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Long-Acting Injectable Risperidone for the Treatment of Schizophrenia

Clinical Perspectives

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Contents

Abstract

Schizophrenia remains a severe disorder that is associated with a poor outcome in a large subgroup of patients. Major efforts should be made to improve treatment for all patients who have this debilitating disease. Second-generation antipsychotics were a major step forward in this respect; however, important unmet needs remain, such as a better solution for frequent noncompliance problems. Depot formulations are known to have advantages in this respect. However, for a long time, only depot formulations of conventional antipsychotics were available, with their high risk of extrapyramidal adverse effects. Therefore, there has been only very restricted use of depot antipsychotics, which mainly focused on patients with chronic disease who were difficult to treat and had a high risk of noncompliance. The situation may change with the advent of a depot formulation of an atypical antipsychotic.

The first depot formulation of an atypical antipsychotic to be introduced to the market is long-acting injectable risperidone. On the basis of the pharmacokinetic properties of the depot formulation, a 2-week interval between administrations is recommended. The antipsychotic efficacy of long-acting risperidone was demonstrated in two 12-week, double-blind, randomised, phase III studies, one versus placebo and the other versus oral risperidone. These two studies, together with one

open-label, long-term study over 12 months, belong to the core group of trials that were relevant for the licensing of long-acting risperidone. A relapse-prevention, control group study comparing the long-acting formulation versus oral risperidone was not performed because of the known principal methodological problems of such a comparison. Instead, as much clinical data as possible was collected from observational studies that investigated questions relevant for clinical practice, such as efficacy, safety and tolerability in different subgroups, and transition from pre-treatment with different kinds of antipsychotics to long-acting risperidone. On the basis of these data, it can be stated that the efficacy of the long-term formulation of risperidone is proven, and that the safety and tolerability are more or less comparable to those of oral risperidone. The local tolerability at the injection site is good.

Because it is well known that noncompliance is a frequent feature of the treatment of schizophrenia, and considering the advantages of atypical antipsychotics, consideration of whether long-acting atypical antipsychotics should have a broader indication than is the case with the depot formulations of the classical antipsychotics is warranted.

The results from long-term studies demonstrate that the outcome of schizophrenia during the era of therapy with classical antipsychotics was, in general, unfavourable in terms of noncompliance and relapse rates.[1,2] Although the advent of the atypical antipsychotics has given clinicians better tools with which to treat their patients,[3] these problems still appear not to have been satisfactorily solved.[4] The question is whether, to a certain degree, the introduction of long-term formulations of atypical antipsychotics can overcome these problems.

1. Noncompliance with Treatment: Impact of Depot Classical Antipsychotics

There is no doubt that noncompliance with treatment is a huge burden on patients with schizophrenia and their relatives, and also on society in general, because noncompliance can be seen as a major cause of relapse. The costs of noncompliance are significant, with an estimated 40% of total costs of the illness being attributed to re-hospitalisations.[5] Given that the preferential use of atypical antipsychotics cannot satisfactorily overcome the problems of noncompliance,[6-8] the question arises whether depot antipsychotics are more successful at guaranteeing compliance.

Most data in this respect are available for depot formulations of classical antipsychotics, which were administered in an attempt to improve the noncompliance rates during long-term oral treatment with these agents. Depot antipsychotics cannot principally prevent a patient discontinuing treatment by the physician and therefore with antipsychotics, but they can at least guarantee that the compliance of patients who continue treatment by their physician improves. Thus, better treatment results with respect to relapse prevention could theoretically be expected, although results of controlled studies comparing a depot with an oral antipsychotic did not always support this expectation.[9] However, the results of these controlled studies should be evaluated critically, since compliance with oral treatment can be better guaranteed under the closely supervised conditions of a clinical trial. Thus, compliance-related advantages of depot antipsychotics may not become

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apparent, although they actually exist in standard everyday care.

