with better

clinical efficacy (11). In addition, another weakness of the dopamine hypothesis involves the time course of the clinical effects of antipsychotics. While neuroleptics block D<sub>2</sub> receptors shortly after crossing the blood-brain barrier, their antipsychotic effects do not reach a clinically significant level until, on average, one to two weeks later. In addition, antipsychotics neither cure the illness, nor stop the relapse of symptoms completely, and about 30% of patients are refractory to treatment with dopamine blockers. In this regard, the atypical antipsychotics, which are less specific blockers of dopamine, may be superior to haloperidol and result in fewer extrapyramidal symptoms. The major limitations of conventional antipsychotic drugs are their marked tendency to cause extrapyramidal symptoms, poor efficacy against negative schizophrenic symptoms, inability to reverse or prevent the development of the cognitive impairment of schizophrenia and inability to permit a normal level of psychosexual and work function (11). These factors lead to a poor quality of life even for patients whose positive and disorganized symptoms respond to neuroleptic treatment. In the past 20 years, several basic research findings have provided hypotheses about pathophysiology of schizophrenia. This research, which spans many different disciplines, includes studies of the receptor pharmacology of neuroleptics at dopamine, serotonin, glutamate, purinergic and muscarinic receptors, electrophysiological studies with rats treated chronically with drugs, and molecular biological studies measuring the expression of immediate early genes (12-15).

### 5-HT hypothesis and schizophrenia

There are at least four lines of evidence that have implicated 5-HT in the pathophysiology of schizophrenia, which are discussed below (3, 16).

### Behavioral studies of LSD-induced psychosis

The involvement of serotonin systems in schizophrenia was suggested by the hallucinogenic effects of drugs, such as LSD, which have an affinity for serotonin receptors (3).

### Post mortem investigations of schizophrenic brains

Although there are conflicting data from schizophrenia/5-HT post mortem studies, one of the more consistent findings is elevated 5-HT levels and its metabolites in basal ganglia.

Another relatively consistent finding is decreased 5-HT<sub>2</sub> receptor densities in prefrontal cortices. Data that

have also been reported, but require replication, include increased 5-

HT2 and 5-HT1A receptor densities in certain limbic areas (3).

### **Pharmacological challenge studies of 5-HT agents and treatment of schizophrenia**

Recent interest in the role of 5-HT in antipsychotic drug actions is largely based upon the discovery of the efficacy of clozapine, risperidone (Janssen Pharmaceutical), olanzapine

(Eli Lilly) and quetiapine (AstraZeneca) in treating the delusions, hallucinations and disorganization of schizophrenic patients who failed to respond to classical neuroleptic drugs. Indeed, an atypical antipsychotic is defined as an agent with low endocrine and extrapyramidal side effects, acceptable efficacy on negative symptoms and, overall, causing a better quality of life compared to typical antipsychotics. The 5-HT hypothesis of schizophrenia suggests that atypical antipsychotics have a high affinity for 5-HT<sub>2A</sub> receptors and a low affinity for D<sub>2</sub> receptors. It should be emphasized that some atypical antipsychotic agents also have affinities for 5-HT<sub>2C</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors (3, 17).

### **Platelet and CSF studies**

Several investigators examined CSF levels of 5-hydroxyindoleacetic acid (5-HIAA), the major 5-HT metabolite in schizophrenic patients, and reported conflicting results of lower and unchanged levels compared to control values. Moreover, human blood platelets, which are neuroectodermal derivatives and share many properties of brain neuronal tissue, have been used to study neurotransmitter function. In general, 5-HT produces antagonistic actions on dopamine-mediated behaviors. Unlike the dopamine systems, which innervate a relatively restricted cerebral area, serotonin fibers emanate from dorsal raphe and project to all areas of cortex and innervate basal ganglia (3).

### **Cyproheptadine, ritanserin and ondansetron**

In several double-blind, placebo-controlled studies, the efficacy of ritanserin cyproheptadine were evaluated. In an add-on protocol, ritanserin, cyproheptadine and ondansetron were effective in concurrent treatment of negative symptoms and reduction of EPS. Beneficial effects of ritanserin have also been demonstrated in antipsychotic induced akathisia or when compared with anticholinergic agents. The efficacy of ritanserin with its pharmacological profile as a 5-HT<sub>2</sub> selective

antagonist is in line with 5-HT hypothesis of schizophrenia (18-20).

