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REVIEW

Risperidone Long-Acting Injection: Safety and Efficacy in Elderly Patients with Schizophrenia

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Abstract: Antipsychotic medication is considered the cornerstone of the treatment in elderly patients with schizophrenia. Long acting risperidone injection was the first antipsychotic available for use in this group of patients. Current scientific literature revealed that long-acting risperidone is effective in treating the positive and negative symptoms of schizophrenia and some improvements in cognition and functioning have also been found. In terms of efficacy, there is a paucity of randomized trials but the studies suggest that long-acting risperidone is efficient in the long-term management of schizophrenia, with a safety profile similar to that of oral risperidone. It seems that patient acceptance of treatment is greater when patients are switched from a traditional oral medication to depot risperidone and some improvements in cognition and functioning might be related. Further long-term comparisons with other oral and long-acting antipsychotic medications are needed. These studies should include cost-effectiveness data. Research into metabolic side effects is also needed.

Keywords: risperidone, long-acting injection, old age, efficacy, safety

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Introduction

At the present time, most research into schizophrenia focuses primarily on younger patients and mainly in the incipient phases of the illness. Nonetheless, population ages and psychiatrists will need to treat an increasingly high number of elderly patients with long-standing schizophrenia or first presentation psychotic disorders. It has been well established that people with schizophrenia usually have an early onset of the disease developing schizophrenia in the second or third decade of life.[1] Notwithstanding, a minority of patients will present the disease onset during their middle years, or even after age 65. Thus, approximately 15% of all patients with schizophrenia have an onset of symptoms after the age of 40 years, 7% after the age of 50 and 3% thereafter.[2] Moreover, in people with Alzheimer's disease, the prevalence of psychotic symptoms ranges from 30% to 50%.[3] In dementia with Lewy bodies, visual hallucinations occur in 80% of cases while auditory hallucinations and paranoid delusions have a prevalence of 20% and 65%, respectively. Between 20% and 60% of people with Parkinson's disease develop psychotic symptoms. Psychotic symptoms are really pervasive in elderly because they tend to be associated with aggressive or disruptive behavior, frequently resulting in institutionalization.[4] In addition, elder people as a group are at increased risk for psychosis because of age-related deterioration of cortical areas and neurochemical changes, comorbid physical illnesses, social isolation, sensory deficits and polypharmacy.[5]

Antipsychotic agents appear to be the mainstay of treatment in elderly patients with schizophrenia at the present time. It seems to be an effective treatment in schizophrenia, but also in schizoaffective disorder, behavioural symptoms in patients with dementia, and mood disorders with psychosis. However, the use of antipsychotics in elder population arise concern amongst clinicians owing to the age-related pharmacokinetic and pharmacodynamic factors, coexisting medical illnesses and concomitant medication usage. Furthermore, the elderly are particularly vulnerable to the adverse effects of antipsychotic agents, such as extrapyramidal and anticholinergic effects. Risk of other adverse effects associated with traditional antipsychotic agents, such as motor effects, postural hypotension, excessive sedation, and anticholinergic effects need to be considered.

The introduction of atypical antipsychotics promised a new scenario and a broader range of treatment options with fewer prescribing complications was established. Atypical antipsychotics allowed that risks for extrapyramidal symptoms and tardive dyskinesia were reduced dramatically compared with traditional agents. However, to take into account the whole panorama about the use of antipsychotics in the elderly, Alexopoulus et al[6] have described the convenience of using clinical guidance and evidence-based practice:

1. Many older patients with psychiatric disturbances are treated by internists, family physicians, general practitioners, or nurse practitioners, some of whom may not be thoroughly familiar with the use of antipsychotic agents.
2. Antipsychotic drugs are both overused and underused in elderly patients. Federal regulations have been imposed on nursing homes, with the intention of reducing the misuse of antipsychotic drugs in older adults. These regulations focus on the limitation of antipsychotic drug use, but there is little guidance for their therapeutic use.
3. Controlled trials to guide clinical decision-making in the use of antipsychotics in elderly patients are limited, and few studies with large numbers of subjects are available. The paucity of studies is not due to lack of clinical necessity but rather due to difficulties in undertaking clinical trials in this population.
4. The clinical care of elderly patients is complex; elderly patients usually have multiple disorders, often take many different medications, and may be more sensitive to adverse drug effects than younger adults.
5. A growing number of atypical antipsychotics are available, enlarging clinicians' options but at the same time making clinical decisions more complex.

