Extrapyramidal Symptoms Probably Related to Risperidone Treatment: A Case Series

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Keywords

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Abstract

Background: Atypical antipsychotics, like risperidone purportedly, score over their typical counterparts in terms of their lower propensity toward producing extrapyramidal symptoms (EPS). However, recent studies have furnished evidence to the contrary. Hereby, we present a case series implicating risperidone as the causative agent for EPS. **Methods:** As a part of the pharmacovigilance programme of India, the authors have assessed 10 physician-reported cases of EPS among the 1,830 patients who were prescribed risperidone within the time period of January 2012–December 2014 in a tertiary care hospital in South India. Causality, severity, and preventability assessments of adverse reaction were done as per Naranjo's, Hartwig's, and Thornton's scale respectively. **Results:** Of the 10 cases, a dose-dependent occurrence of EPS was noted in all and the time duration for development of EPS ranged from 1 week to 2 years. Four patients developed EPS at a dose of 6–8 mg, 4 developed at a

dose of 4–6 mg, and the remaining 2 developed at 2 and 1 mg. **Conclusion:** A strong temporal correlation between risperidone and EPS was noted in all cases. High doses produced EPS early, whereas moderate to low doses produced EPS at a later date. Thus, cautious use and close monitoring are warranted in the chronic use of risperidone.

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Introduction

The introduction of second-generation antipsychotics (SGAs), with their promise of enhanced efficacy and safety, was believed to be a watershed moment in the field of applied neurosciences [1].

Atypical antipsychotics or SGAs score over their typical counterparts in terms of their lower propensity toward producing the gamut of extrapyramidal symptoms (EPS). The theory behind the superiority of SGAs over first-generation antipsychotics is hinged upon their lower affinity toward dopaminergic receptors. However, recent clinical studies and meta-analyses have hinted otherwise [2]. Amongst the various atypical antipsychotics,

risperidone has been associated with EPS with an extremely alarming regularity [2]. Given, risperidone is one of the more widely used antipsychotic around the world, it is of extreme imminence that greater attention be drawn toward this issue. We have attempted to draw out a discourse on the various risk factors associated with development of EPS, the implicated dosage range, and duration of risperidone usage. As a part of the Pharmacovigilance Program of India, we attempt to present a series of cases which have been reported from our center, where risperidone has been implicated in the manifestation of EPS.

Methods

Case Series

Case 1

A 29-year-old lady was brought to the psychiatry outpatient department (OPD) of our hospital in September 2014 with symptoms of generalized slowness of movement, crying spells, neglect of daily activities and poor self-care, decreased interaction with family members, insomnia, fearfulness, irrelevant talk, disinhibition, and inappropriate behavior. Detailed history revealed the presence of depressive illness and suicidal tendencies in a 3rd degree relative with alcohol dependence also existing in 1st and 2nd degree relatives. However, she did not have any other comorbid illnesses. Following a detailed history and examination, a diagnosis of bipolar affective disorder (BAD) was made and she was started on 4 mg risperidone for her psychotic symptoms, 4 mg trihexyphenidyl, and 0.5 mg clonazepam for anxiety. A close scrutiny of the various systems and laboratory investigations did not reveal any anomalies. After 1.5 years of treatment with the above medications, in March 2016, the patient presented to the psychiatry OPD with bilateral hand tremors, cog wheel rigidity, masked facies, and psychomotor retardation. After excluding other causes of EPS, a probable diagnosis of risperidone-induced EPS was made and drug was withdrawn. Symptoms of EPS relieved after treatment with a central anticholinergic, 4 mg trihexyphenidyl. She was started on 400 mg lithium and 20 mg escitalopram for her psychotic symptoms and 4 mg trihexyphenidyl to prevent other EPS side effects.

