Research Journal of Biological Sciences 3 (5): 509-514, 2008
ISSN: 1815-8846


# Extrapyramidal Side Effects of Risperidone in Iranian Schizophrenic Patients

Mohammad-Ali Ghoreishizadeh and Faranak Deldoost
Department of Psychiatry, Razi Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

**Abstract:** Risperidone is one of a new generation of antipsychotic drugs with relatively fewer side effects and better efficacy. Our objects were study of relationship between the incidence of Iranian produced risperidone Extrapyramidal Side Effects (EPSE) and its relationship with age, sex, dosage and duration of treatment in patients with schizophrenia or schizoaffective disorders. One-hundred patients with schizophrenia or schizoaffective disorders admitted in Razi hospital of Tabriz, which underwent treatment with risperidone were selected by convenience method and the incidence of EPSE was evaluated for 6 weeks; the results were analyzed statistically. Seventy-two percent of patients showed no complications and 28% of them affected by EPSE. The incidence of complications was not related significantly with age and sex of patients but there was significant relationship between the duration of medication and dosage of drug ($pv<0.05$). The most EPSE were rigidity, tremor and bradykynesia, but there were not any acute dystonic reaction. Risperidone is one of the new generation antipsychotic drugs with lower side effects and its EPSE are dose-dependent. It is recommended that the treatment be initiated with minimum effective dose.

**Key words:** Risperidone, extrapyramidal side effects, schizophrenia, antipsychotic drugs

## INTRODUCTION

Schizophrenia is a severe, chronic psychiatric disorder affecting approximately 1% of the world's population and is characterized by a range of distinct symptoms, including delusions, auditory hallucinations, behavioral dysfunction and neurocognitive effects (Parellada, 2007). Conventional antipsychotic drugs, used for a half century to treat a range of major psychiatric disorders. Patients will frequently experience side effects of these antipsychotics before they experience clinical improvement. Whereas a clinical response may be delayed for days or weeks after drug are started, side effects will often begin almost immediately. This early onset of side effects is important because a patients interpretation of a drug's effectiveness is often associated with how feel (Parellada, 2007; Gardner *et al*., 2005; Voris and Glazer, 1999).

Extrapyramidal symptoms are the most common reason for non-adherence to schizophrenia treatment, leading to treatment failures and preventable morbidity, mortality and economic costs. The most common and troubling form of EPS is akathisia. Researchers have estimated that 25-75% of patients treated with a high-potency conventional drug will experience akathisia. Dystonia are probably the most frightening type of EPS.

These reactions usually appear within the first few days of therapy. The majority of studies have reported that atypical antipsychotics are less likely cause extrapyramidal symptoms than typical antipsychotics (Park *et al*., 2005).

The atypical or second generation antipsychotics such as risperidone have become the dominant agents for treating schizophrenia. The widespread use of these agents has revealed both their advantages and limitations (Parellada, 2007).

The main goal of this study was assessment of the extrapyramidal side effects of Iranian produced risperidone with generic name of Risperidone in schizophrenic or schizoaffective patients. Our objects also were study of association between the incidence of risperidone side effects with age, sex, dosage of drug and duration of treatment.

## MATERIALS AND METHODS

This descriptive-analytic study performed on 100 schizophrenic or schizoaffective patients presenting to the Tabriz Razi Educational and Therapeutic Center from August 2004 until June 2005. The diagnoses were made by Razi center specialists according to the DSM IV criteria. The patients were selected by convenience sampling method.

**Corresponding Author:** Faranak Deldoost, Department of Psychiatry, Razi Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

Inclusion criteria were:

- Having the diagnosis of schizophrenia or schizoaffective disorder by semi-structured interview and according DSM IV criteria.
- Having the age 18-60 years.
- Male or female sex.
- Old or new episode of disease.

Exclusion criteria were having organic disease, substance or drug abuse, history of medical disease, history of neurological disease, the age <18 or >60 years and use of other psychotropic drugs.