On the other hand, until recently, atypical antipsychotics were available only in oral, short-acting formulations. Additionally, few studies regarding the use of depot antipsychotics in elderly patients were available. Nonetheless, those studies seem to point to positive outcomes in the elderly. But oral antipsychotics are related with one of the most frustrating problems faced by psychiatrists, the

discontinuation of the treatment.[7] Actually, failure to adhere to a prescribed medication regimen by patients with psychosis can be an important limitation because it is associated with a high risk of relapse. Non-adherence in the elder population is further contributed to by age-related factors such as sensory impairment and cognitive decline. For patients with psychosis who will not or cannot take oral medications on a regular daily basis or have other characteristics, such as memory, vision or auditory impairment, which contribute to partial compliance, long-acting injectable antipsychotic medication offers a solution. Of the atypical antipsychotics, risperidone long-acting injection was the first agent to be approved in a long-acting injectable formulation.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Risperidone is a selective monoaminergic antagonist with high affinity by the 5-HT2 serotonergic and dopaminergic D2 receptors. It also binds to alpha 1-adrenergic receptors and has low affinity for H1-histaminergic and alpha 2-agonists. In addition, Risperidone has no affinity for cholinergic receptors. The most important feature of risperidone is being a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia. At the same time, less depression of motor activity and induction of catalepsy than classical antipsychotics are expectable. The balanced antagonism over central serotonin and dopamine activity may decrease the risk of adverse extrapyramidal side effects and it also extends the therapeutic activity to the negative symptoms and affective schizophrenia.

Long-acting risperidone injection (LARI) is an extended release microsphere formulation of risperidone encapsulated in polyglactin for intramuscular injection (Fig. 1). Not only risperidone molecule but also its active metabolite 9-hydroxyrisperidone are considered to have antipsychotic effects. One important feature is that LARI is delivered in an aqueous suspension of risperidone in a carbohydrate matrix of glycolic acid-lactate polymer. Traditional antipsychotic depot preparations are esterified and delivered in an oil-based suspension. Because of its lack of a hydroxyl group, risperidone cannot be esterified, but it is possible to deliver it in a water-based vehicle due to the possibility of its encapsulation in biodegradable polymer microspheres. The polymer dissolves into water and carbon, providing a steady release of medication. Gradual hydrolysis of the copolymer at the injection site ensures slow and steady release of risperidone over several weeks. It has been suggested that the sustained-release aqueous-based agents may provide further benefits given that oil-based injections are associated with pain at the injection site.[8]

After the intramuscular injection, less than 1% of the dose is released followed by a lag of three weeks, which makes it necessary to prescribe an oral antipsychotic during this time. From that point on, release occurs steadily between weeks 4 to 6 and subsides by week 7. Then, injections result in sustained therapeutic plasma concentrations that persist for four to six weeks after the last injection. Risperidone is rapidly distributed. The volume of distribution is 1–2 l/kg. In plasma, risperidone is bound to albumin and alpha-1-acid glycoprotein. The binding of risperidone to

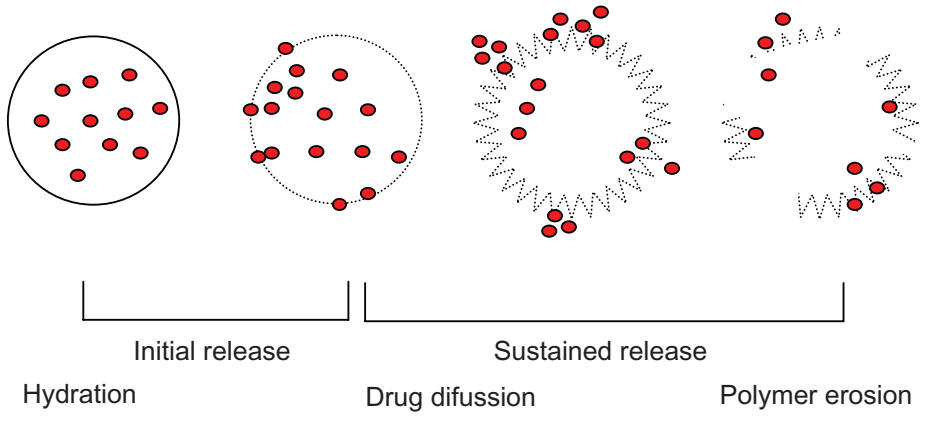

Figure 1. Mechanism of release of the risperidone long-acting injection.

plasma proteins is 90% and the active metabolite 9-hydroxy-risperidone of 77%. Elimination will be complete at seven to eight weeks following microsphere breakdown.

