R E V I E W

Pharmacotherapy Update: Risperidone in the Treatment of Schizophrenia

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Abstract: The paper is a review of the clinical use of risperidone, an antipsychotic introduced in the treatment of schizophrenia in 1994. Randomized controlled trials, naturalistic studies and extensive clinical experience have definitively shown strong efficacy and effectiveness of risperidone in the treatment of schizophrenia and other psychotic disorders. On the basis of available evidence, no other antipsychotic drug has shown superior clinical effectiveness in the treatment of psychotic disorders, with the significant exception of clozapine. The wide use of risperidone in the last 15 years has confirmed a favorable safety index. Some features of risperidone render it uniquely useful in the management of psychotic disorders, including a very wide range of dosage, availability in liquid and long-term injectable forms. Finally, the drug is currently available in generic form, at lower cost. However, risperidone presents major limitations. A substantial number of patients with psychotic symptoms do not respond to risperidone, whatever its dose. Most of these patients will need clozapine. For some risperidone treated patients, extrapyramidal side effects remain a serious concern. Weight gain, metabolic syndrome, and hyperprolactinemia related side effects are frequent and may be severe, unacceptable, and even dangerous in some patients.

Keywords: risperidone, schizophrenia, psychotic disorders, side effects, treatment
Methods of the Review
This is a clinical review. Relevant publications were identified by a search of Medline and by manual bibliographic review, examining the references of selected articles. Since the aim of the paper is not to assess a single and specific topic, but to describe pharmacological characteristics, indications, effectiveness, and side effects of risperidone, I did not use standard meta-analysis methods. Rather, I tried to consider the most relevant published data and to add a few considerations derived by my personal experience of treatment of about 3000 cases with risperidone. Therefore, possibility of bias in the selection of considered papers must be acknowledged.

Pharmacological Characteristics
Risperidone is a benzisoxazole derivative introduced in the clinical treatment of schizophrenia and other psychotic disorders in 1994. It has a very high affinity for serotonin_{2A} (5-HT_{2A}) and dopamine_{2} (D_{2}) receptors, and a moderate affinity for histamine_{1} (H_{1}), and α_{1} and α_{2} adrenergic receptors.

Risperidone is well (bioavailability ≈ 100%) and rapidly absorbed after oral administration (peak plasma levels achieved within 1 hour). Risperidone is 90% plasma protein bound. It is metabolized by hydroxylation and by oxidative N-dealkylation.

Risperidone has a linear pharmacokinetic profile. Its most important active metabolite is 9-hydroxyrisperidone, which has similar pharmacodynamics but specific pharmacokinetic features. Hydroxylation of risperidone is catalyzed by cytochrome P450 (2D6). The level of activity of this enzyme affects the half-life of risperidone and the relative ratio of risperidone to 9-hydroxyrisperidone in plasma. However, the half-life and total area under the serum concentration curve of risperidone plus 9-hydroxyrisperidone are similar in subjects with high or low level of activity of cytochrome P450 (2D6).

Risperidone is available in tablets, fast orally disintegrating tablets, oral solution, and long-acting injectable form.

Mechanism of Action
Antagonist action on post-synaptic D_{2} receptors has been consistently associated with efficacy in the treatment of positive psychotic signs, i.e. delusions, hallucinations, and disorganized thought. It has been hypothesized that also antagonist action on post-synaptic 5-HT_{2A} receptors can have both direct and indirect (facilitating D_{2} antagonism) antipsychotic effect. Furthermore, antagonism on post-synaptic 5-HT_{2A} receptors modulates dopamine (DA) neuronal firing, increasing dorsal striatum, prefrontal cortex, and nigrostriatal DA release. The first two effects might underlie increased efficacy for negative symptoms and cognitive deficits (probably related to prefrontal dopaminergic hypactivity). The third effect might account for milder extrapyramidal side effects (EPS) of risperidone (related to nigrostriatal D_{2} antagonism), in comparison with typical neuroleptics.

Also α_{1} and α_{2} adrenergic antagonism could contribute to the antipsychotic efficacy of risperidone, since some studies have shown antipsychotic efficacy of the α_{2}-adrenergic antagonist idazoxan in the clinical setting and of the α_{1}-adrenergic antagonist prazosin in an animal model of psychosis induced by phencyclidine.

Efficacy
The first registration studies assessed the efficacy of risperidone in the treatment of acute schizophrenia. In the following years, many other studies evaluated risperidone efficacy in different settings of schizophrenia treatment, as well as in the treatment of other mental illnesses.

In the following paragraphs, the main studies assessing risperidone efficacy in the treatment of several disorders characterized by psychotic symptoms are reported.

Schizophrenia: acute treatment
In an USA double-blind, multicenter study, 388 patients with schizophrenia were randomly assigned to 8 weeks’ treatment with placebo, one of four doses of risperidone (2, 6, 10, or 16 mg), or 20 mg of haloperidol, daily. At the study end point, clinical improvement [defined as 20% reduction in total scores on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)] was shown by 35% of the patients receiving 2 mg of risperidone, 57% receiving 6 mg, 40% receiving 10 mg, and 51% receiving 16 mg; and by 30% receiving haloperidol, and 22% receiving placebo. Statistically significant differences in clinical improvement were found between 6 and 16 mg of risperidone versus placebo, and versus haloperidol.
Positive symptom scores were significantly lower after 6, 10, and 16 mg of risperidone and 20 mg of haloperidol than placebo; surprisingly, negative symptom scores were reduced significantly, compared with placebo, only after 6 and 16 mg of risperidone. The incidence of EPS was significantly higher in patients treated with 16 mg of risperidone or 20 mg of haloperidol than placebo. The dose of 6 mg was as effective as 16 mg, and the incidence of EPS in patients receiving 6 mg of risperidone was no higher than that in patients receiving placebo.