We used Sobhan company production with generic name of Risperidone. Sobhan is a famous drug company of Iran especially in producing psychiatric drugs. It made risperidone in tablet form of 1-4 mg. we used the 2 mg tablet. All of our patients were treated with risperidone as the main antipsychotic drug. Risperidone was given orally once or twice daily.

We started risperidone in lower dosages and increased slowly. Because the aim of this study was evaluation of extrapyramidal side effects of risperidone, anti-parkinson drugs did not administered initially and these drugs started when the extrapyramidal side effects occurred.

In this study, extrapyramidal side effects examined by using Abnormal Involuntary Movement Scale (AIMS) (Gharabawi *et al*., 2005). Also, extrapyramidal side effects were assessed according to the DSM IV diagnostic criteria. According to these criteria, extrapyramidal side effects were as following:

- Parkinsonism.
- Dystonia.
- Akathisia.
- Neuroleptic Malignant Syndrome (NMS).
- Rabbit syndrome.
- Tardive dyskinesia.

The patients followed by a questionnaire for measurement of extrapyramidal symptoms (AIMS) in 1, 3 and 6 week of treatment period. The data were collected and assessed according to the age, sex, dosage and type of extrapyramidal side effects and ultimately were analyzed by SPSS 11 statistical software.

## RESULTS

Of 100 schizophrenic or schizoaffective patients, 35 (35%) were female and 65 (65%) were male. Of all patients 72 (72%) remained uncomplicated and 28 (28%) became complicated, of which 23 (82.2%) had Parkinsonism and 5 (17.8%) had akathisia.

Table 1: The occurrence of EPSE with duration of treatment

| Complications | Number (%) |
|---|---|
| No complication | 72 (72%) |
| First week | 5 (5%) |
| Third week | 11 (11%) |
| 6th week | 12 (12%) |
| Total | 100 (100%) |

Table 2: Sex distributions of respridone side effects

| Complication | Sex | Number | Sex group frequency (%) | P-value |
|---|---|---|---|---|
| Rigidity | Male | 9 | 25.7 | >0.05 |
| | Female | 3 | 4.6 | |
| Tremor | Male | 5 | 14.2 | >0.05 |
| | Female | 1 | 15.8 | |
| Bradykynesia | Male | 3 | 8.5 | >0.05 |
| | Female | 1 | 15.8 | |
| Akathisia | Male | 3 | 8.6 | >0.05 |
| | Female | 2 | 3 | |
| Rabbit syndrome | Male | 1 | 2.9 | >0.05 |
| | Female | 0 | 0 | |

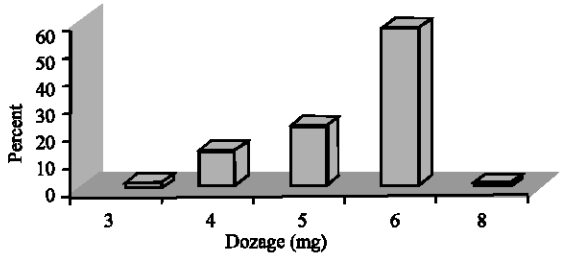


Fig. 1: The comparison of EPSE rate in different dozages of Risperidone

The complications occurred during the first (18%), third (39%) and 6th (43%) week of treatment (Table 1). The relation of initiation time and duration of treatment with rate of extrapyramidal side effects was not statistically significant ($p>0.05$).

The incidence of risperidone complications was not significantly related with patients age ($p>0.05$). However, the incidence of extrapyramidal side effects was increased with risperidone dosage and this increase was statistically significant (Fig. 1) ($p<0.05$).

Of 23 patients with Parkinsonism, 12 (52.1%) had rigidity, 6 (26%) had tremor and 4 (17.3%) had bradykinesia. The sex distributions of all these side effects are showed in Table 2. As showed in Table 2, the frequency of any of these complications is not significantly related with patients' sex.