The CYP 2D6 metabolizes risperidone to 9-hydroxyrisperidone, which has similar pharmacological activity to risperidone. Risperidone and 9-hydroxyrisperidone will form the active antipsychotic fraction. CYP 2D6 is subject to a genetic polymorphism. Faster metabolizers of CYP 2D6 converted into 9-hydroxyrisperidone rapidly, while slow metabolizers of CYP 2D6 make it much more slowly. Although faster metabolizers have lower concentrations of risperidone and higher 9-hydroxy-risperidone than poor metabolizers, the combined pharmacokinetics of risperidone and 9-hydroxyrisperidone, after administration of single doses and multiple, are similar in fast and slow metabolizers of CYP 2D6. Another metabolic pathway of risperidone is the N-dealkylation. In vitro studies with human liver microsomes showed that risperidone at clinically relevant concentrations did not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isoenzymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D CYP 2E1, CYP 3A4 and CYP 3A5. After a week of administration of oral risperidone, 70% of the dose was excreted in urine and 14% in the feces. In urine, risperidone plus 9-hydroxyrisperidone represent 35% to 45% of the orally administered dose. The rest are inactive metabolites. The elimination phase is complete approximately 7 to 8 weeks after the LARI.

Different aspects of the pharmacokinetics of risperidone LARI have specifically investigated. Eerdekens et al[9] conducted a rigorous 15-week open label bioavailability study. 86 participants with schizophrenia whose symptoms were stable were included in the study. Patients were first stabilised on 2 mg, 4 mg or 6 mg of oral risperidone for at least 4 weeks and then switched to receive 25 mg, 50 mg or 75 mg of risperidone intramuscularly every 2 weeks. Plasma levels of the active moiety (risperidone plus the major active metabolite 9-hydroxyrisperidone) and risperidone were prospectively collected. Dose-proportional increase in steady-state plasma concentrations of the active moiety was observed. Mean steady-state maximum concentrations of the active moiety were 25%–32% lower after risperidone LAI than after oral risperidone, but this was not the case for minimum concentrations. Based on these data Eerdekens[9] suggested a bioequivalence of the oral and intramuscular doses tested.

Castberg and Speakset[10] also studied drug plasma levels in a sample of 30 patients. They received LARI and were compared with 278 patients under oral risperidone. They found that serum concentrations of risperidone increased from 38 nm/l to 148 nm/l in a dose-dependent manner. The concentration–dose ratio for oral risperidone was much more variable. The authors stressed the stability of plasma levels favouring LARI over oral risperidone. However, Nesvag and Tanum[11] performed a retrospective analysis of a drug monitoring program in Norway with different results. They found a significant percentage of patients treated with LARI to have plasma levels below what the authors considered to be an established reference range (30–120 nm/l), and they too noted substantial individual variation in serum levels. Different explanations about this discrepancy have been suggested by Fleischhacker[12] such as a putative faulty in the injection technique (into fatty tissue rather than muscular), polypharmacy common in Scandinavian studies, different rates of cigarette smoking, which is known to have an impact on some antipsychotic plasma levels.

Clinical Studies

Kane et al[13] conducted a trial where 440 patients with schizophrenia were recruited and allocated in four-arms in a double-blind randomised controlled trial. The three doses of LARI (25 mg, 50 mg and 75 mg) were tested against placebo. As expected, the end-point scores on all three doses differed significantly from placebo for Positive and Negative Syndrome Scale (PANSS) scores. Nonetheless, higher doses of LARI were associated with more extrapyramidal symptoms, although these were generally considered mild across dose groups. Both patients and investigators rated injection site pain as low. Chue et al[14] tested the same hypothesis in 640 patients with schizophrenia in a double-blind controlled trial. It was a on-inferiority trial, meaning a type of study with the aim of showing that one treatment arm does no worse than another. Patients with schizophrenia were prescribed 1–6 mg of oral risperidone for 8 weeks and patients whose

condition was stable were then randomised to be treated with LARI or to continue with oral risperidone. In both groups a significant improvement over baseline on PANSS scores were found and had statistically equivalent efficacy. As in the study by Kane et al, no unexpected adverse event was observed.