In a Canadian double-blind study, 135 chronic inpatients with schizophrenia were randomly assigned to 8 weeks of treatment with one of six parallel treatments: risperidone, 2, 6, 10, 16 mg/day; haloperidol, 20 mg/day; or placebo. On the Clinical Global Impression (CGI)-Severity of Illness and Improvement, all active medications were superior to placebo except for risperidone (2 mg). On the total PANSS score and PANSS positive subscale, superiority to placebo was observed for all treatment groups except for haloperidol and risperidone (2 mg). On the PANSS negative subscale, only risperidone (6 mg/day) was significantly better than placebo. Risperidone (6 mg) was superior to haloperidol on the total PANSS, General Psychopathology, and Brief Psychiatric Rating Scale (BPRS) subscales. Although there was a linear increase in parkinsonism with increasing risperidone dosage, there were no statistically significant differences between risperidone (2, 6, and 16 mg/day) and placebo. At doses of 6 to 16 mg, risperidone displayed a marked antidyskinetic effect compared with placebo. By contrast, haloperidol produced significantly more parkinsonism than placebo and risperidone (2, 6 and 16 mg), with no effect on tardive dyskinesia (TD).

Schizophrenia: long-term treatment
In a multi-center, parallel-group, double-blind study, patients with chronic schizophrenia were randomly assigned to risperidone 1, 4, 8, 12 or 16 mg or haloperidol 10 mg daily for 8 weeks. The optimum risperidone doses were 4 mg and 8 mg. However, there were no significant differences in PANSS and CGI scores at endpoint between risperidone 4 mg, 8 mg, 12 mg and 16 mg and haloperidol 10 mg. EPS were significantly greater in haloperidol-treated patients than in the risperidone 1, 4, 8 and 12 mg groups.

Schizophrenia: overall effectiveness
In one of the most important and cited study on the effectiveness of antipsychotic drugs, risperidone confirmed to be a highly effective antipsychotic treatment with an excellent safety/effectiveness index ratio. The multicenter double-blind CATIE study on 1493 patients with schizophrenia randomly assigned to receive olanzapine (mean modal daily dose 20.1 mg), perphenazine (mean modal daily dose 20.8 mg), quetiapine (mean modal daily dose 543.4 mg), or risperidone (mean modal daily dose 3.9 mg) for up to 18 months, ziprasidone (mean modal daily dose 112.8 mg), assessed the overall effectiveness of these five treatments. Seventy-four percent of patients discontinued the study medication before 18 months. The time to the discontinuation of treatment for any cause was significantly longer in the olanzapine group than in the quetiapine (P < 0.001) or risperidone (P = 0.002) group, but not in the perphenazine (P = 0.021) or ziprasidone (P = 0.028) group. The times to discontinuation because of side effects were similar among the groups, but the rates differed (P = 0.04); olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for EPS. As in all head to head comparison studies of second generation antipsychotics (SGA), a key problem is the employed dose. In the CATIE study, the use of a higher-than-usual peak dose of olanzapine may have led to the superior results achieved with it. Regarding risperidone, its relatively less than optimal effectiveness in comparison with olanzapine and its favorable side effects profile is probably due to the low mean modal daily dose of this drug used in the study.

In the phase 2 of the CATIE study, subjects with schizophrenia (N = 444) who had discontinued the atypical antipsychotic randomly assigned during phase 1 of the CATIE investigation were randomly reassigned to double-blind treatment with a different antipsychotic (olanzapine, 7.5–30 mg/day [N = 66]; quetiapine, 200–800 mg/day [N = 63]; risperidone, 1.5–6.0 mg/day [N = 69]; or ziprasidone, 40–160 mg/day [N = 135]). The time to treatment discontinuation was longer for patients treated with risperidone (median: 7.0 months) and olanzapine (6.3 months) than with quetiapine (4.0 months) and ziprasidone.
(2.8 months). Among patients who discontinued their previous antipsychotic because of inefficacy (N = 184), olanzapine was more effective than quetiapine and ziprasidone, and risperidone was more effective than quetiapine. There were no significant differences between antipsychotics among those who discontinued their previous treatment because of intolerability (N = 168).

Consistent results were reported in the study of Mullins et al.9 These authors assessed discontinuation at one-year follow-up in a population of patients with schizophrenia initially treated with aripiprazole (n = 446), olanzapine (n = 1705), quetiapine (n = 1467), risperidone (n = 1580), and ziprasidone (n = 700). Most patients discontinued their antipsychotic medication (90.4% adjusted mean discontinuation). The hazard ratio (HR) for discontinuing therapy in patients starting treatment on aripiprazole, risperidone, or ziprasidone was not significantly different from olanzapine [HR 1.047, 0.973 and 0.990, respectively]. Quetiapine was associated with significantly higher hazard of discontinuation [HR 1.130] than olanzapine.

**Studies comparing risperidone with other antipsychotics**

There are many studies comparing risperidone with other first generation antipsychotics (FGA) and SGA. Although the results of these studies are not fully consistent (probably for different study designs and clinical characteristics of the recruited samples), it appears that no other antipsychotic is consistently more efficacious than risperidone, with the possible exception of clozapine. On the other side, quetiapine, aripiprazole, and ziprasidone appear less efficacious than risperidone, at least in the treatment of positive psychotic symptoms, while FGA appear less efficacious than risperidone, at least in the treatment of negative symptoms. The published reviews on this topic suggest similar conclusions.

**Studies showing similar effectiveness of risperidone in comparison with other antipsychotics**

In most head to head comparison studies with other antipsychotics, risperidone showed a clinical efficacy similar to that of other compounds in the treatment of acute psychosis [comparison with olanzapine],10 acute and chronic schizophrenia [comparison with quetiapine],11 acute psychosis in the emergency setting [comparison with olanzapine and quetiapine],12 early psychosis [comparison with olanzapine and quetiapine],13 acute first-episode non affective psychosis [comparison with haloperidol and olanzapine],14 resistant or intolerant schizophrenia [comparison with olanzapine],15 chronic schizophrenia or schizoaffective disorder [comparison with ziprasidone],16 schizophrenia-spectrum disorders in children and adolescents [comparison with olanzapine and quetiapine],17 first-episode schizophrenia [comparison with haloperidol].18

Studies showing superior effectiveness of risperidone in comparison with other antipsychotics

A randomized open-label trial19 for a minimum of 3 weeks in acutely ill patients with schizophrenia, schizoaffective disorder or schizophreniform disorder found that haloperidol (89%), olanzapine (92%) and risperidone (88%) were significantly more effective than aripiprazole (64%), quetiapine (64%) and ziprasidone (64%) in improving mental status so that the patients no longer required acute in-patient care. Changes in BPRS ratings were not significant among treatments, however.