## DISCUSSION

In our samples, we have not any dystonic reaction which is more prevalent with conventional drugs. A typical antipsychotic agents were developed in response

to problems with typical agents, including lack of efficacy in some patients, lack of improvement in negative symptoms and troublesome adverse effects, especially Extrapyramidal Symptoms (EPSs) and Tardive Dyskinesia (TD). Atypical antipsychotics differ from typical psychotics in their "limbic-specific" Dopamine type 2 (D2)-receptor binding and high ratio of serotonin type 2 (5-HT2)-receptor binding to D2 binding (Gharabawi *et al*., 2005; Worrel *et al*., 2000).

Atypical antipsychotics offer several additional advantages over old neuroleptics (Masand *et al*., 2002; Manning, 2000). They are associated with a lower incidence of the extrapyramidal syndrome (Gareri *et al*., 2006) in most patients obviating the need to add additional anticholinergic or dopaminergic medications to treat this side effect common to older agents. They are also associated with a lower risk of tardive dyskinesia (Masand *et al*., 2002; Manning, 2000) the dreaded and treatment-refractory complication of neuroleptic therapy. Finally and perhaps most significantly, the atypical antipsychotics offer potential efficacy in a broad range of nonschizophrenic illness (Manning, 2006). Several preliminary studies have now demonstrated that atypical antipsychotics, including risperidone, olanzapine, clozapine, quetiapine and ziprasidone, are efficacious in patients with bipolar and schizoaffective disorder (Masand *et al*., 2002).

Risperidone is an atypical antipsychotic commonly used for treatment of schizophrenia and other psychotic disorders (Boerth *et al*., 2005). Risperidone, a benzisoxazol derivative, is a novel antipsychotic agent which combines potent serotonin (5-hydroxytryptamine) 5-HT2 and dopamine D2 and $\alpha_1$ receptor antagonism (Gardner *et al*., 2005; Grant and Fitton, 1994). Development of the drug was stimulated by reports that the selective serotonin 5-HT2 antagonist ritanserin improved the negative symptoms of schizophrenia and decreased extrapyramidal symptoms when combined with haloperidol. The relatively low incidence of extrapyramidal symptoms with risperidone may reflect a preferential action on mesolimbic rather than nigrostriatal dopaminergic pathways. Recent clinical investigation suggests that risperidone is of at least comparable efficacy to haloperidol and perphenazine in improving the symptoms of acute and chronic schizophrenia on short term administration. Advantages offered by risperidone over haloperidol include a faster onset of antipsychotic action, a lower incidence of extrapyramidal effects and possibly greater efficacy against the negative symptoms of schizophrenia (Grant and Fitton, 1994).

Jayaram *et al*. (2006) suggest that 25% of people using risperidone required medication to alleviate extrapyramidal symptoms. This result is consistent with our study in which 28% of our patients treated with risperidone became complicated.

Neuroleptic-induced movement disorders, or Extrapyramidal Side effects (EPS), can be classified into acute and tardive syndromes. Among the former are Parkinsonism, dystonia and akathisia. Conventional neuroleptics that have traditionally been used to treat psychiatric disorders are often associated with EPS. The newer atypical antipsychotics provide a more promising treatment strategy for psychiatric disorders and have a lower potential for producing EPS than conventional neuroleptics (Lieberman, 2004; Wirshing, 2001). Atypical antipsychotics such as risperidone carry a minimal risk of Acute Dystonic Reactions (ADR) (Raja and Azzoni, 2001).

In this study, we did not find any case with ADR. However, many atypical antipsychotics can cause other potentially harmful side effects such as anticholinergic side effects. Peripheral and central anticholinergic side effects can cause physical and mental impairment. Awareness of the medications that have the potential to cause anticholinergic side effects as well as proper management of these symptoms can aid physicians in treating patients who need antipsychotic therapy (Lieberman, 2004).

Since atypical antipsychotics tend to have lower rates of side effects than the conventional agents, they can be invaluable to the treatment of schizophrenia. The risk of side effects does exist, though and anticholinergic side effects, if left untreated, have the potential to cause serious medical complications. Physicians can help patients avoid these medical complications through awareness of the signs and symptoms of anticholinergic side effects and of effective management of these symptoms (Lieberman, 2004).