Case 2

A 40-year-old gentleman presented with a 6-year history of auditory hallucination, grandiose delusion of ability, decreased sleep, violence, and suspiciousness to the psychiatry OPD of our hospital in December 2013. The patient had been initiated on 4 mg of risperidone since November 2016 from a local hospital. On admission, in December 2013, his investigations including biochemical and serological tests had been normal, and mental status examination (MSE) revealed impaired judgement, abstractability, grandiose idea, and grade 1 insight. Thus, a diagnosis of paranoid schizophrenia was made and the dose of risperidone was increased to 8 mg due to poor symptom control from a dose of 4 mg. However, in January 2014, after 2 months of increased dose of risperidone, patient presented to our hospital with symptoms of difficulty in

walking, stooped posture, and tingling sensation in dorsum of both feet with a tendency to fall. A detailed examination of the central nervous system (CNS) revealed cog wheel rigidity on bilateral upper limbs, short, shuffling gait, and normal reflexes. After ruling out other possible causes of EPS, a probable diagnosis of risperidone-induced EPS was thought of and risperidone was withdrawn. Symptoms of Parkinsonism were treated using a central anticholinergic trihexyphenidyl 4 mg and her psychotic symptoms were controlled using injection zuclopenthixol 200 mg given as intramuscular depot preparation.

Case 3

A 67-year-old woman visited the psychiatry OPD of our hospital in December 2013 with delusions of persecution and reference, anger outbursts, and multiple episodes of intentional self-harm dating back to 10 years. History revealed that the above symptoms were a manifestation of an exacerbation of her underlying paranoid schizophrenia. The details of her treatment history were sketchy due to lack of patient documents. She was started on 50 mg clozapine along with 4 mg risperidone. On admission, routine investigations were carried out and was found to be normal. As her symptoms could not be controlled at 4 mg, the dose of risperidone was increased to 6 mg for better symptom control. After 9 months of therapy, she presented on September 2014 with 1 month history of tremors, sleep disturbances, reduced interaction with family members, and poor self-care. A complete physical examination revealed reduced blink rate, poor self-care, and CNS examination revealed bilateral tremors in both upper limbs and other parts of the body, cog wheel rigidity with brisk reflexes. After a detailed work-up, a probable diagnosis of risperidone-induced EPS was thought of and drug was withdrawn, after ruling out other possibilities for EPS. All antipsychotics were stopped and symptoms were treated using a central anticholinergic trihexyphenidyl 4 mg. EPS resolved within few weeks and patient was discharged on 5 mg olanzapine.

Case 4

A previously normotensive and premorbidly normal 25-year-old woman presented to the psychiatry OPD on September 2015, with a 5 month-history of slowness of activity, decreased social interaction, and disorganisation of routine activities, insomnia, fearfulness, and irrelevant talks. After admission, a detailed evaluation was done, and a diagnosis of acute and transient psychosis was made. Patient was started on 5 mg haloperidol along with 4 mg risperidone and 0.5 mg clonazepam. Within a period of 1 week, she developed acute dystonia in the form of severe spasm of neck, facial, and lingual muscles. Haloperidol and risperidone were withdrawn and EPS was relieved by injection of 50 mg promethazine intramuscularly and a central anticholinergic 4 mg trihexyphenidyl. This anticholinergic was later changed to 10 mg procyclidine and symptoms of dystonia subsided. Patient and family members were educated regarding the disease condition and side effects of the medications and she was discharged on 10 mg olanzapine.

Case 5

A premorbidly normal and well-adjusted 53-year-old woman was brought to the psychiatry OPD in April 2015 with symptoms of generalized slowness of movement, crying spells, neglect of daily activities and poor self-care, decreased interaction with family members, insomnia, fearfulness, irrelevant talk, disinhibition, and

inappropriate behavior. Examination of the various systems did not reveal any findings. History, physical, and psychological evaluation pointed to a diagnosis of acute and transient psychosis and she was initiated on 4 mg risperidone; 0.5 mg oral clonazepam was also added to relieve anxiety and sedate the patient. She came back on June 2015 with symptoms of rigidity, tremors, and slurring of speech. CNS examination revealed mask like facies, slight slurring of speech, bilateral tremors, and rigidity on upper limbs, which were manifestations of EPS. Dose of risperidone was reduced to 2 mg and a low dose central anticholinergic 4 mg trihexyphenidyl was added to counter the symptoms of EPS. Her symptoms of EPS improved and she was maintained on olanzapine 5 mg, risperidone 2 mg, and trihexyphenidyl 4 mg.