In a double-blind, randomized, controlled flexible-dose trial,20 that compared risperidone (mean modal dose = 3.3 mg) and haloperidol (mean modal dose = 2.9 mg), first-episode psychosis patients (N = 555, mean age = 25.4 years) treated with both treatments achieved initial clinical improvement, defined as >20% reduction in total PANSS score. However, among those who achieved clinical improvement, 42% of the risperidone group experienced a relapse compared with 55% of the haloperidol group. The median time to relapse was 466 days for risperidone-treated subjects and 205 days for those given haloperidol.

In the Intercontinental Schizophrenia Outpatient Health Outcomes21 non-interventional, prospective observational study, olanzapine and risperidone were superior to haloperidol and clozapine in reducing aggression in psychotic patients.

In a naturalistic study,22 the effectiveness and safety of quetiapine, risperidone and olanzapine were compared in the treatment of non selected...
acutely psychotic patients admitted to a psychiatric intensive care unit. It was observed that the rate of antipsychotic switch because of a lack of efficacy or side effects was higher in the quetiapine treated cases in comparison with the risperidone or olanzapine treated cases. The proportion of cases concomitantly treated with typical neuroleptics was significantly higher in the quetiapine group compared with the other two groups. In the outcome of non crossover cases, there were more improvements in the risperidone and olanzapine groups than in the quetiapine group.

Studies showing inferior effectiveness of risperidone in comparison with other antipsychotics

A study comparing switching to clozapine with switching to olanzapine, quetiapine, or risperidone in patients with resistant schizophrenia who had discontinued treatment with a newer atypical antipsychotic in the context of the CATIE investigation found clozapine was more effective than switching to another newer atypical antipsychotic.

In the Intercontinental Schizophrenia Outpatient Health Outcomes naturalistic, prospective observational study on outpatients with chronic schizophrenia, at 6 months, olanzapine resulted in significantly greater improvements in overall, positive, negative, depressive, and cognitive symptoms compared with quetiapine, risperidone or haloperidol (p < 0.001). Improvements in overall, negative, and cognitive symptoms were significantly higher for risperidone compared with haloperidol (p < 0.001), whereas improvements across all symptoms were comparable for quetiapine and haloperidol.

Reviews

Although some reviews found that risperidone has similar efficacy in comparison with all other SGA [amisulpride, aripiprazole, olanzapine, quetiapine, ziprasidone and zotepine], [olanzapine], the most extensive and systematic reviews suggest that clozapine, risperidone, olanzapine and amisulpride have superior efficacy in comparison with other SGA.

In a review of 124 randomized controlled trials in patients with schizophrenia or schizoaffective disorder with efficacy data on 10 SGA vs FGA and 18 studies of comparisons between SGA, efficacy effect sizes of clozapine, amisulpride, risperidone, and olanzapine were 0.49, 0.29, 0.25, and 0.21, greater than those of FGA, with P values of 2 × 10–8, 3 × 10–7, 2 × 10–12, and 3 × 10–9, respectively. The remaining 6 SGAs (aripiprazole, quetiapine, remoxipride, sertindole, ziprasidone, and zotepine) were not significantly different from FGAs, although zotepine was marginally different. No efficacy difference was detected among amisulpride, risperidone, and olanzapine.

A Meta-Analysis of Head-to-Head comparisons of SGA in the treatment of schizophrenia found that risperidone was significantly more efficacious than quetiapine (N = 1,953, weighted mean difference = −3.2, p = 0.003) and ziprasidone (N = 1,016, weighted mean difference = −4.6, p = 0.002). It was less efficacious than olanzapine (N = 2,404, weighted mean difference = 1.9, p = 0.006). No difference compared with amisulpride (N = 291), aripiprazole (N = 372), clozapine (N = 466), and sertindole (N = 493) emerged (the number of participants combined for the two second-generation antipsychotics compared, the difference in PANSS scores (weighted mean difference), and the p value).

In a meta-analysis of 150 double-blind, randomized controlled studies, with 21,533 participants. To compare the effects of SGA and FGA in patients with schizophrenia, four SGA were better than FGA for overall efficacy, with small to medium effect sizes (amisulpride −0.31 [95% CI −0.44 to −0.19, p < 0.0001], clozapine −0.52 [−0.75 to −0.29, p < 0.0001], olanzapine −0.28 [−0.38 to −0.18, p < 0.0001], and risperidone −0.13 [−0.22 to −0.05, p = 0.002]). The other SGA were not more efficacious than the FGA, even for negative symptoms.

Schizophrenia: prevention of relapses

In a double-blind, multicenter, prospective study, 397 outpatients in stable condition with chronic schizophrenia or schizoaffective disorder were randomly assigned to receive flexible doses of either risperidone or haloperidol for a minimum of one year. The median duration of treatment was 364 days in the risperidone group and 238 days in the haloperidol group (P = 0.02). Of the 177 patients assigned to risperidone and the 188 assigned to haloperidol who remained in the analysis, 44.1 percent and 52.7 percent, respectively, discontinued treatment for reasons other than relapse. The Kaplan-Meier estimate of the risk of
Schizophrenia: first episode
In an open trial, risperidone was more effective and better tolerated at 2–4 mg/day than at 5–8 mg/day in patients presenting first-episode schizophrenia.