A meta-analysis by Davis et al.[10] compiled data from studies that had used different methodologies, including 'mirror image' studies (i.e. outcomes before and after depot injections) and medication discontinuation trials. Of the 613 outpatients evaluated in mirror image studies (n = 6), significant differences were noted in number of hospitalisation days between those receiving oral medications (75 492 days) and those receiving depot treatments (17 860 days). The researchers also assessed relapse rates across several studies (n = 6) and found the rates to differ among the subjects (n = 520) treated with oral typical agents (47.1%) versus depot preparations (30.0%). The time to relapse was not clearly defined and the duration of the studies ranged from 40 weeks to 2 years. Nevertheless, these authors concluded that depot agents were superior in overall relapse and recurrence prevention.

Adams et al.[11] performed a meta-analysis of randomised depot trials that had utilised a comparative arm (placebo or oral typical antipsychotic or several doses of the same agent). Data were extracted from all reviews of long-acting depot antipsychotics for schizophrenia in the Cochrane Database. The final data compiled results from 119 studies and evaluated a total of 6615 subjects. According to the authors, depot typical antipsychotic agents were safe and effective, and showed a small benefit over oral drugs on global outcome. Only one of the three reviews that compared depot antipsychotics with placebo reported on relapse; this review found significantly lower relapse rates favouring the active drug fluphenazine (18.1% vs 59.5%). The same review revealed a greater antipsychotic-related incidence of movement disorders in studies that had compared the active drug with placebo. Unlike in the previous analysis,[10] a lower relapse rate for depot typical agents was not demonstrated when compared with oral typical agents (34.8% vs 36.0%). Adams and colleagues[11] postulated that the trials recruited only patients who were already receiving continuous outpatient treatment and, therefore, this sampling bias could help to explain the equivalent relapse rates. In addition, the meta-analysis incorporated results from both short-term and long-term trials (ranging from 2 weeks to 3 years), which may have biased the results. Finally, it is also feasible that participation in either of the arms of the depot trials provided more intensive follow-up, which may have led to an additional bias on relapse rates. Therefore, true beneficiaries of depot preparations (i.e. noncompliant patients), who generally do not come for follow-up, are also excluded from participation in these trials.

The general results of these two meta-analyses, that the superiority in relapse prevention can barely be demonstrated in such control group studies, is disappointing and, in particular, does not fit with the positive experiences with depot antipsychotics in clinical practice.[12] Despite these results, clinical experience has shown that depot antipsychotic preparations are useful in relapse prevention when used for patients who have difficulties with medication compliance.[13]

Besides efficacy aspects, depot antipsychotics have pharmacokinetic advantages. Depot antipsychotics produce more constant plasma concentration than oral medication,[14] which is absorbed in an unpredictable manner. Parenterally administered drugs are not subjected to first-pass processes, so that a relatively higher concentration of the unaltered drug is presented to the CNS.[15-17]

It is known from clinical practice that the use of classical antipsychotics is complicated by the comparatively high risk of extrapyramidal side effects (EPS), especially tardive dyskinesia, when used under long-term conditions.[13] The occurrence of tardive dyskinesia has been examined in the depot typical antipsychotic trials, and although its incidence varies from study to study, the generally

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accepted rate is between 30% and 60%,[11,18] and some studies suggest that patients treated with depot antipsychotics are at increased risk of developing tardive dyskinesia.[19] Other risk factors associated with tardive dyskinesia include patient age, female sex, previous occurrence of EPS, duration of exposure to antipsychotics, medical risk factors such as diabetes mellitus and psychiatric comorbidities such as affective disorders.[18-20] Adams et al.,[11] in their meta-analysis of the depot typical antipsychotic studies, found a comparable occurrence of tardive dyskinesia between oral and depot typical antipsychotics (0.14% and 0.09%, respectively).

It is generally accepted that the introduction of oral atypical agents has had a positive effect in tardive dyskinesia management, with the demonstration that newer agents may reduce the occurrence and severity of tardive dyskinesia.[20-23]

Apparently, the depot formulations of classical antipsychotics have significant limitations to overcoming compliance problems. Their risk of EPS, especially tardive dyskinesia when used long-term, and also the disadvantages related to different clinical efficacy aspects compared with the atypical antipsychotics are unsatisfactory. Therefore, the solution to this dilemma seems to be the development of long-acting formulations of second-generation antipsychotics. Risperidone was the first atypical antipsychotic to become available in a long-acting formulation and other long-acting atypical agents are being developed.