Case 6

A 22-year-old premorbidly well-adjusted lady, presented to the psychiatry OPD in September 2012 with delusions of persecution and reference, auditory hallucinations, repetitive movements along with fearfulness, depressive features, decreased social interactions, and thought withdrawal. On admission and detailed evaluation, a diagnosis of paranoid schizophrenia, episodic course with obsessive compulsive disorder (OCD) was made. Routine investigations were found to be normal and patient was prescribed risperidone 1 mg, clonazepam 0.5 mg, and fluoxetine 20 mg. After 3 months of treatment in December 2012, patient presented with bilateral tremors, stiffness of body, inability to do any work, and insomnia. Physical examination revealed bradykinesia, mask-like facies, exotropia of right eye, fine perioral, and lingual tremors; CNS examination revealed bilateral upper limb and lower limb rigidity, cog wheel rigidity at bilateral wrists, superficial reflexes were absent. MSE showed the presence of obsessive thoughts, compulsive actions, persecutory ideas, sad mood, and anxiety. Considering the probable cause of EPS to be risperidone, drug was withdrawn and symptoms were treated using a central anticholinergic trihexyphenidyl 4 mg. Olanzapine 2.5 mg was started to address her psychotic symptoms along with trihexyphenidyl 4 mg and fluoxetine 20 mg.

Case 7

A 38-year-old female patient diagnosed as a case of BAD presented with 1st episode of depression in 1996 and was started on amitriptyline 75 mg along with electroconvulsive therapy. Second episode of a mixed state was observed in 1997 when trifluoperazine 5 mg was added. The third episode was of mania with psychotic symptoms in 2013 when risperidone 4 mg and lithium 900 mg was added. After 2 years of risperidone therapy in December 2015, the patient presented with bilateral upper and lower limb rigidity, cog-wheel rigidity at the wrist (symptoms suggestive of EPS), drug was withdrawn and symptoms were treated using a central anticholinergic trihexyphenidyl 4 mg. Antipsychotic was changed to olanzapine 2.5 mg along with clonazepam 0.5 mg and fluoxetine 60 mg.

Case 8

A previously normotensive and premorbidly normal 31-year-old married gentleman visited the psychiatry OPD in January 2014 with symptoms of anxiety, persecutory delusions, referential delusion, delusion of infidelity, and grandiose delusion of ability since 2 weeks. As he had no other psychotic symptoms or mood disorders, he was diagnosed as a case of delusional disorder and started on risperidone 6 mg with haloperidol 5 mg. During the course of

treatment, haloperidol was stopped due to akathisia. Akathisia was treated using propranolol 10 mg, which was later increased to 40 mg. Patient was discharged on risperidone 6 mg and trihexyphenidyl 4 mg. However, he came back on February 2014 with a history of increased restlessness with impulsive nature, inability to sit in one place, and insomnia due to the above symptoms. A complete physical examination revealed mask-like facies, decreased arm swing, increased salivation, and cog wheel rigidity in bilateral upper limbs. After a detailed evaluation and after ruling out other possible causes of EPS, a current diagnosis of akathisia and drug-induced EPS probably due to risperidone was thought of and the drug was withdrawn. EPS was treated using a central anticholinergic trihexyphenidyl 8 mg, propranolol 80 mg, and diazepam 20 mg for anxiety. Patient was also given cognitive behavioral therapy and on discharge, he reported improvement in symptoms. Furthermore, he was managed on trifluoperazine 10 mg as an antipsychotic.