In a 52-week randomized, double-blind, flexible-dose, multicenter study, the overall effectiveness (as measured by treatment discontinuation rates) of olanzapine, quetiapine, and risperidone was evaluated in patients early in the course of psychotic illness (<5 years), randomly assigned to treatment with olanzapine (mean modal daily dose 11.7 (±5.3) mg), quetiapine (506 (±215) mg), or risperidone (2.4 (±1.0) mg). Reductions in total score on the PANSS were similar for the three treatment groups, but reductions in PANSS positive subscale scores were greater in the olanzapine group (at 12 weeks and at 52 weeks or withdrawal from study) and the risperidone group (at 12 weeks).

Treatment resistant schizophrenia
In the Marder and Meibach study, a subgroup of patients hospitalized for at least six months before entering the study (presumed to be resistant to previous treatment) responded better to risperidone (6 mg/day and 16 mg/day) than to haloperidol 20 mg/day or placebo.

In a group of patients with resistant to treatment schizophrenia, risperidone (6 mg/day) was more effective than haloperidol (15 mg/day) in the first four weeks with fixed doses of drug. The difference between risperidone and haloperidol vanished in the following four weeks at flexible dose (mean risperidone dose: 7.5 mg/day; mean haloperidol dose: 15 mg/day), however.

In a randomized, controlled, double-blind study on 86 patients affected by schizophrenia and resistant or intolerant to typical neuroleptics, risperidone (mean dose 4.6 mg/day) was as effective as clozapine (mean dose 292 mg/day).

In a 12-months open study on 184 patients with treatment resistant schizophrenia, rates of response were higher in the group treated with risperidone than in the group treated with haloperidol.

In a small sample, open label study, patients with refractory schizophrenia were randomly assigned to clozapine or risperidone treatment for 10 weeks and treatment outcomes were assessed blindly. Twenty-one patients were recruited and nineteen entered the randomized phase. Five of 10 participants allocated to clozapine and one of nine risperidone participants dropped out before study completion. Five clozapine patients and six risperidone patients achieved clinical improvement, defined as a 20% decrease in the PANSS total score. No significant differences between the groups were detected in baseline or endpoint positive or negative symptoms, disease severity, or global or social functioning scores.

In a 14 weeks, double-blind, randomized, trial on 157 inpatients with a history of suboptimal treatment response, clozapine, risperidone, and olanzapine (but not haloperidol) resulted in statistically significant improvements in total score on the PANSS. The effects were statistically significant but clinically modest, however.

Despite the above cited results, the weight of evidence suggest that clozapine remains the gold standard in the management of treatment resistant schizophrenia. A review assessed all trials of SGA in patients with schizophrenia unresponsive to at least one drug. Overall, clozapine was consistently shown to be effective in refractory schizophrenia, even when stringently defined. Data relating to olanzapine and risperidone were found equivocal at best, and there was some evidence to suggest that they were less effective than clozapine. The authors conclude that there is essentially no cogent evidence to support the use of any other atypical in refractory schizophrenia and that clozapine remains the drug of choice in this condition.

Risperidone can be useful as adjunctive treatment in some patients with severe schizophrenia who respond to clozapine poorly, however. Several data encourage the use of risperidone as an adjunctive agent in patients with clozapine-resistant schizophrenia or schizoaffective disorder. However, the effectiveness of add-on risperidone therapy in patients with poor response to clozapine is at least uncertain. In a randomized, double-blind study, the addition of risperidone to clozapine did not improve symptoms in 68 patients with severe schizophrenia and poor
response to clozapine. The patients continued to take clozapine and were randomly assigned to receive eight weeks of daily augmentation with 3 mg of risperidone or with placebo. This course of treatment was followed by an optional 18 weeks of augmentation with risperidone. There was no statistically significant difference in symptomatic benefit between augmentation with risperidone and placebo.

**Childhood onset schizophrenia**

Risperidone has now been approved by the FDA for the treatment of schizophrenia in the adolescent population. This new indication has been a result of data obtained from two pivotal double-blind trials with supplemental information from open-label and retrospective trials.39

A 12 weeks, open-label, randomized, prospective study,40 comparing the tolerability and effectiveness of risperidone (0.25–4.5 mg/day, mean dose 1.62 ± 1.02 mg/day) vs olanzapine (2.5–20 mg/day, mean dose 8.18 ± 4.41 mg/day) in the treatment of patients with childhood-onset schizophrenia (mean age 11.09 ± 1.55 years) showed comparable significant (p < 0.001) within-group improvement from baseline to endpoint (LOCF) in PANSS total and subscale scores. No significant differences between risperidone-treated children and olanzapine-treated children were observed on Barnes Akathisia Rating Scale (BAS) and Simpson-Angus Scale (SAS) rating scales. Both treatment groups showed significant (p < 0.001) increase in weight from baseline to endpoint.

A double-blind multisite trial41 randomly assigned pediatric patients with early-onset schizophrenia and schizoaffective disorder to treatment with either olanzapine (2.5–20 mg/day), risperidone (0.5–6 mg/day), orolindone (10–140 mg/day, plus 1 mg/day of benztropine) for 8 weeks. Response to treatment, (defined as a CGI improvement score of 1 or 2 and ≥20% reduction in PANSS total score after 8 weeks of treatment) was similar (molindone: 50%; olanzapine: 34%; risperidone: 46%), as well as magnitude of symptom reduction. Olanzapine and risperidone were associated with significantly greater weight gain, while akathisia was more frequently reported in subjects receiving molindone.

In adolescent schizophrenia, standard doses (1.5–6.0 mg/day) of risperidone are more efficacious than very low doses (0.15–0.6 mg/day), and well tolerated.42

**Cognitive symptoms in schizophrenia**

Several studies have suggested that risperidone can improve cognitive symptoms of schizophrenia including a favorable effect on verbal working memory,33 performance in reaction time and manual dexterity,44 and on the acquisition of new verbal information.45

Although modest, improvement of cognitive symptoms, can have clinical importance, improving global functioning, especially in patients in the early phase of psychotic illness.

In a 52-week double-blind, multicenter study,46 on 81 patients early in the course of psychotic illness (<5 years) randomly assigned to treatment with olanzapine [mean modal daily dose 11.7 (±5.3) mg], quetiapine [506 (±215) mg], or risperidone [2.4 (±1.0) mg], modest improvements on the CATIE neurocognitive battery and on the Brief Assessment of Cognition in Schizophrenia were observed with all the 3 drugs, with no significant overall difference between treatments. Improvement in neurocognition was related with improvement in functional outcome.