2. Clinical Position of Oral Risperidone

Risperidone was the first novel second-generation antipsychotic to be developed and licensed after the prototype of all atypical antipsychotics, clozapine. It was primarily developed for the indication of schizophrenia. There is a broad database of evidence demonstrating the efficacy of risperidone in treating positive and negative symptoms, and showing a more favourable EPS tolerability profile than conventional antipsychotics, especially in the lower dose range.[24] There is also some evidence for the efficacy of risperidone in treating depressive symptoms and cognitive disturbances in patients with schizophrenia.[24] The overall tolerability is favourable. In particular, there is no corrected QT interval problem, and only a low to moderate liability to weight gain and related complications (metabolic syndrome). However, in comparison with most of the other second-generation antipsychotics, the risk of hyperprolactinaemia and the related symptoms is more pronounced.[25] Besides the efficacy and tolerability data for the acute schizophrenic episode, data from a well designed relapse-prevention study are also available, demonstrating the advantage of risperidone over haloperidol.[26] Risperidone has certain advantages and disadvantages compared with other second-generation antipsychotics, which may be especially relevant in the treatment of individual patients. Since risperidone does not completely lack the risk of inducing EPS, the dose should be kept as low as possible.[24]

Because of its clinical characteristics, risperidone is well accepted by doctors treating patients with schizophrenia and, with olanzapine, is one of the most frequently prescribed second-generation antipsychotics in this field. Therefore, it is not surprising that the manufacturer decided to develop a long-acting formulation.

3. Long-Acting Injectable Risperidone

Long-acting injectable risperidone was introduced to the market in 2002. This long-term formulation is not of the classic kind in which esterified long-chain fatty acids are injected intramuscularly in an oily solution; it is a new galenic principle, binding in 'microspheres',[14] which consist of a glycolic acid-lactate polymer. *In vitro* studies have indicated that a small amount of risperidone at the surface of the microspheres is released by diffusion within 24 hours. This is followed by a latent period

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of ≈3 weeks, while most of the release occurs by erosion of the glycolic acid-lactate polymer during weeks 4–6.[27] Following administration, the copolymer gradually breaks down in the body, releasing risperidone at a constant rate.[27,28] Eventually, the copolymer is fully metabolised into naturally occurring lactic acid and glycolic acid, which are eliminated as carbon dioxide and water.[29] It was the clinical aim that, *in vivo*, this sustained release of risperidone from microspheres would translate into continuous antipsychotic coverage[28] by eliminating the peaks and troughs seen with oral medication.[14]

3.1 Pharmacological Aspects

Single-dose studies have demonstrated that, after a latent period of ≈2–3 weeks, plasma concentrations of risperidone gradually increase dose dependently to reach therapeutic concentrations from 3–4 weeks after injection. Peak concentrations are attained at about week 5 and sustained therapeutic levels are reached by week 6 after administration. The *in vivo* release profile is further characterised by a monophasic decay (half-life 3–4 days) starting at about week 5, with detectable levels of risperidone remaining until 7 weeks after administration.[30] The pharmacokinetic profile of long-acting risperidone has also been evaluated in multidose studies.[14] As a result of these pharmacokinetic studies, one can summarise that long-acting risperidone exhibits controlled and predictable release of active drug. Following an initial latency period of 3 weeks, during which most patients require overlapping oral therapy, stable plasma concentrations are attained from 3–4 weeks after administration onwards. Subsequently, reduced fluctuations are noted in plasma concentrations of the active moiety when compared with oral therapy. When patients are treated with long-acting risperidone once every 2 weeks, steady release of risperidone from the microspheres provides patients with continuous plasma concentrations of the active moiety. As a result of this sustained drug delivery, even patients considered to be clinically stable on their previous antipsychotic medication can achieve further improvements in symptom control with long-acting risperidone.[14]

The dopamine D_2 receptor occupancy of long-acting injectable risperidone in patients with schizophrenia was investigated using positron emission tomography.[31] This study, which also included pharmacokinetic parameters, found a stable plasma concentration after the third injection and steady-state concentrations of the active drug and the active metabolite (risperidone and 9-hydroxyrisperidone) after the fourth injection. Steady-state plasma concentrations were maintained for 4–5 weeks after the last injection and then declined rapidly. After injection of risperidone 25, 50 and 75mg on day 44 or day 71, D_2 receptor occupancy ranged from 25 to 48%, 59 to 83% and 62 to 72%, respectively, while plasma active moiety concentrations ranged from 4.4 to 8.8, 15.0 to 31.1 and 22.5 to 26.3 ng/mL, respectively. The authors concluded that the results indicate that brain D_2 receptor occupancy at steady state after injections of long-acting risperidone was in the range found in patients effectively treated with oral risperidone 2–6mg.