Simpson et al[15] conducted a randomised double-blind 52-week study comparing 25 mg and 50 mg of LARI given every 2 weeks. Of the 324 patients who were randomised, only 51% of them completed the study. Time to relapse was comparable for the two treatment groups at the same time that lower relapse risk was found on the higher dose. Unfortunately, those results did not reach a statistical significance. Nonetheless, these findings were associated with improved psychosocial functioning on the higher dose group although differences again were statistically non-significant. Bai et al[16] reported a single-blind randomised trial between daily oral risperidone and risperidone injections (25 mg, 37.5 mg or 50 mg) every 2 weeks. Patients were under oral risperidone before the study. Sample was recruited in Taiwan amongst 50 hospitalised patients with symptomatically stable schizophrenia. Attrition was low because 90% of patients completed the study. Although PANSS score change was no different between oral risperidone and risperidone LAI groups, the authors described a reduced efficacy of LAI at doses below 50 mg every 2 weeks. With regard to safety, patients in the LAI group were reported to experience fewer extrapyramidal symptoms and to have a lower score on the Udvalg for Kliniske Undersøgelser (UKU) side-effect rating scale, as well as lower prolactin levels.

Keks et al[17] reported a randomized controlled clinical trial comparing LARI with olanzapine tablets. A total of 200 patients receiving a mean dose of 14.6 mg oral olanzapine daily were compared with 155 patients who received a mean modal dose of 40.7 mg risperidone LAI every 2 weeks. It is important to remark that a large number of patients were excluded from analysis because of protocol amendments and violations. In any case, no substantial group difference in primary and secondary efficacy outcomes was found, including PANSS scores, Clinical Global Impression (CGI) scores and maintenance of effect. Unfortunately, patients on LARI showed a higher risk of extrapyramidal symptoms and were more often prescribed anticholinergic drugs. On the other side, olanzapine group had a greater risk of weight gain and body mass index increase. As Fleischhaker[12] has stressed, in this study two patients died in the LARI group and six died in the olanzapine group, a fact that the authors do not comment on in the original report.

Despite the accumulated evidence favouring the use of LARI in schizophrenia patients, extrapolating the results of clinical trials on younger patients to the elderly may not be a reliable approach. Studies with elder populations are the best way to determine the validity of LARI with elder schizophrenia patients. Different studies have directly tested this question. Lasser et al[18] conducted a 1-year open label international multicentre trial in stable patients (n = 725) with schizophrenia or schizoaffective disorder. It was designed to examine the long-term safety and efficacy of LARI and tested different doses (25, 50 and 75 mg every 2 weeks). The authors performed a subanalysis of 57 elderly patients ≥65 years, being average 70.9 years. Efficacy was assessed using the PANSS, and Quality of Life (QoL) measures using the 36 item Short Form Health Survey (SF 36). Safety and tolerability were assessed by spontaneously reported adverse events, and various accepted ratings including the Extrapyramidal Symptom Rating Scale (ESRS). Mean modal doses of LARI were 25 mg in 27 patients, 50 mg in 21 patients and 75 mg in 9 patients. There was a statistically significant decrease from baseline in mean PANSS total score at endpoint in all three LARI groups. Scores on each of the five PANNS factors decreased significantly from baseline in the LARI 50 mg and combined treatment groups and on four of the five factors in the 25 mg group. Clinical improvement (≥20% reduction in PANSS total scores) was achieved by 49% of these stable patients, and 55% improved on the CGI scale by at least 1 point.