Case 9

A 23-year-old woman visited the psychiatry OPD in April 2015 with a 2 months history of increased talk, sad mood, decreased concentration, irritability, insomnia, and decreased self-care. Her symptoms started at the age of 18 years with first episode suggestive of early onset dysthymia, alleged history of intentional self-harm, following which there was a 2-month history suggestive of a hypomanic episode. A probable diagnosis of BAD was made and was started on tablet 15 mg asenapine. Due to incomplete remissions, she was started on oral escitalopram 10 mg and desvenlafaxine 50 mg. Previous history revealed thyroid dysfunction for which she was on treatment. History was suggestive of BAD in mother, grandmother, and 1st degree relatives. In view of the above symptoms, and good response to lithium in mother, she was started on tablet lithium 800 mg, which was hiked to 1,000 mg with periodic monitoring of serum lithium levels (0.7 mEq/L). Concomitant medications also included risperidone 2 mg. But within a period of 2 weeks, patient developed EPS in the form of acute muscle dystonia, rigidity, and tremors. After a thorough evaluation, risperidone was thought to be the culprit and was withdrawn. Patient and family were psychoeducated about the illness, the need of continuation of medication, and regular follow-ups. Symptoms of EPS were controlled using trihexyphenidyl 4 mg and she was discharged with aripiprazole 15 mg along with lithium.

Case 10

A 70-year-old woman diagnosed with recurrent depressive disorder with an episodic pattern since 1990 with concomitant diabetes and hypertension for last 6 years, on treatment with amlodipine 5 mg and glimepiride 500 mg, presented to our hospital on June 2012 with a 1-month history of decreased self-care, decreased food intake, and social withdrawal. She was admitted and a detailed evaluation was done which revealed no abnormality in laboratory parameters. She was started on risperidone 6 mg, escitalopram 20 mg, and sertraline 50 mg. However, her symptoms worsened within a period of 1 week and she developed slowness of movements with bilateral tremors of the upper limbs. MSE revealed a delayed reaction time, poverty of speech, mask-like facies, bilateral hand tremors, short shuffling gait, and decreased arm swing. In view of the current symptoms and history of having been on psychotropics, an initial diagnosis of drug-induced EPS, probably due to risperidone was considered. All antipsychotics and antidepressants

sants were stopped and symptoms were treated using trihexyphenidyl 8 mg along with promethazine injection. Insomnia was treated using newer benzodiazepines zolpidem and symptoms improved within a few weeks. Patients and relatives were psychoeducated regarding the disease and was discharged on amitriptyline 100 mg, quetiapine 60 mg, and clonazepam 1 mg.

Discussion

EPS include acute dystonia, akathisia, Parkinsonism, and tardive dyskinesia. These symptoms are serious, sometimes debilitating and stigmatizing adverse effects and require additional pharmacotherapy. EPS develops in 2 phases. Early acute EPS which most often develops at the beginning of treatment with antipsychotics or when the dose is increased. The later-onset EPS usually occur after prolonged treatment and presents as tardive dyskinesia. The motor manifestations include akathisia (restlessness and pacing), acute dystonia (sustained abnormal postures and muscle spasms), and Parkinsonism (tremor, skeletal muscle rigidity, and bradykinesia). Acute EPS usually responds to dose reduction of the antipsychotic agent or require additional pharmacological treatment [3].

Development of EPS is not a uniform phenomenon and has been associated with a host of risk factors that include long-term antipsychotic drug exposure, increasing age, female gender, non-Caucasian race, the presence of affective disorders, organic brain damage, development of acute EPS at an early age, history of diabetes mellitus, alcohol abuse, genetic vulnerability, disease-related vulnerability, and decreased functional reserve [4].

Gender has been considered a possible risk factor. Some studies have reported a male predominance whereas others have reported no gender difference. The onset of tardive dystonia seems to occur earlier in men than in women. It is thought to result from hypersensitivity of post-synaptic receptors associated with continuous blockade of dopaminergic neuronal transmission due to antipsychotic drugs. An anti-noradrenergic action may play an important role because the amount of noradrenaline has been shown to be reduced in the hypothalamus, mammillary body, and other areas.

Parkinsonian features induced by antipsychotics occurs between few days and up to several months after the initiation of the treatment. Risk factors for drug-induced Parkinsonism are age (elderly), gender (females), cognitive deficit, and early-onset EPS. Antipsychotic-induced Parkinsonism is considered a reversible condition although its duration is variable. The treatment of choice is

not established but dose reduction and anticholinergic drugs may be useful [4].