Another pharmacokinetic study tried to take into account the variability in doses and schedules that may occur in clinical practice,[32] and modelled mathematically estimated blood concentrations in a variety of clinical scenarios that have not been studied empirically. The model calculations help to clarify the complex clinical situation and may lead to more informed decision making.

The other pharmacokinetic aspects, for example, drug-drug interactions, are similar to those of oral risperidone.[14]

3.2 Clinical Efficacy

Two double-blind, randomised phase III studies, one versus placebo and the other versus oral risperidone, have demonstrated antipsychotic efficacy for

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long-acting injectable risperidone. These two studies, together with one open-label, long-term study (12 months), belong to the core group of trials that were relevant for the licensing of long-acting risperidone. Some details of these studies are reported in this section (for further details of these and other studies, see table I).

In the study by Kane et al.,[54] the dose-related efficacy of long-acting injectable risperidone was evaluated in a large sample of patients with schizophrenia in a randomised, double-blind study. In a 1-week run-in phase, previously administered antipsychotics were tapered out and the patients were given oral risperidone up to 4 mg/day. They then received fortnightly injections of placebo or long-acting risperidone 25, 50 or 75mg as a double-blind treatment for 12 weeks. Administration of oral risperidone was continued in the first 3 weeks in all groups treated with risperidone injections, to ensure an adequate plasma risperidone concentration in these first weeks. A total of 554 patients with schizophrenia were screened, 461 patients entered the 1-week oral risperidone run-in period, treatment with long-acting risperidone was initiated in 400 patients and 370 received at least one post-baseline assessment. The improvements in the Positive and Negative Symptoms Scale (PANSS) total score were significantly larger in the group of patients who received long-acting risperidone than in the placebo group ($p < 0.001$ for all doses). The improvements from baseline on the PANSS were significant in all risperidone groups ($p < 0.05$). There were improvements in the PANSS score at the end of the study of >20% in 47%, 48% and 39% of the three risperidone groups, respectively, and 17% of the placebo group ($p < 0.001$ for all doses). There was no additional advantage of risperidone at doses >50mg. On average, >80% of the patients reported that they had no pain at the injection site with the new formulation. Tolerability was otherwise the same as with oral risperidone. In the group receiving risperidone 25mg there was a similar amount of EPS as in the placebo group (10% vs 13%). This study also measured health-related quality of life (QOL). Long-acting injectable risperidone improved the scores toward normal levels. After 2 weeks, the scores of patients receiving 25mg were not significantly different from normal.[57] A subanalysis of the patients who were inpatients at study initiation was performed, and it found that long-acting risperidone was associated with a significant reduction of total PANSS score and was well tolerated, as in the whole sample.[56] The authors concluded that long-acting risperidone initiated during inpatient treatment may be an important strategy in improving outcomes among patients with schizophrenia.

Chue et al.[40] conducted a double-blind study of long-acting risperidone and orally administered risperidone in 640 patients. The previously administered antipsychotic was gradually tapered out during the first 2 weeks of the 8-week run-in phase and treatment with risperidone commenced. In weeks 3 and 4 the patients were given flexible doses of risperidone (2, 4 or 6 mg/day), followed by a stable dose during weeks 5–8. Patients were randomised at the end of the run-in phase and continued in weeks 9–20 with long-acting risperidone (active drug as injection, oral placebo) or oral risperidone (placebo injection, active drug administered orally). The stable dose that was achieved during weeks 5 to 8 was continued over weeks 9 to 20. The average difference in the PANSS score changes was small when related to the noninferiority analyses, and the upper limit of the confidence interval (CI) significantly lower than the predetermined level of six points (average 0.9; CI −0.90, 2.87). No unexpected adverse events were reported during treatment with long-acting risperidone; 4.7% of the patients receiving oral treatment and 5.6% of those receiving long-acting risperidone discontinued the study prematurely because of adverse effects. More than 95% of the patients reported no or only slight injection pain.