With regard to safety, there was a significant decrease in total ESRS scores from baseline to endpoint in the combined treatment group ($P < 0.001$). Adverse events were reported by 74% of the LARI combined group, 74% of the 25 mg group, 71% of the 50 mg group, and by 78% of the 75 mg group. No cases of emergent tardive dyskinesia were reported. Adverse events reported in >10% of patients were insomnia (14%), constipation (12%), bronchitis (12%), psychosis (11%) and rhinitis (11%). The incidence of

adverse events was not dose related. There were no clinically significant changes in laboratory findings, electrocardiograms, and vital signs reported. The average increase in body weight was 0.3 kg at endpoint. The authors conclude that LARI was associated with significant symptom improvements in stable elderly patients with schizophrenia or schizoaffective disorder. Treatment was well tolerated.

Kissling et al[19] used the same strategy performing a subgroup analysis of 52 patients aged ≥65 years from the Switch to Risperidone Microspheres (StoRMi) study. This study was an open label study 6 month, non-randomised, investigating the efficacy and safety of LARI in clinically stable patients with schizophrenia or another psychotic disorder. The transition to LARI occurred without an oral risperidone run-in, but the previous antipsychotic therapy was continued for 3 weeks. The recommended starting dose of LARI was 25 mg every 2 weeks, however, higher doses (37.5 mg or 50 mg) could have been initiated and dose adjustments were permitted. Eighty one percent of the elderly patients completed the study. While most patients received 25 mg as the initial dose (89%), at endpoint 60%, 26%, and 14% of patients were on 25 mg, 37.5 mg, and 50 mg every 2 weeks, respectively. There was a significant decrease in PANSS total score after conversion to LARI at each assessment ($P = 0.0001$). From baseline to study endpoint, there was a mean reduction in PANSS total score of 15.8 ± 19.9 points. Significant improvements from baseline were also seen on the PANSS positive, negative, and general psychopathology subscales as well as in all five Marder symptom factors. Significant improvements ($P < 0.001$) from baseline to endpoint were also observed on the CGI-S, GAF (Global Assessment of Functioning), and patient satisfaction scale. All mental health factors of the SF 36 were significantly improved from baseline to endpoint ($P < 0.05$), except for vitality. Adverse events (AEs) occurring in >5% of patients included: parkinsonism (n = 8), extrapyramidal disorder (n = 8), tremor (n = 4), depression (n = 3), diarrhoea (n = 3), dizziness (n = 3) and insomnia (n = 3). Serious adverse events were reported by 11 patients and the most common were psychiatric disorders and general medical conditions (n = 3 each). There were no cerebrovascular adverse events. There was one case of new onset diabetes mellitus. The mean ESRS total score and the Parkinsonism subscale were significantly improved from baseline to endpoint.

Tadger et al[20] performed a retrospective chart review to evaluate remission associated with the use of LARI in elderly patients over a oneyear period. Three of 25 patients treated with LARI, 19 (76%) continued uninterrupted treatment for 6 months or longer. In six patients treatment was discontinued due to insufficient response. The clinical severity ratings with the CGI of all patients were in the range 57 prior to treatment. Following six months of LARI treatment, mean dose 36.0 mg/2 weeks, 18 patients were rated as "improved" or "very much improved" on the CGI global improvement item scale. In 60% patients (15/25) symptomatic remission was achieved. The authors conclude that LARI may be effective in achieving remission amongst elderly schizophrenia patients. Singh and O'Connor[21] performed a retrospective case review of 18 patients (aged 66 to 84 years), who had received LARI for an average of 17.2 months. All patients experienced some symptomatic improvement and four became free of all positive and negative symptoms. Seven of the patients have had history of extrapyramidal symptoms in the previous treatments. Now, all of them showed improvement on extrapyramidal effects and two became totally symptom free.

A further two women, with no past history of extrapyramidal symptoms, developed parkinsonism and akathisia. The authors conclude that overall, their experience with LARI in elderly patients was promising. It was generally well tolerated with good improvement in both positive and negative symptoms.

Finally, Harrington et al[22] described eight case studies of patients over 65 years of age receiving LARI for the treatment of schizophrenia. 5 Patients were initiated on LARI for various reasons including issues of adherence, lack of response to other medications, side effects from other medications or other symptoms of their illness. All patients commenced LARI at 25 or 37.5 mg every two weeks.