Even though there has been increase in adverse drug reactions (ADR) reporting in the last decade, causality assessment has been the greater challenge for academicians and even industry. Causality refers to the relationship of a given adverse event to a specific drug which is crucial for risk-benefit assessment, particularly when it involves post-marketing safety signals. We have therefore individually assessed the causality, severity, and preventability of these ADRs using suitable standard scales [5–7].

In case 1, EPS was triggered within a period of 1.5 years at a dose of 4 mg of risperidone. Some of the risk factors in this case were the following: female gender, presence of psychiatric disease, that is, bipolar disease, and a non-Caucasian race. As this patient had received risperidone as her main antipsychotic drug and there were no history of EPS in the past, this episode of pseudo-Parkinsonism, could be most probably due to risperidone. Causality, severity, and preventability is as follows: Naranjo's causality score of 7, making it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Case 2 developed EPS within 2 months at a dose of 8 mg. A pharmacological explanation could be that at a dose of 6 mg/day or more, risperidone may lose the balanced 5HT₂/D₂ blocking effect, resulting in more affinity for D₂ receptors, thereby producing EPS comparable with classical antipsychotics. As the same dose continues for a long time, it can lead to supersensitivity of D₂ receptors in the nigrostriatal system producing Parkinsonian features. A study conducted by Jeste et al. [8] have reported that Asian patients require lower doses of most psychotropics than Caucasian patients which may explain why certain patients in India respond to risperidone at doses that are as low as 1 mg/day and react unfavourably to the therapeutic dose range of 6–8 mg/day [8]. Naranjo's causality score of 7, making it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Case 3 describes a 67-year-old female patient who developed Parkinson's like symptoms within a period of 9 months at a dose of 6 mg. In this patient risk factors such as age, gender and a sudden escalation of dose could have been the possible risk factors. Naranjo's causality score of

7, making it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe, and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7]. The likelihood of developing EPS with a first-line SGA depends not only on the specific agent, but also on the rapidity of dose escalation, the target dose, and the patient's intrinsic vulnerability to EPS. Even with the SGAs, clinicians should not be lulled into believing EPS cannot happen, but need to be able to recognize and manage both overt and subtle manifestations of EPS.

Case 4 describes a 25-year-old woman who developed dystonia to risperidone and haloperidol at a dose of 4 mg, within a period of 1 week. Risk factors for acute dystonia are age and male gender, history of substance abuse, family history of dystonia, and concomitant use of a typical antipsychotic.

Naranjo's causality score of 7, making it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe, and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7]. The psychiatric aspects of acute dystonic reaction are related to the fear and anxiety associated with the unpredictable, sudden onset of involuntary movements and the loss of control of specific muscle groups. The exact mechanism responsible for acute dystonic reactions is not entirely understood. Although they are related to blockade of the D2 receptor, in common with all antipsychotics, the delay between receptor blockade and onset of clinical symptomatology suggests involvement of additional mechanisms, possibly secondary dopamine receptor hypersensitivity [4, 9]. Our patient was on haloperidol, which could have probably led to the rapid development of dystonia.

Case 5 describes a 53-year-old female patient who developed Parkinsonian features at a risperidone dose of 4 mg within a period of 2 months. Risk factors in this patient could be her advanced age, gender, and the psychiatric illness itself. Naranjo's causality score of 6, making it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Case 6 describes a 22-year-old female with OCD and paranoid schizophrenia who presented with Parkinson's like symptoms within a period of 3 months at a dose of 1 mg. This rapid development of EPS could be probably