In our series, we had one case of Rabbit Syndrome (RS). Rabbit syndrome is an uncommon extrapyramidal side effect of typical antipsychotics and risperidone which is characterized by rhythmic movements of the mouth and may be secondary to blockade of dopamine D2 receptors (Hoy and Alexander, 2002; Catena Dell'osso *et al*., 2007). Long-term exposure to the older neuroleptics has clearly been associated with RS, but of particular interest and importance is the risk of RS with exposure to the newer atypical antipsychotics. This syndrome is considered a distinct neuroleptic-induced extrapyramidal syndrome. There is evidence that RS combines features of both Parkinson's disease and tardive dyskinesia (Catena Dell'osso *et al*., 2007). Catena Dell'osso *et al*. (2007) suggested that to date, there are 11 reported cases of RS related to newer antipsychotics, which seven of them are linked to

risperidone. Risperidone is considered to be the atypical antipsychotic with the highest incidence of extrapyramidal symptoms. This high incidence may be caused by the high affinity for the serotonin type 2 and dopamine type 2 receptors and the low affinity for cholinergic muscarinic receptors (Catena Dell'osso *et al*., 2007).

Neuroleptic Malignant Syndrome (NMS) is the most serious of acute neurological side effects produced by antipsychotic medications, characterized by hyperthermia, rigidity, altered consciousness and autonomic dysfunction, the prevalence of which varies from 0.4-1.4%. NMS is usually seen in treatment with high potency typical antipsychotics and very rarely with atypical antipsychotics (Mishra *et al*., 2007). Virtually all neuroleptics are capable of inducing the syndrome, including the newer atypical antipsychotics clozapine, risperidone and olanzapine (Pelonero *et al*., 1998). However, in our series we have not any case of NMS.

Tardive Dyskinesia (TD) associated with antipsychotics is an important treatment concern. Recent long-term trials were consistent with previous reports, suggesting lower rates of dyskinesia with atypical antipsychotics compared to conventional agents. Among 458 patients, 0.87% receiving risperidone and 2.33% receiving haloperidol met criteria for new-onset TD. Annualized rates were 0.72 and 1.87%, respectively. Mean modal doses were 3.4 and 3.2 mg $day^{-1}$, respectively (Gharabawi *et al*., 2006; Hong *et al*., 1999). However, in 100 patients receiving risperidone, we have not any case of this complication in 6 weeks follow up period.

In our study, the incidence of extrapyramidal side effects was increased significantly with risperidone dosage. Simpson and Lindenmayer evaluated EPS in 523 patients with chronic schizophrenia who, after a 1-week washout period, received placebo, risperidone (2, 6, 10, or 16 mg $day^{-1}$), or haloperidol (20 mg $day^{-1}$) for 8 weeks. Severity of EPS was assessed by means of the Extrapyramidal Symptom Rating Scale (ESRS). Mean changes (increases) in ESRS scores from baseline to worst score were significantly lower in each risperidone group than the haloperidol group on the total ESRS (Parkinsonism + dystonia + dyskinesia). At the clinically most effective risperidone dose (6 mg $day^{-1}$), the mean ESRS change score was not significantly different from that of the placebo group. A significant linear relationship was noted between mean change scores and increasing risperidone dose on 4 of the 12 ESRS subscales; nevertheless, even at 16 mg $day^{-1}$ of risperidone, mean change scores were lower than in the haloperidol group. A linear relationship between increasing risperidone dose and use of anti-Parkinsonian medications was also apparent Simpson and Lindenmayer, 1997). Katz *et al*. (1999) study on 625 patients suggests that more adverse events were reported by patients receiving 2 mg $day^{-1}$ of risperidone than 1 mg $day^{-1}$. The most common dose-related adverse events were EPS, somnolence and mild peripheral edema. The frequency of EPS in patients receiving 1 mg $day^{-1}$ of risperidone was not significantly greater than in placebo patients.