One patient experienced a negative response to LARI, 2 patients had no change compared to their previous antipsychotic treatment and 5 patients had marked improvements. Patients with long-term exposure to depot antipsychotics, while requiring higher doses of LARI, generally achieved better outcomes with reduced side effects compared to their previous

therapy. Patients with no or minimal prior exposure to antipsychotic drugs were maintained on lower doses of LARI. Martin et al[23] published case reports of four patients, including one elderly patient, who was enrolled in the one year, open label trial described above. The patient was initiated on LARI 50 mg every 2 weeks, with oral risperidone supplementation (4 mg/day) for the first 2 weeks. The patient showed a good response to the treatment and, after 3 months, no longer experienced hallucinations. Over the course of 1 year, he was more alert and socially interactive and less anxious and depressed. Moderate difficulty in abstract thinking remained. Extrapyramidal symptoms disappeared after 9 months.

Safety and Tolerability

Treating elderly patients with antipsychotics is complicated by concerns about tolerability, safety and other treat-limiting side effects. Movement disorders, including tardive dyskinesia, occur more commonly in elderly patients compared with younger adults. Movement disorders can be particularly troublesome in the elderly because they reduce ability to independently perform activities of daily living.[24] Antipsychotics may also produce additional undesired anticholinergic effects and an increased risk of cognitive loss. Risperidone has been widely studied in the management of aggression, agitation and psychosis of dementia, with trials suggesting efficacy and safety when lower doses are utilized[25] However, concern exists that risperidone is associated with an increased risk of cerebrovascular adverse events in this population.[26] Unfortunately, few data on the use of risperidone for elderly patients with schizophrenia open-label studies are available. In any case, it has been described a clinical improvement but frequent adverse side-effects have been also reported.[27]

Fortunately, Long-acting injectable antipsychotic medications have not been associated with higher incidences of adverse effects than oral preparations. Glazer and Kane[28] reviewed and analysed published data on extrapyramidal symptoms, tardive dyskinesia and neuroleptic malignant syndrome for traditional antipsychotic agents given orally and in depot formulations. They concluded that depot antipsychotic agents were not associated with an increase in extrapyramidal symptoms, tardive dyskinesia or presence of neuroleptic syndrome. Thus, they recommended the use of these agents. However, long-acting injectable antipsychotics cause pain or discomfort at the injection site in some patients. To minimise local reactions, rotate injection sites and limit the volume of the injections can be a solution.

The StoRMi clinical trial was designed to evaluate the long-term efficacy and safety of direct conversion from oral or depot antipsychotic to LARI without an oral risperidone run-in phase. Data from this European study consisting on a multinational open label study of 6-month have been reported by Möller et al.[29] A total of 1876 patients were evaluated finding significant improvements in clinical symptoms and functioning. Most importantly, LARI was well tolerated with only 6% of patients discontinuation attributed to an AE. Kissling[19] performed a subgroup analysis on this international study, specifically of patients aged 65 years. From the whole sample 52 elderly patients (>65 years) with psychosis stabilized on oral or depot antipsychotic were considered for the subanalysis. Study outcomes included psychiatric symptoms, movement disorder severity, adverse events, functional ability, patient satisfaction and quality of life. In addition, the change in the Positive and Negative Syndrome Scale at endpoint was considered the primary outcome. The most common dosage of LARI used at endpoint was 25 mg every 14 days (60%). The trial was completed by 81% of patients, with six patients discontinuing treatment due to an adverse event. Tolerability was good and most side effects were mild to moderate. Serious adverse events occurred in 11 patients. Two of these (suicidal attempt, n = 1; exacerbation of disease, n = 1) were considered possibly related to LARI.

Rainer[30] has summarised all the subanalysis from the SToRMi study. Taking into account these studies, it can be concluded that elderly patients with psychotic illnesses may be safely converted to long-term LARI from an oral or depot antipsychotic. There is some evidence favouring the idea that LARI is well tolerated with improvements in psychiatric symptoms in this population (Table 1). The long-term dosage selected for most elderly patients in these studies was the lowest dosage of 25 mg every 2 weeks.

Singh and O'Connor[35] have performed a complete review about the topic of long-acting injections in elderly schizophrenia. It is concluded that there is no evidence from the published studies about

Table 1. Major published subgroup analyses of the StoRMI trial.