### **Glutamate hypothesis and schizophrenia**

From the NMDA receptor hypofunction model of schizophrenia, glutamate agonists should be effective in ameliorating positive or negative symptoms of schizophrenia. Clearly, if a specific defect in NMDA receptor-mediated neurotransmission were identified, therapy aimed at compensating for that specific defect would be indicated. Nevertheless, attempts to develop therapeutic agents directed at the NMDA subtype of the glutamate receptor have been unsuccessful, in part because of adverse effects, which include potential neurotoxicity. Another possible therapeutic approach targets the strychnine-insensitive glycine recognition site of the NMDA receptor complex, which facilitates opening of the NMDA channel. However, there is a considerable problem regarding application of glycine. In fact, glycine poorly penetrates the blood-brain barrier and accumulation of unmetabolized milacemide in the brain may antagonize the effect of glycine at the NMDA receptor complex (21-22). On the other hand, D-cycloserine, a partial agonist with ≈60% activity at the glycine site of the NMDA receptor, which readily facilitates learning in animals, has produced promising results (21). The involvement of glutamatergic system in schizophrenia may have important implications for dopamine neurotransmission and receptor function. In another words, any hypothesis of schizophrenia that does not explain the involvement of dopaminergic system is a weak hypothesis. It is possible to improve the explanatory power of either the dopamine or glutamate hypothesis by incorporating the former into the latter. For example, because one action of dopamine receptors is to inhibit glutamate release (21), a primary defect in the dopamine system that causes dopamine hyperactivity could result in excessive suppression of glutamate release at NMDA receptors, with consequential hypofunction of the NMDA receptor system as the basis for schizophrenic symptoms (21). The NMDA receptor hypofunction hypothesis also suggests that activation of GABA receptors may be therapeutic. Although a positive response to benzodiazepine treatment has been reported in a few studies that used high doses or that investigated the catatonic subtype of schizophrenia or negative aspects of the illness, most studies have shown that benzodiazepines have little or no value when compared to placebo in the treatment of schizophrenia (21). These are in line with the knowledge that benzodiazepines do

## Pharmacotherapy of schizophrenia

not by themselves open the GABA chloride ion channel (21). They act only to potentiate the action of GABA. In the presence of NMDA receptor hypofunction, GABAergic neurons are inactivated so that in the synaptic cleft there is little GABA to potentiate. Certain barbiturates directly open the GABA chloride ion channel and therefore would theoretically be more effective in treating patients with schizophrenia (21). However, they would probably not be of practical value because at the doses required to open the GABA chloride ion channel, they act as sedative hypnotics.

### Piracetam and D-cycloserine

Piracetam, a member of the nootropic class of drugs and a positive modulator of glutamate receptor, may be of therapeutic benefit in treating schizophrenic patients in combination with antipsychotics. Akhondzadeh et al., in a double blind, randomized trial added 3200 mg /day piracetam to haloperidol in patients with schizophrenia for 8 weeks. They reported that piracetam may be of therapeutic benefit in treating the positive and general psychopathological symptoms of schizophrenia (22). Another approach is to use a partial agonist: D-cycloserine. In a dose-finding study, Goff et al. found an inverted-U dose response curve, with maximum therapeutic efficacy at 50 mg/day and loss of efficacy with doses below 50 mg/day or above 100 mg/day (21-25). In subsequent studies, positive results have been observed in patients who received D-cycloserine (50–100 mg/day) and who were treated with conventional antipsychotics (23-25). Negative results have been observed when patients were treated with doses other than 50 mg/day or when D-cycloserine was added to clozapine (23–25). Goff et al. also found that the observed therapeutic effect was mainly on negative symptoms, including patients with deficit or primary negative symptoms. One study used the Sternberg working memory paradigm and reported a benefit for D-cycloserine in an effort to alleviate affective symptoms in schizophrenic psychoses (21).

### Purinergic hypothesis of schizophrenia

There is a large amount of data showing that adenosine plays a role opposite to dopamine in the brain (14). Adenosine agonists and antagonists produce behavioral effects similar to dopamine antagonists and dopamine agonists, respectively. Preclinically, adenosine and its analogs exert antipsychotic, anxiolytic, sedative, anticonvulsant and anti aggressive effects (26). Similarly to amphetamine and NMDA receptor antagonists, caffeine and theophylline produce

hyperlocomotor responses in rodents, which can be reversed by antipsychotics. In healthy subjects, high doses of adenosine antagonists can produce psychosis (26, 27). Allopurinol, a well-known hypouricemic drug that inhibits xanthine oxidase, has been used as add-on drug in the treatment of poorly responsive schizophrenic patients. Indeed, the neuropsychiatric effects of allopurinol in schizophrenia have been suggested to be secondary to its inhibitory effect of purine degradation, enhancing adenosinergic activity (27). Unfortunately, direct or indirect adenosine agonists with clear effects on the brain are not yet available for human use.

