Risperidone for Individuals with Refractory Schizophrenia

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Abstract

Background: Risperidone has been shown to be as effective as other atypical antipsychotic medications in the treatment of psychotic symptoms, but its effectiveness in refractory psychotic symptoms is unclear.

Objective: In this paper, we aim to review the available evidence related to the use of risperidone in refractory schizophrenia.


Results: The available literature is conflicting on the use of risperidone as an augmentation of clozapine or of other antipsychotics and methodological problems make drawing firm conclusions difficult. Studies using Risperidone Long Acting Injection have included both individuals with recent-onset schizophrenia and those with refractory schizophrenia, which makes it difficult to interpret its effectiveness specifically for those with refractory schizophrenia. Risperidone may reduce potentially disabling cognitive symptoms of schizophrenia, but these effects do not differ significantly from that of other typical and atypical antipsychotic medications.

Conclusion: Further and more rigorous research is required on risperidone for refractory schizophrenia.

Keywords: schizophrenia, refractory, resistant, atypical, risperidone
Introduction, Objective and Method

Risperidone is a benzoxazole compound. Its antipsychotic effects are related to potent dopamine D2 antagonism and affinity to serotonergic 5HT2C receptors. Its common adverse effects include hyperprolactinemia, extra-pyramidal motor effects, sedation and weight gain. It is metabolised by the cytochrome P450 2D6 enzyme and is excreted primarily by the urinary system. Its half life is between 4 and 20 hours; hence it is required to be taken daily or twice a day. It is currently available as an oral regular preparation, an oral solution and a long-acting microsphere preparation (Risperdal consta) also known as Risperidone Long Acting Injection (RLAI). Its active metabolite paliperidone is also available as a long-acting preparation in the United States (Invega Sustenna) and as an oral preparation (Invega) more widely.

Risperidone has been reported to improve positive symptoms of schizophrenia, reduce negative symptoms of schizophrenia, minimize extra-pyramidal adverse effects and prevent relapse, more than haloperidol. Although Risperidone’s presumed superiority with regards to efficacy or adverse effects when compared with typical antipsychotics has recently come into question after the widely publicised results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, it has been demonstrated in this study to be at least as efficacious as any other antipsychotic (aside from clozapine) in the treatment of psychotic symptoms.

Refractory schizophrenia consists of psychotic symptoms with substantial functional disability and/or behavioral deviance that persist in persons with an established diagnosis of schizophrenia despite standard pharmacological and psychosocial care that has been provided continuously for an adequate time period. At least 20%–30% of individuals with schizophrenia have positive symptoms that are only partially responsive or entirely refractory to antipsychotic medications (antipsychotics), including Clozapine, with a recent review by Van Os et al suggesting that about a third of patients with schizophrenia remain symptomatic despite anti-psychotic medication and psychosocial interventions. Psychosocial interventions for persistent psychotic symptoms, particularly cognitive behavioural therapy (CBT) for psychosis, appear to be partly helpful as an adjunct to antipsychotics. Antipsychotic effectiveness for this sub-population with refractory schizophrenia continues to remain under-researched and challenging.

In this article we aim to review the available evidence in relation to the use of risperidone in treatment-refractory schizophrenia. English language articles ranging from 1985 to 2009 (inclusive) were retrieved from Pubmed in December 2009 using search terms ‘schizophrenia’, ‘refractory’, ‘resistant’, ‘risperidone’, ‘atypical’, ‘combination’ and ‘anti-psychotic’. Abstracts that were found in this search were scanned visually for information relevant to the present article. Full-text articles that were found in this scan were then retrieved and hand searched. Any relevant references found in these papers were also reviewed.