**Mood disorders**

Results of double-blind randomized and open trials consistently show risperidone effectiveness in the treatment of bipolar disorder with or without psychotic symptoms, both as monotherapy or adjunctive therapy.

In a 3-week randomized, double-blind, placebo-controlled study47 on 156 bipolar disorder patients with a current manic or mixed episode who received a mood stabilizer (lithium or divalproex) and placebo, risperidone, or haloperidol, risperidone (mean dosage 3.8 mg/day) plus a mood stabilizer was more efficacious than a mood stabilizer alone, and as efficacious as haloperidol (mean dosage 6.2 mg/day) plus a mood stabilizer, for the rapid control of manic symptoms, both in patients with psychotic features and in those without psychotic features at baseline. EPS were severer in the haloperidol than in the risperidone group.

In a 28-day randomized, controlled, double-blind trial48 of either 6 mg daily of risperidone, 10 mg daily
of haloperidol, or 800 to 1200 mg daily of lithium, risperidone was of equivalent efficacy to lithium and haloperidol in the management of acute mania. The EPS of risperidone and haloperidol were not significantly different.

An open, multicentre, 6-month study on 96 DSM-IV acutely manic bipolar patients with a Young mania rating score (YMRS) of 20 or more showed that monotherapy with risperidone (mean dose 4.2 mg/day) was effective and well tolerated in acute and continuation treatment of mania. Efficacy was assessed with the YMRS, the PANSS and the CGI.

A 3-week multicenter, double-blind, placebo-controlled study evaluated the efficacy and safety of risperidone monotherapy (n = 134) (flexible dose: 1–6 mg/day; mean modal dose of risperidone: 4.1 mg/day) or placebo (n = 125) in the treatment of acute bipolar mania. The improvement in mean YMRS total score, CGI, the Montgomery-Asberg Depression Rating Scale, PANSS, and GAS was significantly greater in the risperidone than in the placebo group.

In a 10-week continuation phase study, 290 in-patients with bipolar I disorder with current manic or mixed episode and a baseline YMRS score of ≥20 received flexible doses of risperidone (1–6 mg per day) (n = 146) or placebo (n = 144). Greater improvements in total YMRS were observed with risperidone than with placebo, at weeks 1 and 2, and at end-point (P < 0.01).

An open label, 3 weeks, multicentre trial examined risperidone monotherapy (mean maximal dosage of 5.5 ± 0.9 mg/day) in a sample of 30 severe manic inpatients. Two-thirds of the patients showed a reduction of 50% in the YMRS score, and 69% of the patients were rated as very much improved or much improved on the CGI-BP mania scale, at study exit.

Dementia
Symptoms such as aggression, agitation, sleep disturbances and wandering, as well as delusions, illusions, and hallucinations, are common in patients affected by dementia, cause distress to caregivers and are likely to lead to institutionalization of patients. Antipsychotics, including risperidone, are widely used to treat these symptoms in people with dementia. However, most clinical trials in which the efficacy of antipsychotics was studied for the treatment of neuropsychiatric symptoms in dementia were of short duration, and thus they cannot provide information on their true efficacy over the long term.

Regarding risperidone, an analysis on pooled data from three randomized, placebo-controlled trials that examined the efficacy and safety of risperidone (mean dose 1.0 mg/day) for the treatment of agitation, aggression, and psychosis associated with dementia in elderly nursing home residents, found that risperidone was more efficacious than placebo. However, more patients discontinued due to adverse events (EPS, mild somnolence and rare cerebrovascular adverse events) in the risperidone-treated group (17.2%) than in the placebo group (11.2%).

Bhana and Spencer found that, in the treatment of agitation, aggression, and psychosis associated with dementia, risperidone 1 mg/day was at least as effective as haloperidol and superior to placebo, as assessed by the rating scales for global behavior, aggression and psychosis and was associated with fewer EPS and an incidence rate of TD (2.6%) one-tenth compared with haloperidol.

Although effective, antipsychotics, including risperidone, have a modest effect on the neuropsychiatric symptoms of dementia, and an excess risk of death and morbidity is associated
with their use in older patients. Potential risks with antipsychotics include EPS, weight gain, diabetes mellitus, cardiac conduction abnormalities (including QTc interval prolongation), cerebrovascular adverse events and mortality. A 42-site, double-blind, placebo-controlled trial including 421 outpatients with Alzheimer’s disease and psychosis, aggression, or agitation randomly assigned to receive olanzapine (mean dose, 5.5 mg/day), quetiapine (mean dose, 56.5 mg/day), risperidone (mean dose, 1.0 mg/day), or placebo, found that adverse effects offset advantages of these drugs in the treatment of psychosis, aggression, or agitation of patients with Alzheimer’s disease.

A meta-analysis on six phase-2/3, double-blind trials comparing risperidone with placebo in 1721 patients found that the mortality was 4.0% with risperidone versus 3.1% with placebo (relative risk, 1.21; 95% confidence interval, 0.71–2.06) during treatment or within 30 days after treatment discontinuation. The most common adverse events associated with death were pneumonia, cardiac failure or arrest, or cerebrovascular disorder. No relationship was found between risperidone dose and mortality.

In the treatment of neuropsychiatric symptoms associated with dementia, there is no evidence to suggest differences in effectiveness between SGA and FGA or among SGA. Therefore, the choice of an antipsychotic for neuropsychiatric symptoms in dementia often relies on side effect profile and individual patient circumstances.