because of the interaction of a selective serotonin reuptake inhibitor (SSRI) with risperidone, which is in accordance with this case report [10]. Naranjo's causality score of 4, making it a possible ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe, and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Case 7 describes a 38-year-old woman, with a long-term disease of BAD, who presented with Parkinsonian features after 2 years of therapy with a risperidone dose of 4 mg. Risk factors in this case could be gender (female), cognitive deficits and BAD. Antipsychotic-induced Parkinsonism is considered a reversible condition although its duration is variable. The treatment of choice is not established, but dose reduction and anticholinergic drugs may be useful. Naranjo's causality score of 7, making it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe, and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Case 8 describes a 31-year-old gentleman with delusional disorder, with nil comorbidities, on SSRI (fluoxetine) and developed EPS at a dose of 6 mg within 1 month. Common causes of akathisia include diabetes, renal disease, Parkinson's disease, and peripheral neuropathy, none of which our patient suffered from. Iron deficiency and hyperthyroidism were also ruled out in this case. Naranjo's causality score of 6, makes it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe, and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Case 9 describes a 23-year-old woman with BAD developed within a period of 2 weeks at a dose of 2 mg. Naranjo's causality score of 6, making it a probable ADR, Hartwig and Siegel severity assessment scale denoted level 3, which indicates that ADR was moderately severe, and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Case 10 describes a 70-year-old female with comorbidities such as diabetes and hypertension who developed EPS at a risperidone dose of 6 mg, within a period of 1 week. This early development could be due to her associated comorbid conditions and long duration of disease itself. Naranjo's causality score of 6, making it a probable ADR, Hartwig and Siegel severity assessment scale de-

noted level 3, which indicates that ADR was moderately severe, and preventability criteria according to Schumock and Thornton scale showed that this reaction was probably preventable [5–7].

Role of other Drugs in Causing EPS

Any drug that blocks the action of dopamine is likely to cause Parkinsonism. Neuroleptics are possibly the major cause of drug-induced Parkinsonism worldwide. Drugs associated with causation of EPS include the following: SSRIs like fluoxetine, paroxetine, sertraline, amisulpiride, typical antipsychotics like haloperidol, chlorpromazine, flupenthixol, fluphenazine pimozide, prochlorperazine, atypicals like clozapine, quetiapine, risperidone, sulpiride, thioridazine, trifluoperazine, zuclopenthixol, and zotepine. Some other drugs that are responsible for drug-induced Parkinson's disease also include amiodarone, cinnarazine, lithium, methyl dopa, metoclopramide, and trazodone [11, 12].

Mechanism of Risperidone-Induced EPS

It is a common understanding that the development of EPS with usage of antipsychotics hinges primarily on the blockade of dopamine 2 (D₂) receptor, producing relative dopamine deficiency and an acetylcholine excess. However, the lower propensity of development of EPS with SGAs has been attributed to the relatively loose binding of SGAs to the D₂ receptors as compared to the FGAs. This is very eloquently explained by the “fast off” theory, which states that the SGAs bind sufficiently long enough to the D₂ receptors to produce their therapeutic effects, but not enough to produce the adverse effects. Nonetheless, risperidone is a weakly atypical antipsychotic that binds tightly to the receptors thereby possessing an innate capacity of producing the gamut of adverse effects, similar in its profile to the ones produced by the FGAs. Besides these hypotheses, it has also been suggested that postsynaptic dopamine hypersensitivity, damage to striatal interneurons, and damage of striatal cholinergic interneurons as a result of prolonged antipsychotic drug use can also contribute to the development of EPS [13, 14].

Use of risperidone has gained wider acceptance in recent years; in fact, these agents have novel receptor binding profiles, good efficacy regarding negative symptoms, and few adverse effects, particularly in terms of reduced EPS.

There is another school of thought that suggests co-initiating an anti-cholinergic with risperidone, if the psychiatrist suspects the development of EPS in the patient

[15, 16]. Though, pharmacologically sound, this trend was not observed in any of our patients. Rather, in a few instances, anti-cholinergics were prescribed only as rescue medications once the EPS had set in. Thus, in an effort to curtail the chances of development of EPS and its associated pitfalls, the suggestion of initiating an anti-cholinergic at the beginning of therapy is not without merit and deserves a closer second look.