Antipsychotics for Refractory Schizophrenia

Current antipsychotics for schizophrenia can be considered partly effective with only 1 in 5 individuals experiencing complete symptomatic remission. The rest are non-adherent and/or partially responsive or entirely refractory to typical or atypical antipsychotic medication. A 30% reduction of positive symptoms, usually measured by the Positive and Negative Syndrome Scale (PANSS) or by the Brief Psychiatric Rating Scale (BPRS), is commonly considered adequate response to treatment. In the CATIE study, real-world effectiveness of typical and atypical antipsychotics was similar, with 3 in 4 individuals on any antipsychotic medication discontinuing treatment within 18 months. Such non-adherence can be due to treatment non-response and/or intolerance. Studies evaluating the use of antipsychotic medication in refractory schizophrenia are limited and when available have methodological challenges that make interpretation of the results difficult. Studies comparing high dose olanzapine to clozapine, the latter being the medication that is commonly considered to be the gold-standard treatment for refractory schizophrenia, have reported mixed findings. In their review of high dose olanzapine as a treatment for refractory schizophrenia, Citrome and colleagues concluded that it may be somewhat effective in the treatment of refractory psychosis. The efficacy of other antipsychotics appears similar, e.g. evidence from case series and open label studies similarly support the effectiveness of high dose quetiapine in refractory...
schizophrenia. In one study, quetiapine and risperidone were similar in efficacy to fluphenazine for refractory schizophrenia. Aripiprazole has also been reported to be of benefit in improving symptoms of individuals with refractory schizophrenia. In general, there is no robust evidence that antipsychotics are very effective for refractory schizophrenia, particularly as monotherapy, other than clozapine but even this is only in about a third of patients.

Risperidone as Augmentation of Clozapine

Complementary receptor binding properties are recommended by the ECNP consensus meeting when choosing combination antipsychotic treatment. The partly different receptor affinities of clozapine and risperidone provide sound theoretical pharmacodynamic rationale for the augmentation of the former with the latter drug.

Several open label trials and case series studying augmentation of clozapine with risperidone have been published to date. Kontaxakis et al. review these studies and point out the methodological challenges encountered in pooling data for a meta-analysis and in drawing meaningful conclusions. These challenges include inadequate trials of clozapine monotherapy prior to augmentation, incomplete demographic and clinical data of patients in open trials, lack of outcome measures and concurrent use of other psychotropic medications in case series. Since the publication of this study, Zink et al. conducted a randomized controlled trial (RCT) augmenting partial responders to clozapine with either risperidone or ziprasidone. They reported significant psychopathology reduction in both groups but different adverse effects across these groups. The sample size of 12 in each arm, the follow-up period of 6 weeks, the lack of a placebo control and presence of industrial funding warrant that the results be interpreted with caution. Josiassen et al. conducted a double blind RCT and reported that risperidone was superior to placebo as augmentation in improving overall positive and negative symptoms. These results conflict with the results of Horner et al. who conducted a methodologically superior comparison of risperidone versus placebo augmentation of Clozapine. Their trial had a double blind 8 week phase and a significant proportion of their sample also completed the 18 week extension phase. They reported no significant improvement in the risperidone group as compared to placebo, even during the 16 week extension phase of the trial, and even some cognitive worsening with risperidone as compared to placebo. In a study using a similar methodology but a smaller sample size, Freudenreich et al. also found no benefit with the augmentation of clozapine by risperidone.

A recent Cochrane database review of the augmentation of clozapine with other antipsychotic medication points to serious methodological concerns and recommends larger well-conducted non-industry funded randomized controlled studies before any clinically meaningful conclusions are drawn about the therapeutic benefits of augmenting clozapine with risperidone.

Risperidone as Augmentation of Other Antipsychotics

Suzuki et al. conducted an open label trial of switching non-responders on monotherapy of Olanzapine, Quetiapine or risperidone to a combination of risperidone and olanzapine. They reported that about 40% of the sample had a 30% drop in BPRS scores while an equal proportion showed no therapeutic benefit on the combination. The mean maximum dose of risperidone was 3.14 mg daily in this study, with doses between 2 mg and 12 mg daily administered to patients. In those who responded to the treatment, hyperprolactinemia, elevated total cholesterol and weight gain were significant adverse effects. The authors conclude that a combination of risperidone and olanzapine may be beneficial to a sub-group of individuals with refractory schizophrenia but caution about the risk of increased adverse effects. Another open label trial on 5 individuals deemed to be treatment-refractory also reported clinical effectiveness on a combination of olanzapine and risperidone. Other than case reports, there are no published studies supporting the use of risperidone in combination with quetiapine for refractory schizophrenia. One case report supports the combination of risperidone with thioridazine for the treatment of psychotic symptoms. Another case report supports the combination of risperidone with reserpine in treatment-refractory psychotic symptoms. In summary, the combination of risperidone with other antipsychotics is not well-studied and requires more rigorous
research before firm conclusions can be drawn about such combinations.