	Subanalysis	Sample	PANSS changes	Adverse events
Marinis et al[31]	Switch from first-generation antipsychotic	Switched from oral drug = 100;	–15.3 ± 17.5	58%
		Switched from depot medication = 565	–9.1 ± 19.5	60.4%
Schmauss et al[32]	Switch from monotherapy with risperdal oral	586 patients (60% men, age 36–40) pre-treated with 4 mg or less	–11.9 ± 17.3	53%
		429 (75%) pre-treated with 6 mg or more	–8.7 ± 20.8	62%
Saleem et al[33]	Young adults	119 patients (age 18–30)	Consistently improved	Not reported
Kissling et al[19]	Elderly patients	52 patients (age, 65 or more)	–15.8 ± 19.9	69%
Curtis et al[34]	Patients with prominent negative symptoms	842 patients (PANSS negative subscale score of 21 or higher)	–15.4 ± 20.4	58%

Adapted from Rainer et al.[30]

increased cerebrovascular events although the number of patients was relatively small and only a few were very old aged. This is an important point regarding the concerns about cerebrovascular events and mortality in patients with dementia. Schneider[36] perfomed a meta-analysis of mortality in 17 placebo-controlled trials of four atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) found a pooled incidence of mortality of 3.5% versus 2.3% for placebo, a small but statistically significant difference. However, these findings were not replicated in a population linkage study of stroke in older people prescribed risperidone or olanzapine.[37]

However, none of the studies considered before have addressed the undesired effects on prolactin. Petty[38] found that risperidone and conventional antipsychotics raise prolactin levels by blocking dopamine in the tuberoinfundibular pathway. Consequently, short-term side effects of raised prolactin will appear including sexual dysfunction and loss of libido. Furthermore, longer-term problems include decreased bone density and osteoporosis.[39] It is obvious that research of these topics is totally necessary. The risk of hyperprolactinemia, which risperidone shares with older neuroleptics, and which can precipitate side effects such as sexual dysfunction, infertility, and osteoporosis, cannot be expected to be alleviated by a LAI formulation, because the active metabolite, 9-OH-risperidone, appears to be responsible rather than risperidone itself.[40]

Since aging is associated with decreased rates of renal blood flow, and other glomerular filtration and renal clearance, some caution is required in patients with renal or hepatic impairment. Plasma levels are normal in patients with hepatic insufficiency, but may be raised by 60% in patients with renal impairment. That is important since an age-related fall in total body water results in higher plasma concentrations of this water-based medication, increasing both its activity and the potential for adverse effects. For instance, Singh and O'Connor[20] have stressed that risperidone should be used with caution with other centrally acting medicines because it antagonizes the effects of levodopa and other dopamine agonists and potentiates the orthostatic effects of tricyclic antidepressants and antihypertensives. Thus, caution is advised when combining risperidone with drugs known to prolong the QT interval because of the risk of cardiac arrhythmias. For tahat reason, some safety practices can be followed as stated in Table 2. Moreover, Risperidone levels are increased by cytochrome 450 2D6 inhibitors such as paroxetine and fluoxetine and decreased by cytochrome 450 3A4 inducers like carbamazepine, corticosteroids, and barbiturates.

Finally, Volkow[41] suggested that with age, the loss of ascending dopaminergic neurones and postsynaptic dopamine receptors can halve the levels of striatal dopamine by age 65 years, resulting in parkinsonism and tardive dyskinesia given risperidone's high affinity

Table 2. Safety practices

1. Incorporate an ECG with corrected QT (QTc) before and after the instauration of the treatment
2. When QTc > 500 milliseconds reject this particular antipsychotic agent
3. When there is an increment of more than 50 milliseconds in the QTc after the instauration of the treatment reject this particular antipsychotic agent
4. When basal QTc > 450 milliseconds increasing surveillance and repeat the ECG at 4 weeks
5. Always, look for reversible causes that might be contributing to QTc interval prolongation, including:
   a. Untreated heart disease
   b. Electrolytic disturbances (hypokalemia, hypocalcemia, hypomagnesemia)
   c. Diabetes, metabolic syndrome, hypotiroidism
   d. Polypharmacy (tricyclic antidepressantss, macrolide antibiotics or methadone)
6. When cardiac risk factors (metabolic syndrome, personal antecedents of antipsychotic syncope, familiar history of sudden death before 40 years, or syndrome of prolonged QTc) were present increasing vigilance and repeat the ECG at 4 weeks

for dopaminergic D2 receptors. Masand[42] showed that reduced cerebrovascular perfusion and the increased sensitivity of alpha-1 adrenergic receptors also make the elderly more susceptible to orthostatic hypotension, dizziness and unexpected falls.