Furthermore, risperidone is equally potent in blocking D₂ and 5-HT₂ receptors and its potency in blocking D₂ receptors depends on the dose used. Increasing dosages of risperidone are able to proportionally block D₂ receptors. This explains why risperidone may facilitate the onset of EPS, especially at dosages greater than 2 mg/day. Atypical drugs transiently occupy D₂ receptors and then rapidly dissociate to allow normal dopamine neurotransmission (hit and run mechanism). The difference in development of EPS could be mostly due to the involvement of others drugs and genetic susceptibility [17].

Risperidone is now available as gastro-retentive dosage forms (GRDFs) that are particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. Floating microparticles as a type of GRDFs were chosen to formulate risperidone to retain the drug in the stomach as the absorption of this drug mainly takes place in the upper part of the gastrointestinal tract, that is, duodenum and jejunum and as this drug is a weak base with a pK_a value of 7.9, which make it suitable candidate to be formulated in such dosage form [18].

Study conducted by Mas et al. [19] concluded that the mTOR pathway has been related to EPS susceptibility and antipsychotic response. Validate a powerful pharmacogenetic predictor of AP-induced EPS. For the first time, the mTOR pathway has been related to EPS susceptibility and AP response.

Gründer et al. [20] proposed that the low incidence of EPS, which characterizes atypical antipsychotics, can be ascribed to the fact that the drugs leave dopaminergic neurotransmission in extrapyramidal motor systems intact.

Busting the Myth of Superiority of SGAs

Recent studies have raised serious questions over the claims of SGAs like risperidone being superior to the typical antipsychotics. It would be pertinent to remember that risperidone received its approval on the basis of it producing better improvement in terms of the psychiatric symptoms, which at best can be termed as surrogate markers in short-duration trials. There have been very few studies that have evaluated the overall patient safety

and efficacy over a long duration. Further, in light of recent studies, the cost-utility of SGAs has serious question marks hanging over it.

A study by Rosenheck et al. [21], have concluded that SGAs revealed no added advantage over FGAs in terms of treatment adherence, symptoms, EPS, or quality of life [22]. Also, Lieberman et al. [1] have reported an 18-month double-blind trial in which patients were randomized to receive either a SGA or FGA, have also concluded that the use of SGA did not lead to any improvement in quality of life and side effects profile [22]. Thus, a close scrutiny of risperidone's ability to produce marked and sustained improvement in the psychiatric symptoms over a long duration, improve the quality of patient's life, and score higher than typical antipsychotics on the safety scales, is the need of the hour to validate (or not) the claims of its superiority over FGAs.

Another point of contention with risperidone's use relates to its discontinuation with the onset of EPS. Overwhelming evidence is in favor of discontinuance of risperidone, as evidence in our cases as well as various studies that seem to have concurred with our findings.

The North American trial was the pivotal study that gained risperidone approval for use in the US. It demonstrated that all 4 doses of risperidone used in the trial (2, 6, 10, and 16 mg) were more effective than placebo and as effective as haloperidol. However, at 10 mg and above, the side-effect profile was similar to haloperidol, and at doses more than 6 mg, the need for anticholinergic treatment was greater. Furthermore, low-dose risperidone (mean dose 2.8 mg) has been associated with increased grey matter in the superior temporal gyrus and middle temporal gyrus of patients [23].

The European First Episode Schizophrenia Trial which studied the efficacy of 5 antipsychotic drugs concluded that low doses of these atypical agents appear to be effective as well as acceptable to FEP patients. After 1 month of treatment, the incidence of Parkinsonism was highest in patients receiving haloperidol and 10.1% of the patients were taking anticholinergic drugs in the haloperidol group [24].

The study conducted by Kopala et al. [25] concluded that low dose risperidone (2–4 mg) led to lower rates of EPS and improved clinical outcomes compared to those patients receiving recommended or high doses (5–8 mg). Merlo et al. [26] has further demonstrated that over an 8-week treatment phase, risperidone at 2 mg/day was equally effective as 4 mg/day in first-episode patients and was associated with significantly less impact on fine motor function, a highly sensitive measure of EPS. In relation

to chronic outcomes, Schooler [27] demonstrated that chronic low dose (3.3 mg) risperidone treatment (median 192 days) was associated with greater clinical improvement, less relapse, and less frequent and severe EPS compared to low-dose haloperidol (at a mean dose 2.9 mg) [23].