Patients treated with FGA have an increased incidence of cardiac arrhythmias and EPS in comparison with patients treated with SGA. Compared with placebo, treatment of neuropsychiatric symptoms of dementia with SGA leads to little or no increase in EPS and no significant weight change. Compared with FGA, treatment of neuropsychiatric symptoms of dementia with SGA leads to a reduced risk of EPS, lower incidences of TD and no significant weight gain. Although metabolic effects (i.e. increased risk of diabetes, weight gain) have consistently been documented in patients treated with SGA, this effect tends to be attenuated with advancing age and in elderly patients with dementia. Conversely, users of SGA are exposed to an increased risk of venous thromboembolism and aspiration pneumonia. Both FGA and SGA have been associated with cardiac conduction abnormalities, with the magnitude of QTc prolongation being slightly smaller with SGA. Randomized controlled trials suggest that SGA are associated with an increased risk of cerebrovascular adverse events, such as stroke, and an increased mortality compared with placebo. It is not clear whether FGA have similar, higher, or lower risks of cerebrovascular adverse events and death. An increased risk of anticholinergic adverse effects and falls must also be considered with both FGA and SGA.

The US Food and Drug Administration issued a warning for all atypical antipsychotics as a result of a meta-analysis of 17 placebo-controlled clinical trials using various SGA for the treatment of neuropsychiatric symptoms of dementia.

Antipsychotics, both FGA and SGA, including risperidone, are associated with potentially serious adverse events, and are not considered first choice for the treatment of behavioral and psychotic symptoms of dementia, currently. Nevertheless, a trial of these agents may be indicated in instances in which the severity of symptoms is extreme, or symptoms do not respond to nonpharmacologic methods or other medications. Before prescribing these medications in elderly dementia patients, baseline EPS, ECG abnormalities and concomitant medications should be assessed, and the presence of cardiovascular, cerebrovascular and metabolic risk factors should be taken into consideration when benefits and risks are being weighed. A discussion of the risk-benefit ratio of antipsychotics with the patient’s family and/or caregivers should precede the decision to use these agents.

**Risperidone Long-Acting Injectable**

Risperidone long-acting injectable (RLAI) is the first second-generation depot antipsychotic. RLAI consists of encapsulated risperidone in a glycolide/lactide matrix in the form of microspheres such that after a single intramuscular injection, significant plasma levels of the drug are achieved after week 3. Steady state, after repeated administration at 2-week intervals, is achieved after 3 injection cycles. Since poor compliance is frequent among patients affected by psychotic disorders and a leading cause of treatment ineffectiveness, long-acting risperidone has the potential to improve compliance and be more effective than the oral drug.
In a multi-center, open-label study, 67 188 patients with schizophrenia or schizoaffective disorder, judged clinically stable and maintained on stable antipsychotic doses receiving conventional depot antipsychotic monotherapy were treated with 25–75 mg of RLAI every 2 weeks for 50 weeks. PANSS-total scores improved after receiving RLAI (64.2 +/- 18.9 to 58.2 +/- 20.3; P < 0.001). Clinical improvement of ≥20%, 40%, or 60% reduction in PANSS-total score, occurred in 52%, 34%, and 16% of patients, respectively. EPS subjective ratings and objective physician ratings decreased significantly (P < 0.001).

In a prospective, naturalistic, controlled, and open-label study over 2 years in first-episode schizophrenia, 68 the 22 patients treated with RLAI showed significantly lower relapse rate and higher medication adherence than the 28 control patients treated with oral risperidone.

A review of studies published between 2002 and 2005 on the effectiveness of RLAI in specific subgroups of patients with schizophrenia (elderly, young adults, those with a first episode of illness, and patients with schizoaffective disorder) found that RLAI is effective and well tolerated in these patients. All patient groups demonstrated improvements in mean total PANSS scores and CGI Severity Scale scores. RLAI also reduced relapse rates and had a favorable tolerability profile.

In a 6-months naturalistic study, 70 outcome of RLAI treatment was better when prescribed because of prior poor adherence and for more elderly patients and worse for patients who have previously received clozapine.

The results of a 48-week randomized, prospective, single-blind pharmacokinetic study 71 suggest that the equivalent switching dose be adjusted as follows: patients originally on an oral risperidone dose of 3 mg/day or less should receive 25 mg of RLAI, those taking an oral dose of 3–5 mg/day should receive 37.5 mg, and those taking an oral dose of more than 5 mg/day should receive 50 mg of risperidone long-acting injection.

Side Effects
In the USA registration study, 3 fatigue, sedation, accommodation disturbances, orthostatic dizziness, palpitations or tachycardia, weight gain, diminished sexual desire, and erectile dysfunction were significantly related to risperidone dose. 1

In a safety study on 17 psychotic patients, 72 even at extremely high doses (25 mg/day), usually not recommended in clinical practice, risperidone showed to be safe. Except for the sedation observed with higher doses, risperidone was well tolerated. No clinically relevant effects on cardiovascular and ECG parameters were noticed, and except for a slight increase of aspartate aminotransferase and alanine aminotransferase in one patient, no laboratory abnormalities were observed. Prolactin showed an expected increase, while the other endocrinological parameters revealed no changes.

In a safety post marketing study on 7684 patients, 73 drowsiness/sedation was the most frequent reason for stopping risperidone and the most frequently reported event (4.6 cases per 1000 patients-months). EPS were rarely reported, the incidence being 3.2 per patients-months; they were more frequent in elderly patients (7.8 cases per 1000 patients-months).

Extrapyramidal side effects
Risperidone induces dose-related EPS, but at concentrations lower than those of FGA.

Regarding the incidence and the severity of PSE, consistent results indicate that risperidone has a much more favorable profile than haloperidol or other FGA.

The risk of acute dystonic reactions in patients treated with risperidone is very low, even in the emergency setting where high doses of the drug are started immediately. 74

In the USA registration study, 3 the incidence of EPS [measured by the Extrapyramidal Symptom Rating Scale (ESRS)] was significantly higher in patients treated with 16 mg of risperidone or 20 mg of haloperidol than placebo while there was no significant differences between the other lower dosages of risperidone and placebo.