Schooler *et al*. (2005) compared long-term effectiveness of risperidone versus haloperidol in 555 psychotic patients. Treatment-emergent extrapyramidal signs and symptoms were significantly more frequent and more severe in the haloperidol-treated group. There was significantly less emergent dyskinesia in the risperidone group than in the haloperidol group but no significant difference in persistent dyskinesia. On the specific ESRS subscales, the risperidone group had significantly lower maximum change in score from baseline on total, Parkinsonism and Parkinsonism dystonia symptoms. Significantly lower akathisia scores were seen in the risperidone-treated group as well as a tendency for lower dyskinesia scores. Haloperidol was associated with significantly greater acute extrapyramidal signs and symptoms. For the haloperidol- and risperidone-treated patients, 49.5 and 41.7%, respectively, received anticholinergic agents; 61.7 and 54.7% received benzodiazepines to control agitation as well as extrapyramidal signs and symptoms 10.5 and 5.0% received beta blocking agents to control akathisia.

Atypical antipsychotic are not interchangeable: The risk of incurring adverse effects is high with clozapine and olanzapine, moderate with risperidone and quetiapine (but perhaps increasing at higher doses) and minimal with ziprasidone and aripiprazole. The atypicals have proved useful as monotherapy in treating schizophrenia (Simpson 2005).

Madhusoodanan *et al*. (1995) used risperidone to treat 11 elderly patients between 61 and 79 years with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia. The reduction of both positive and negative symptoms of schizophrenia and the lack of significant EPS, TD, sedation and anticholinergic side effects indicated that risperidone is a safe and effective medication for the elderly.

Because of their improved tolerability, the atypicals offer the prospect of improved compliance and reduced risk of relapse, thus decreasing costs by the need for less hospitalization (Simpson, 2005). Also, treatment costs and dose of concomitant medications were lower in risperidone-treated patients (Masand *et al*., 2002).

A typical antipsychotic drugs, with superior tolerability (Simpson, 2005; Mortimer and Al-Agib, 2007) and possibly superior efficacy, were expected to give

schizophrenia patients better Quality of Life (QOL) than conventional treatment (Mortimer and Al-Agib, 2007). Although atypical agents are substantially more expensive than their typical antipsychotic counterparts in some countries (Worrel *et al*., 2000) in our country, Iran, Risperidone is cheaper than many old antipsychotics. Also, these agents such as haloperidol are associated with significantly greater EPSE and a greater need for concomitant medications to treat those EPSE than risperidone (Schooler *et al*., 2005).

The most frequent complications of risperidone in our study were Parkinsonism and akathisia. A common and serious drawback of the conventional antipsychotics is their association with a range of motor disturbances: acute extrapyramidal symptoms, including Parkinsonism, acute akathisia and acute dystonia; and chronic motor problems such as tardive dyskinesia, chronic akathisia and tardive dystonia. In addition to physical disability directly related to abnormal movements, the acute movement disorders can cause considerable subjective discomfort and distress and are frequently cited as a reason for poor compliance with medication, at least during acute treatment. They can also confound clinical assessment of mental-state phenomena because of symptom overlap with the psychotic illness being treated. The results of clinical trials of the newer antipsychotic drugs such as risperidone suggest a lower liability for acute extrapyramidal symptoms than conventional antipsychotic drugs such as haloperidol and chlorpromazine (Barnes and McPhillips, 1998).

First- and second-generation antipsychotics also differ in acquisition costs, with second-generation antipsychotics being several times more expensive. However, second-generation antipsychotics may be more cost-effective over time because hospitalizations and specialist treatments of patients may be prevented (Opolka *et al*., 2004). The lower prevalence of extrapyramidal signs and symptoms in the risperidone-treated patients has possible implications regarding adherence to medications, since extrapyramidal signs and symptoms are associated with poorer compliance (Schooler *et al*., 2005). Compared with the first-generation or "typical" antipsychotic drugs, second-generation or atypical antipsychotics cause fewer extrapyramidal (motor) problems (Mathews and Muzina, 2007). The results indicate that the risk of EPS appears to be lower in Second-Generation Antipsychotics (SGAs) than in First-Generation Antipsychotics (FGAs) (Yang *et al*., 2007; Tarricone *et al*., 2006). However, among the SGAs, risperidone had the highest crude co-prescribing rate of anti-Parkinson drugs (66.50%). The considerably high rate of EPS in some of the newer generation of antipsychotics warrants clinical attention (Yang *et al*., 2007). Available literature data seem to suggest that among SGAs, risperidone seems to be associated with the highest risk of inducing EPS at doses lower than 6 mg $d^{-1}$ (Gentile, 2007). However, treatment-emergent extrapyramidal symptoms were more numerous for risperidone- than placebo- or olanzapine-treated patients (Deberdt *et al*., 2005).