**Risperidone Long Acting Injection**
Risperidone is the oldest atypical antipsychotic medication available as a long-acting injection. Long acting antipsychotic medications may increase treatment response primarily by increasing adherence to treatment or by better bio-availability. There are no published studies to date especially designed to evaluate the effects of risperidone long acting injection (RLAI) on refractory schizophrenia.

Lambert et al conducted a multi-center European open-label study where participants with stable schizophrenia were switched from their original antipsychotic medication to RLAI. They reported that 1 in 3 patients experienced symptomatic remission lasting at least 6 months but when improvement in quality of life and functioning measures were included as outcomes, remission was met by only 1 in 5 participants. The results reported are similar to a study by Rossi et al who also reported sustained symptomatic remission at 1 year in 1/3 of participants in their open label study where participants with stable schizophrenia were switched from their original antipsychotic medication to RLAI. Re-hospitalization rates and symptoms severity were reported to have reduced significantly after a switch to RLAI preparation in an observational study. Interestingly, the degree of this improvement was greater in participants with a recent diagnosis.

**Effect of Risperidone on Negative Symptoms and Cognitive Impairments**
Negative symptoms and cognitive impairments may contribute to psychiatric disability related to schizophrenia, and as such may be addressed by a broad characterization of treatment (non)response. The effect of risperidone on serotonergic and dopaminergic neurons resulted in early hypotheses that Risperidone is of likely benefit in the treatment of negative symptoms of schizophrenia. However, there are no clinical trials to date that we are aware of that robustly support the use of risperidone or any other antipsychotic medication (aside from clozapine) in the treatment of negative symptoms.

Cognitive impairments are an important feature of schizophrenia and predict poor social and occupational functioning in individuals with schizophrenia. 5HT1A agonism has been proposed as a mechanism by which atypical antipsychotics may improve cognition. Woodward et al conducted a review of 43 open-label and double blind prospective studies of atypical antipsychotic medications on cognitive function. Their analysis demonstrated that atypical antipsychotic medications—in this study risperidone, olanzapine, clozapine and quetiapine—improved overall cognitive function compared to typical antipsychotic medications, particularly in the learning and processing speed domains. They also demonstrated that risperidone was better in this respect than haloperidol, but showed the least benefit on vigilance and selective attention (compared to Quetiapine and Olanzapine) and on verbal fluency (compared to Quetiapine and clozapine). Keefe et al reported no differences between typical and atypical antipsychotic medications on cognitive impairments in the CATIE study. It is noteworthy that improved cognitive impairments may not necessarily result in improved quality of life for all individuals, and an improvement in cognitive test results may not always translate into improved real world cognitive functioning in all individuals. In summary, risperidone may be of benefit in improving some cognitive impairments in individuals with schizophrenia, at least as demonstrated by standardized tests, but whether this translates into real-world outcomes is, at this stage, inconclusive.

**Conclusion**
In summary, oral risperidone has been in clinical use for over a decade and a half and has been proven to be efficacious in clinical trials. Recent large randomized control trials comparing it with other antipsychotics have demonstrated that it is only as effective as other antipsychotics with regards to therapeutic benefit in the real world setting. The evidence on risperidone’s augmentation effects on refractory schizophrenia is mixed. Studies reviewing the cognitive benefits of risperidone have been limited by the lack of methodological soundness and results are at best inconclusive. Long acting risperidone microsphere injection may be superior to other antipsychotics but this may be the result of improved adherence to the antipsychotic drug. Methodologically stronger studies are required before firm conclusions can be drawn on the usefulness of risperidone in the treatment of refractory schizophrenia.
Disclosure
This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

References