In the Canadian registration study, 4 there was a linear increase in parkinsonism with increasing risperidone dosage. However, there were no statistically significant differences between risperidone (2, 6, and 16 mg/day) and placebo. At doses of 6 to 16 mg, risperidone displayed a marked antidyskinetic effect compared with placebo. This effect was more pronounced in patients with severe dyskinesia.
By contrast, haloperidol produced significantly more parkinsonism than placebo and risperidone (2, 6 and 16 mg), with no effect on TD. In the study of Peuskens,\(^5\) risperidone (1, 4, 8 and 12 mg/day) induced a lower incidence of side-effects, assessed by the ESRS, than haloperidol (10 mg/day).

A combined analysis\(^7^5\) of double-blind studies with risperidone vs. placebo and other antipsychotic agents confirmed that risperidone induced EPS are dose-related. After covariance analysis to adjust for baseline ESRS scores, sex, rage, height, duration of symptoms, age at first hospitalization, hospitalization status, and diagnosis, the effects of the maximum dose of risperidone on the mean shift to worse ESRS total scores were 1.4 (CI = 0.73–2.03) at 1–4 mg/day (n = 319); 2.1 (CI = 1.65–2.50) at 4–8 mg/day (n = 932); 3.3 (CI = 2.61–3.89) at 8–12.5 mg/day (n = 439); 3.8 (CI = 2.99–4.55) at ≥13 mg/day (n = 361). The higher the dose of risperidone, the more frequent was the use of antiparkinsonian drugs: 14% at 1–4 mg/day (n = 319), 25% at 4–8 mg/day (n = 900), 27% at 8–12.5 mg/day (n = 407), 31% at ≥13 mg/day (n = 335).

Although it is still a subject of debate, risperidone should not be considered first line treatment of patients affected by Parkinson’s disease or Lewy Body Disease. Quetiapine and clozapine are much better tolerated in these patients.

### Tardive dyskinesia

Risperidone can induce TD occasionally. The incidence of TD in patients with chronic schizophrenia is said to be 0.34% per year. Advanced age and dementia may be contributing factors.\(^7^6\)

In a prospective longitudinal study\(^7^7\) on middle-aged and older patients (mean age 66 years) with different diagnoses treated with haloperidol (1 mg/day) or risperidone (1 mg/day), the 9-month incidence of TD was significantly higher in the haloperidol group (30%) than in the risperidone group (<5%).

In the relapse prevention study of Csernansky et al\(^1^0\) the new onset of TD was reported in one of 177 patients assigned to risperidone (0.6%) and five of 188 patients assigned to haloperidol (2.7%).

### Weight gain and metabolic syndrome

Compared with the general population, patients with schizophrenia have up to a 20% shorter lifespan, with cardiovascular disease as the leading cause of death, an increased prevalence of the metabolic syndrome (obesity, insulin resistance, dyslipidemia, impaired glucose tolerance, and hypertension), increased prevalence of other risk factors for atherosclerosis such as smoking, alcohol abuse, and sedentary life. Unfortunately, some effective treatments of schizophrenia, including risperidone, carry a significant risk of worsening an already precarious situation.

An often cited meta-analysis and random effects meta-regression\(^7^8\) on 81 articles that included data on weight change in antipsychotic-treated patients estimated the weight change after 10 weeks of treatment of several antipsychotics at a standard dose found that risperidone induced weight gain was 2.10 Kg. Weight change induced by risperidone was intermediate between the group of antipsychotics associated with low or no risk of weight gain (molindone –0.39 Kg; ziprasidone +0.04 kg) and the group of drugs associated with high risk (thioridazine +3.19; olanzapine +4.15 kg, clozapine +4.45).

Results from the recent CATIE study show that clozapine and olanzapine produce substantial weight gain and an increased risk of associated metabolic disturbances. Risperidone and quetiapine produce intermediate changes in mean weight in comparison with other atypical antipsychotics, and are associated with an uncertain metabolic risk, while aripiprazole and ziprasidone produce minimal or no weight gain and carry no risk for adverse metabolic changes.

### Hyperprolactinemia (HPRL)

To some extent, HPRL is an inevitable consequence of treatment with antipsychotic agents because prolactin response to antipsychotics is related to dopamine blockade. HPRL often remains asymptomatic, but can also exhibit clinical symptoms resulting from either the direct effects of prolactin on body tissues (galactorrhoea, gynecomastia) or endocrine-related secondary effects (oligomenorrhea and amenorrhea, sexual and reproductive dysfunction in the short term, and possibly the risk of tumorigenesis and osteoporosis in the longer term). The distinction between asymptomatic and symptomatic HPRL is important but is often not made in the literature.
HPRL is the most troublesome side effect of risperidone, which sometimes results in discontinuation. Similar to the benzamide derivates, risperidone increases the levels of prolactin even more than FGA.79–81 Paliperidone, the principal active metabolite of risperidone, carries a similar risk.82 Actually, 9-hydroxyrisperidone and not risperidone appears to be the main contributor to the increased serum levels of prolactin.83,84

Plasma prolactin concentrations in females are much higher than in males. The polymorphisms of the dopamine receptors are not predominantly associated with plasma concentration of prolactin.85

There are conflicting data on whether HPRL is associated with an increased risk of breast cancer in women. Some data suggest that risperidone-induce HPRL may be associated with increased risk of pituitary tumors. In a retrospective pharmaco-vigilance study86 on disproportionate reporting patterns of pituitary neoplasia reports for seven antipsychotics with different affinities for blocking D2 receptors (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and haloperidol), risperidone had the strongest association with HPRL, galactorrhea, and pituitary tumor among the seven antipsychotics, and one of the highest scores for all drugs in the United States Food and Drug Administration’s Adverse Event Reporting System database.

While longitudinal studies are warranted to shed light on this important aspect, it is imperative to exclude the presence of current or previous pituitary tumor or breast cancer in patients candidate to treatment with risperidone, paliperidone, amisulpride or other agents characterized by strong anti-dopaminergic activity. In patients with a history of previous pituitary tumor or breast cancer, antipsychotics with no impact on prolactin level (quetiapine, aripiprazole, clozapine) should be preferred.