The most compelling point emphasized by these data is that risperidone should not be dosed to the neuroleptic threshold. Since it is impossible to predict the neuroleptic threshold in a given patient prior to treatment, it is necessary to begin therapy at a low dose and slowly titrate to efficacy not toxicity. A general guideline is to begin dosing at 1 mg twice daily (0.5 mg daily for the elderly) and to slowly titrate by 1 mg increments every 5–7 days. Once target symptoms have begun to show a therapeutic response, the titration should be halted. The dose should be increased further only if the ultimate therapeutic effect obtained is inadequate. If demonstrable neurotoxicity (in the form of drug-induced EPS) emerges, the dose should be decreased. The most commonly prescribed dose range for chronic schizophrenia is 4–6 mg. Regardless of the necessary optimum risperidone dosage, the guiding concept should be dose to antipsychotic efficacy below the neuroleptic threshold.

Conclusion

In all our cases, the existence of a strong temporal association was a common feature. This would lend itself to suggestion that it would be in everybody's interest to avoid initiation of risperidone at high doses as well as eschew long-term usage of risperidone since the chances of development of EPS has been observed to increase with time. Details of the dose and duration of development of EPS has been mentioned in Table 1.

SGAs have not completely fulfilled the expectation of being EPS-free antipsychotic drugs. Though recommended by current guidelines as the first-line therapy in the treatment of schizophrenia, the superiority of these drugs in terms of better efficacy and tolerability is not clear. Despite their popularity and widely held belief, it would seem that SGAs like risperidone has failed to prove their superiority, be it in terms of their overall safety, with special emphasis on curtailing the odd of developing EPS or cost-utility. In our opinion, risperidone should be used cautiously, especially with an eye on the risk factors that could, in future, define the population demographics for risperidone use. Furthermore, the issue of co-administering anti-cholinergic needs to be explored as it is still a

Table 1. Effect of dose, duration, and demographical risk factor in causing EPS

S. No.	Diagnosis	Age, years	Gender	Dose of risperidone used	Time duration for development of EPS	Demographical risk factor
1	BAD	29	Female	4 mg	1.5 years	Female, psychiatric disease (BAD)
2	Paranoid schizophrenia	40	Male	8 mg	2 months	Dose of risperidone, age
3	Paranoid schizophrenia	67	Female	6 mg	9 months	Age, gender
4	Acute and transient psychosis	25	Female	4 mg	1 week	Gender, psychiatric disease
5	Acute and transient psychosis	53	Female	4 mg	2 months	Age, gender
6	Paranoid schizophrenia with obsessive compulsive disorder	22	Female	1 mg	2 months	Gender, concomitant use of SSRI (fluoxetine)
7	BAD	38	Female	4 mg	2 years	Gender, psychiatric disease
8	Delusional disorder	31	Male	6 mg	1 month	Nil
9	BAD	23	Female	2 mg	2 weeks	Gender, comorbidities like hypothyroidism
10	Recurrent depressive disorder	70	Female	6 mg	1 week	Age, gender, comorbidities like hypertension and diabetes

BAD, bipolar affective disorder; EPS, extrapyramidal symptoms.

virgin area with the potential of producing a paradigm shift in risperidone prescription. Additional questions relating to its cost-utility need to be answered before further clarity can be obtained over the manner in which risperidone should be used.

Written informed consent was obtained from the patient (or other approved parties) for publication of this case series.

All authors hereby declare that all experiments have been examined and approved by the appropriate Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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Authorship Contribution

S.R.T. has done acquisition of data, drafting, and revision of the intellectual content. B.C. has done revision of the draft's intellectual content, proof reading, and final approval of the version to be published. D.B. has done drafting and revision of the intellectual content. S.A. has done acquisition of data and table compilation.

Disclosure Statements

This article complies with the ICMJE recommendations and author has declared no competing interest.

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