Patient Prefrerence and Place in Therapy

Long-acting injectable antipsychotic medication should be considered for elder schizophrenia patients for whom long-term treatment is indicated. The choice of which drug to use should be based on patients' history of response and personal preference, clinician's previous experience and pharmacokinetic properties. Moreover, patient preference and opinion about their own treatment are being increasingly recognized in the practice of psychiatric therapeutics. Nonetheless, as Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study has revealed,[7] one important reason for discontinuing antipsychotic medication has been proved to be related with patient satisfaction and patient's own choice. Desai et al[43] reported in their study that patient acceptance of treatment was greater when patients were switched from a traditional depot to oral risperidone. Thus, it is thought that a long-acting injectable atypical formulation would be very well received by patients and compared mental healthcare providers.

Oral and long-acting injectable risperidone seemed to be associated with improved functioning in neurocognition, escecifically in the domains of attention/vigilance, verbal learning and memory, and reasoning and problem solving, as well as psychomotor functioning.[44] In our institution we performed a 48-week, open label, non comparative trial with 40 patients who were switched to risperidone long-acting injectable from their previous antipsychotic without a washout phase. Patients were tested with cognitive assessment battery. Change from baseline to endpoint was assessed for all cognitive measures. Significant improvements were noted in 4 of the 6 domains evaluated, with improvements of many domains occurring at time of first re-assessment (week 12). These improved domains (baseline to endpoint) included attention ($P < 0.05$), processing speed ($P < 0.001$), working memory ($P < 0.05$) executive function ($P < 0.05$).[45] Interestingly, differences in symptomatology, global functioning and attitudes toward medication were also found.[46] More specifically, the improvement in attitudes toward medication showed a significant correlation with improvements in psychomotor speed ($P < 0.001$) and working memory ($P < 0.05$). Obviously, these only are preliminary results and further analyses will need to explore the relationship between cognitive functioning and attitudes toward medication and putative relationship with a more favorable subjective experience of long-acting injectable in schizophrenics. It goes without saying that studies must be done in genuinely old people.

Conclusions

In conclusion, long-acting risperidone injection appears as an effective and generally well tolerated treatment in elderly patients with schizophrenia. It can be considered safe and it has also shown to be a useful

treatment modality for patients with difficulties in oral medication. Although optimal dose and frequency of LARI are still being debated, the recommended dose of 25 mg fortnightly can be safely doubled in some cases as it has been observed in published case series. The commonest dose in the majority of studies previously reviewed in this paper points to an average 37.5 mg dose. Singh and O'Connor[20] suggested that it seems reasonable to start LARI treatment at a dose of 25 mg fortnightly after a period of treatment with oral risperidone (0.5 to 3 mg daily) to confirm tolerability. In some cases, oral supplementation is required for three weeks after the first injection. Thus, the requirement of initial oral risperidone supplementation remains problematic for routinely clinical practice. Lastly, do not forget that the high economic cost of this medication needs to be considered in some clinical and socioeconomic settings.

All in all, elderly patients with psychotic illnesses may be safely converted to long-term LARI from an oral or depot antipsychotic without a risperidone run-in. LARI was well tolerated in this population proving significant improvements in psychiatric symptoms and better functioning. Extrapyramidal side effects do occur in these patients and it should be monitored regularly. Although there is no evidence to date of an increase in cerebrovascular events, some prolactin levels increment, and subsequent osteoporosis have been reported. On the other hand, in patients with schizophrenia, orally administered risperidone seemed to improve functioning in different cognitive domains. Interestingly, these improvements seem lead to better attitudes to medication. Unfortunately, no data on elderly people with schizophrenia is available. More research is needed in order to establish a better understanding of this putative relationship. Finally, it is necessary to state that more randomised clinical trials in elderly patients are needed, especially comparing the various long-acting injectable formulations. Nevertheless, LAI has become a useful option for maintenance treatment of elderly patients with 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 and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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