This hypothesis is based on the idea that several aspects of schizophrenia can be attributed to a disorder of the purinergic system. These aspects will be separately dealt with, followed by the findings involving purine metabolism in schizophrenic patients. In a study by Akhondzadeh et al. (27), acute schizophrenia inpatients were randomized to haloperidol 15 mg per day plus allopurinol 300 mg per day vs. haloperidol 15mg plus placebo. Among the n=37 study completers of the n=46 enrolled, there was a significantly greater improvement in the allopurinol group on the Positive and Negative Syndrome Scale (PANSS) positive, negative, general, and total scores over the 8 week study period. In another recent clinical trial in schizophrenia (28), patients with treatment resistant schizophrenia received 600 mg per day of adjunctive allopurinol in a crossover design; each patient received 6 weeks of either adjunctive allopurinol or adjunctive placebo and then 6 weeks of the alternative agent for another 6 weeks. Among the n=22 completers of the n=35 enrolled, there was a significantly greater improvement on PANSS positive symptoms in the allopurinol phase compared with baseline and placebo phases (28). Propentofylline is a xanthine derivative which was developed for treatment of degenerative and vascular dementia. Salimi et al in an eight week double blind trial reported that propentofylline as a potential adjunctive treatment strategy for chronic schizophrenia (29)

### Antidepressants and schizophrenia

Clinical studies reported the successful augmentation of antipsychotics with antidepressive agents such as imipramine, reboxetine, several serotonin reuptake inhibitors (SSRIs), venlafaxine, selegiline and mirtazapine (30-33). It has been reported that mirtazapine would be helpful for treating negative symptoms in schizophrenia. Akhondzadeh et al, in an eight week trial of mirtazapine added to risperidone reported that the mirtazapine group had significantly

greater improvement in the negative symptoms over the 8 weeks trial. No significant difference was observed between the means of the two groups on the positive and general psychopathology scores. This study indicates mirtazapine as a potential adjunctive treatment strategy for treatment of negative symptoms of schizophrenia (34). In conclusion, schizophrenia is clinically heterogeneous and is believed to be the common syndrome resulting from a number of different etiopathogenic processes (35, 36). The advent of the novel antipsychotics during the last 15 years represents a significant improvement over the effectiveness of conventional antipsychotics. However, these agents are not a magic bullet and are associated with their own attendant treatment complications. For all of these reasons, advances in the treatment of schizophrenia have been and continue to be urgently needed.