## CONCLUSION

Regarding that the risperidone is one of newest antipsychotic drugs with lower side effects and that these side effects are dose-dependent, it is recommended that the treatment be initiated with minimum effective dose.

## REFERENCES

Barnes, T.R. and M.A. McPhillips, 1998. Novel antipsychotics, extrapyramidal side effects and tardive dyskinesia. Int. Clin. Psychopharmacol., 13: 49-57.

Boerth, J.M., C.F. Caley and J.W. Goethe, 2005. Interpreting serum risperidone concentrations. Pharmacotherapy, 25: 299-302.

Catena Dell'osso, M., A. Fagiolini, F. Ducci, A. Masalehdan, A. Ciapparelli and E. Frank, 2007. Newer antipsychotics and the rabbit syndrome. Clin. Pract. Epidemol. Ment. Health, 11: 3-6.

Deberdt, W.G., M.W. Dysken, S.A. Rappaport, P.D. Feldman, C.A. Young, D.P. Hay, D.L. Lehman, M. Dossenbach, E.K. Degenhardt and A. Breier, 2005. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am. J. Geriatr. Psychiatry, 13: 722-730.

Gardner, D.M., R.J. Baldessarini and P. Waraich, 2005. Modern antipsychotic drugs: A critical overview. CMAJ., 172: 1703-1711.

Gareri, P., P. De Fazio, S. De Fazio, N. Marigliano, G. Ferreri Ibbadu and G. De Sarro, 2006. Adverse effects of atypical antipsychotics in the elderly: A review. Drugs Aging, 23: 937-956.

Gentile, S., 2007. Extrapyramidal adverse events associated with atypical antipsychotic treatment of bipolar disorder. J. Clin. Psychopharmacol., 27: 35-45.

Gharabawi, G.M., C.A. Bossie and Y. Zhu, 2006. New-onset tardive dyskinesia in patients with first-episode psychosis receiving risperidone or haloperidol. Am. J. Psychiatry, 163: 938-939.

Gharabawi, G.M., C.A. Bossie, R.A. Lasser, I. Turkoz, S. Rodriguez and G. Chouinard, 2005. Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): Cross-scale comparison in assessing tardive dyskinesia. Schizophr. Res., 77: 119-28.

Grant, S. and A. Fitton, 1994. Risperidone. A review of its pharmacology and therapeutic potential in the treatment of schizophrenia. Drugs, 48: 253-73.

Hong, K.S., S.S. Cheong, J.M. Woo and E. Kim, 1999. Risperidone-induced tardive dyskinesia. Am. J. Psychiatr., 156: 1290.

Hoy, J.S. and B. Alexander, 2002. Rabbit syndrome secondary to risperidone. Pharmacotherapy, 22: 513-515.

Jayaram, M.B., P. Hosalli and S. Stroup, 2006. Risperidone versus olanzapine for schizophrenia. Cochrane Database Sys. Rev., 19: CD005237.

Katz, I.R., D.V. Jeste, J.E. Mintzer, C. Clyde, J. Napolitano and M. Brecher, 1999. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: A randomized, double-blind trial. Risperidone Study Group. J. Clin. Psychiatr., 60: 107-115.

Lieberman, J.A., 2004. Managing anticholinergic side effects. Prim Care Companion J. Clin. Psychiatr., 6: 20-23.