Management of HPRL
Management should be tailored to the individual patient. Since the long-term effects of antipsychotic drug-induced HPRL are not well documented, especially regarding osteopenia, infertility, growth, and pubertal delay, risperidone should be administered with caution to children and adolescents.87

In patients prescribed antipsychotics with confirmed HPRL, other causes of prolactin elevation should be excluded, in particular tumors in the hypothalamic-pituitary area.

There is a lack of robust recommendations for monitoring prolactin elevation among patients receiving risperidone. Possibly, when amenorrhea lasts for ≥1 year, bone mineral density should be monitored. Decreasing the dose or switching to a prolactin-sparing medication are possible management options.

Dopamine agonists (pramipexole, ropinirole) widely used for PRL-secreting disorders can be used in the treatment of risperidone-induced HPRL. However, they carry a serious risk of worsening psychotic symptoms. Actually, they are not routinely recommended since the efficacy and risks of this treatment option has not been systematically examined.88

In a Chinese cross-over study on 20 women affected by schizophrenia and diagnosed with risperidone-induced HPRL (serum PRL levels >50 μg/L), and experiencing oligomenorrhea or amenorrhea, the herbal preparation called Peony-Glycyrrhiza Decoction produced a significant baseline-end point decrease in serum PRL levels, without exacerbating psychosis, similar to that induced by bromocriptine. The improvement of adverse effects associated with HPRL was higher in the course of Peony-Glycyrrhiza Decoction than in the bromocriptine treatment.89

Disorders of ejaculation
Several case reports of risperidone-induced absence of ejaculation or retrograde ejaculation have been published.90,91 While the reduced ejaculatory volume may be caused by HPRL, retrograde ejaculation is probably due to the alpha1-receptor antagonist action of risperidone.

Conclusions
Many randomized controlled trials, naturalistic studies and extensive clinical experience have definitively shown clear efficacy and effectiveness of risperidone in the treatment of schizophrenia, schizoaffective disorders and other schizophrenia spectrum disorders, as well as of other psychotic disorders.

On the basis of available evidence, no other antipsychotic drug (neither of 1st nor of 2nd generation) has shown superior clinical effectiveness
in the treatment of psychotic disorders, with the significant exception of clozapine.

Even at high dose, risperidone is characterized by a profile of motor side effects much more favorable in comparison with FGA. Currently, FGA should not be considered first line treatment of psychotic disorders.

In comparison with SGA, risperidone is characterized by a very potent antagonist action on post-synaptic dopaminergic receptors, roughly similar to that of olanzapine, amisulpride, and sertindole, which accounts for its high efficacy and effectiveness on positive psychotic symptoms.

Other SGA, including quetiapine, aripiprazole, ziprasidone show a somewhat inferior efficacy on positive psychotic symptoms probably due to a less strong antagonist action on post-synaptic dopaminergic receptors.

With the possible exception of clozapine, there are no data pointing to a difference in efficacy on so called negative (primary or secondary) symptoms among SGA.

Furthermore, there are some other unique features of risperidone that render it uniquely useful in the management of psychotic disorders, currently.

First, risperidone dosage officially indicated in the treatment of schizophrenia gives unique opportunities to clinicians. There is evidence of efficacy and safety of risperidone dosage up to 16 mg/day. With the possible exception of clozapine (maximal officially indicated daily dosage: 900 mg), no other 2nd generation antipsychotic can be used at comparable maximum dosage on the basis of current available evidence. The highest officially indicated daily doses of the other SGA are the following: olanzapine: 20 mg; amisulpride 1200 mg, quetiapine 800 mg; aripiprazole 30 mg; ziprasidone 160 mg; sertindole 20 mg. Considering the potency of antagonist action on post-synaptic dopaminergic receptors of these drugs and their clinical effectiveness on positive psychotic symptoms, all of them are officially indicated at maximum daily dosages significantly inferior to the 16 mg/day maximum dose of risperidone. That means, that risperidone is the unique choice among SGA for patients with psychotic symptoms who need antipsychotic treatment at very high daily dosage, including:

1. patients with severe positive psychotic symptoms, hostility, aggressiveness and violent behavior;
2. patients with high drug metabolism due to enzymatic induction caused by smoking, alcohol or drug (e.g. carbamazepine) or due to genetic factors;
3. patients long-term treated with high dosage of anti-dopaminergic drugs, especially FGA, who present a supersensitivity of their post-synaptic dopaminergic receptors and show a severe relapse of positive psychotic symptoms whenever the antagonistic post-synaptic dopaminergic action lessens.

Actually for these patient needing unusually high doses of antipsychotics, risperidone or clozapine are the only alternatives to haloperidol treatment. In my own experience, about 1% of acutely psychotic patients require doses of risperidone > 10 mg/day (unpublished data). Most of them present mild or tolerable side effects and fewer EPS than when treated with corresponding high doses of haloperidol.

Other useful and unique features of risperidone which might induce clinicians to prefer this drug to other SGA are the following.

1. The drug is available in liquid form. This allows easier and more reliable drug administration in the elderly patients and in patients reluctant to assume treatment (who try not to take drugs, secretly). Furthermore, it makes possible the use of very low doses (down to 0.1–0.5 mg) in special populations of patients (very old patients, patients with severe hepatic or renal failure, patients unusually sensitive to anti-dopaminergic action of the drug).
2. The drug is available in injectable long-term form. This allows the switch from oral risperidone to this form of drug very useful in patients unwilling to take medicine on a daily basis or with poor compliance.
3. The generic form of risperidone is now available. This allows a significant reduction of the costs of drug treatment in comparison with other SGA.

Among the SGA, risperidone is probably the drug best suited to substitute haloperidol in the clinical practice, in all settings. However, risperidone presents major limitations both on the level of efficacy and of side effects. A substantial of patients with psychotic symptoms do not respond to risperidone, whatever its dose. Most of these patients are unlikely to respond to other FGA or SGA (although trials are worthwhile) and will need clozapine. For a minority of risperidone
treated patients, EPS and TD remain a serious concern. HPRL related side effects may be severe, unacceptable and even dangerous in some patients.

Disclosure
The author reports no conflicts of interest.

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