## References

- Andreasen NC. Schizophrenia: the fundamental questions. *Brain Res Brain Res Rev* 2000;31(2-3):106-12.
- Akhondzadeh S, Malek-Hosseini M, Ghoreishi A, Raznahan M, Rezazadeh SA. Effect of ritanserin, a 5HT<sub>2A/2C</sub> antagonist, on negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(8):1879-83.
- Akhondzadeh S. The 5-HT hypothesis of schizophrenia. *IDrugs* 2001;4(3):295-300.
- Akhondzadeh S. Pharmacotherapy of schizophrenia: the past, present and future. *Curr Drug Ther* 2006;1(1):1-7.
- Mohammadi MR, Akhondzadeh S. Schizophrenia: etiology and pharmacotherapy. *IDrugs* 2001;4(10):1167-72.
- Nieratschker V, Nöthen MM, Rietschel M. New Genetic Findings in Schizophrenia: Is there Still Room for the Dopamine Hypothesis of Schizophrenia? *Front Behav Neurosci* 2010;4:23.
- Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. *Schizophr Bull* 2010;36(3):472-85.
- Jablensky A, Sartorius N, Ernberg G. Schizophrenia: manifestation, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Med Mono Supplement* 1992;20(suppl):1-97.
- Nestler EJ. Schizophrenia. An emerging pathophysiology. *Nature* 1997;385(6617):578-9.
- Wright I, Woodruff P. Aetiology of schizophrenia Review of theories and their clinical and therapeutic implications. *CNS Drugs* 1995;3:126-44.
- Heyman I, Murray RM. Schizophrenia and neurodevelopment. *J R Coll Physicians Lond* 1992;26(2):143-6.
- Littrell RA, Schneiderhan M. The neurobiology of schizophrenia. *Pharmacotherapy* 1996;16(6 Pt 2):143S-147S; discussion 166S-168S.
- Snyder SH. The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. *Am J Psychiatry* 1976;133(2):197-202.
- Johnstone EC, Crow TJ, Frith CD, Carney MW, Price JS. Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet* 1978;1(8069):848-51.
- Carlsson A. The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 1988;1(3):179-86.
- Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic-epidemiologic perspective. *Schizophr Bull* 1993;19(2):261-85.
- Meltzer HY, Lee MA, Ranjan R. Recent advances in the pharmacotherapy of schizophrenia. *Acta Psychiatr Scand Suppl* 1994;384:95-101.
- Arndt S, Allinger RJ, Anderson NC. The distinction of positive and negative symptoms. The failure of a two dimensional model. *Br J Psychiatry* 1991;158:317-22.
- Akhondzadeh S, Mohammadi MR, Amini-Nooshabadi H, Davari-Ashtiani R. Cyproheptadine in treatment of chronic schizophrenia: a double-blind, placebo-controlled study. *J Clin Pharm Ther*. 1999;24(1):49-52.
- Akhondzadeh S, Malek-Hosseini M, Ghoreishi A, Raznahan M, Rezazadeh SA. Effect of ritanserin, a 5HT<sub>2A/2C</sub> antagonist, on negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(8):1879-83.
- Akhondzadeh S, Mohammadi N, Noroozian M, Karamghadiri N, Ghoreishi A, Jamshidi AH, et al. Added ondansetron for stable schizophrenia: a double blind, placebo controlled trial. *Schizophr Res* 2009;107(2-3):206-12.
- Akhondzadeh S. The glutamate hypothesis of schizophrenia. *J Clin Pharm Ther* 1998;23(4):243-6.
- Noorbala AA, Akhondzadeh S, Davari-Ashtiani R, Amini-Nooshabadi H. Piracetam in the treatment of schizophrenia: implications for the glutamate hypothesis of schizophrenia. *J Clin Pharm Ther* 1999;24(5):369-74.
- Goff DC, Freudenreich O, Evins AE. Augmentation strategies in the treatment of schizophrenia. *CNS Spectr* 2001;6(11):904, 907-11.
- Goff DC, Herz L, Posever T, Shih V, Tsai G, Henderson DC, et al. A six-month, placebo-controlled trial of D-cycloserine co-administered with conventional antipsychotics in schizophrenia patients. *Psychopharmacology (Berl)* 2005;179(1):144-50.

## Pharmacotherapy of schizophrenia

25. Goff DC, Cather C, Gottlieb JD, Evins AE, Walsh J, Raeke L, et al. Once-weekly D-cycloserine effects on negative symptoms and cognition in schizophrenia: an exploratory study. *Schizophr Res* 2008;106(2-3):320-7.
26. Akhondzadeh S, Shasavand E, Jamilian H, Shabestari O, Kamalipour A. Dipyridamole in the treatment of schizophrenia: adenosine-dopamine receptor interactions. *J Clin Pharm Ther* 2000;25(2):131-7.
27. Akhondzadeh S, Safarcherati A, Amini H. Beneficial antipsychotic effects of allopurinol as adjunctive therapy for schizophrenia: A double blind, randomized and placebo controlled trial. *Prog Neuropsychopharmacol Biol Psych* 2005;29(2):253-9.
28. Brunstein MG, Ghisolfi ES, Ramos FL, Lara DR. A clinical trial of adjuvant allopurinol therapy for moderately refractory schizophrenia. *J Clin Psychiatry* 2005;66(2):213-9.
29. Salimi S, Fotouhi A, Ghoreishi A, Derakhshan MK, Khodaie-Ardakani MR, Mohammadi MR, et al. A placebo controlled study of the propentofylline added to risperidone in chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(3):726-32.
30. Erhart SM, Marder SR, Carpenter WT. Treatment of schizophrenia negative symptoms: future prospects. *Schizophr Bull* 2006;32(2):234-7.
31. Buckley PF, Stahl SM. Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or cul-de-sac? *Acta Psychiatr Scand* 2007;115(2):93-100.
32. Agid O, Kapur S, Remington G. Emerging drugs for schizophrenia. *Expert Opin Emerg Drugs* 2008;13(3):479-5.
33. Amiri A, Noorbala AA, Nejatisafa AA, Ghoreishi A, Derakhshan MK, Khodaie-Ardakani MR, Hajiazim M, Raznahan M, Akhondzadeh S. Efficacy of selegiline add on therapy to risperidone in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. *Hum Psychopharmacol* 2008;23(2):79-86.
34. Abbasi SH, Behpourmia H, Ghoreishi A, Salehi B, Raznahan M, Rezazadeh SA, et al. The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. *Schizophr Res* 2010;116(2-3):101-6.
35. Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. *Schizophr Res* 2006;84(2-3):405-10.
36. Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnam B. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. *Schizophr Res* 2007;90(1-3):179-85.