Madhusoodanan, S., R. Brenner, L. Araujo, A. Abaza, 1995. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: A case series. J. Clin. Psychiatr., 56: 514-518.

Manning, J.S., 2000. Anticholinergic Side Effects in Perspective. Prim Care Companion J. Clin. Psychiatr., 2: 116.

Masand, P.S., X. Wang, S. Gupta, T.L. Schwartz, S. Virk and A. Hameed, 2002. Comparison of Risperidone and Olanzapine in Bipolar and Schizoaffective Disorders. Prim. Care Companion J. Clin. Psychiatr., 4: 70-73.

Mathews, M. and D.J. Muzina, 2007. Atypical antipsychotics: New drugs, new challenges. Cleve. Clin. J. Med., 74: 597-606.

Mishra, B., B. Mishra, S. Sahoo, M. Arora and C.R. Khes, 2007. Atypicality in presentation of neuroleptic malignant syndrome caused by olanzapine. Indian J. Med. Sci., 61: 570-573.

Mortimer, A.M. and A.O. Al-Agib, 2007. Quality of life in schizophrenia on conventional versus atypical antipsychotic medication: A comparative cross-sectional study. Int. J. Soc. Psychiatr., 53: 99-107.

Opolka, J.L., K.L. Rascati, C.M. Brown and P.J. Gibson, 2004. Ethnicity and prescription patterns for haloperidol, risperidone and olanzapine. Psychiatr. Serv., 55: 151-156.

Parellada, E., 2007. Long-acting injectable risperidone in the treatment of schizophrenia in special patient populations. Psychopharmacol. Bull., 40: 82-100.

Park, S., D. Ross-Degnan, A.S. Adams, J. Sabin, P. Kanavos and S.B. Soumerai, 2005. Effect of switching antipsychotics on antiparkinsonian medication use in schizophrenia: Population-based study. Br. J. Psychiatr., 187: 137-42.

Pelonero, A.L., J.L. Levenson, A.K. Pandurangi, 1998. Neuroleptic malignant syndrome: A Review. Psychiatr. Serv., 49: 1163-1172.

Raja, M. and A. Azzoni, 2001. Novel antipsychotics and acute dystonic reactions. Int. J. Neuropsychopharmacol, 4: 393-7.

Schooler, N., J. Rabinowitz, M. Davidson, R. Emsley, P.D. Harvey and L. Kopala *et al.*, 2005. Risperidone and haloperidol in first-episode psychosis: A long-term randomized trial. Am. J. Psychiatr., 162: 947-953.

Simpson, G.M. and J.P. Lindenmayer, 1997. Extrapyramidal symptoms in patients treated with risperidone. J. Clin. Psychopharmacol., 17: 194-201.

Simpson, G.M., 2005. Atypical antipsychotics and the burden of disease. Am. J. Manag. Car, 11: 235-241.

Tarricone, I., M. Casoria, B.F. Gozzi, D. Grieco, M. Menchetti, A. Serretti, M. Ujkaj, F. Pastorelli and D. Berardi, 2006. Metabolic risk factor profile associated with use of second generation antipsychotics: A cross sectional study in a Community Mental Health Centre. BMC. Psychiatr., 16: 6-11.

Voris, J.C. and W.M. Glazer, 1999. Use of risperidone and olanzapine in outpatient clinics at six Veterans Affairs hospitals. Psychiatr. Serv., 50: 163-164, 168.

Wirshing, W.C., 2001. Movement disorders associated with neuroleptic treatment. J. Clin. Psychiatr., 21: 15-18.

Worrel, J.A., P.A. Marken, S.E. Beckman and V.L. Ruehter, 2000. Atypical antipsychotic agents: A critical review. Am. J. Health Syst. Pharm., 57: 238-255.

Yang, S.Y., Y.H. Kao Yang, M.Y. Chong, Y.H. Yang, W.H. Chang and C.S. Lai, 2007. Risk of extrapyramidal syndrome in schizophrenic patients treated with antipsychotics: A population-based study. Clin. Pharmacol., 81: 586-594.