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Table I. Overview of efficacy results and withdrawal rates from studies performed with long-acting injectable risperidone

Study	No. of pts	Duration	Design	Previous med	Dosage at endpoint (% pts)	Reduction PANSS total (%)[a]	Reduction PANSS pos (%)[a]	Reduction PANSS neg (%)[a]	Reduction CGI (%)	Responder rate PANSS (%)	Reduction ESRS total (%)	Dropout rate (%)	QOL (SF-36)
Studies with direct transition from pre-treatment to long-acting injectable risperidone													
Möller et al.[33]	1876	6mo	nr, 1-arm, mc	AP (oral, depot)	25, 37.5, 50 mg/2wk 25mg (44) 37.5mg (26) 50mg (30)	14.0[b]	12.9[b]	16.3[b]	15.4[b]	38	48.3	26	Sig imp in 5 dmns
Parellada et al.[34]	382	6mo	nr, open, 1-arm, mc	AP (oral, depot)	25, 37.5, 50 mg/2wk 25mg (45) 37.5mg (27) 50mg (28)	15.7[b]	ns	ns	ns	40	50	27	Imp in 9 of 10 dmns
Mohl et al.[35]	249	6mo	nr, 1-arm, mc	AP (oral, depot)	25, 37.5, 50, 75 mg/2wk 25mg (48.8) 37.5mg (23.6) 50mg (27.3) 75mg (0.4)	17.6.	12.6[b]	15.9[b]	ns	ns	ns	26	$p < 0.01$ in all 10 dmns
Kissling et al.[36]	715	12mo	nr, 1-arm, mc, ext phase	AP (oral, depot)	25, 37.5, 50 mg/2wk 25mg (39) 37.5mg (23) 50mg (37)	20.3[b]	18.1[b]	21.7[b]	ns	47	ns	29	ns
Rubio et al.[37]	115	6mo	r, open, f-up, vs ZUC	Cnv AP (oral)	47.2 mg/2wk	30.8[c]	39.4	27.6[c]	ns	89	ns	5.3	ns
Gastpar et al.[38]	192	6mo	Pros, open, mc, phase IIIb	OLA	25–50 mg/2wk	11.3[b]	ns	ns	ns	32	13.3	30	Sig imp in 7 of 10 dmns
Turner et al.[39]	196	12wk	Open, mc	AP (cnv, depot)	25–50 mg/2wk 25mg (62)	6.0[b]	4.7A[b]	10.2A[b]	13.0[b]	48	40	8C	ns
Chue et al.[40]	640	8+12wk	db, dd, mc, non-i	AP (oral, depot)	Wk 8: 2/4/6mg oral	9.1	ns	ns	10.3	ns	ns	17.7	ns
					Wk 12: 25, 50, 75mg depot (49.8)	7.5	9.3A[b]	7.7A[b]				16	
					Wk 12: 2/4/6mg oral (48.8)	8.7	10.5A[b]	8.1A[b]				20	

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Table I. Contd

Study	No. of pts	Duration	Design	Previous med	Dosage at endpoint (% pts)	Reduction PANSS total (%)[a]	Reduction PANSS pos (%)[a]	Reduction PANSS neg (%)[a]	Reduction CGI (%)	Responder rate PANSS (%)	Reduction ESRS total (%)	Dropout rate (%)	QOL (SF-36)
Studies with a 2-week run-in phase with oral risperidone prior to administration of long-acting injectable risperidone													
Lasser et al.[41]	725	50wk	Open	AP	25/50/75 mg/2wk		ns	ns	ns	ns	ns	20.3	Sig imp in
					At baseline 'no remission' (68)	27.6A[b] D	7.5A[b] D	14.6[b] D	ns				5 dmns
					At baseline 'remission' (32)	11.0A[b] D	28.1A[b] D	30.1[b] D	ns				
Fleischhacker et al.[42]	615	12mo	Open, mc	AP (oral, depot)	25, 50, 75 mg/2wk	9.1[b]	9.1[b]	11.7[b]	ns	49	34.2	35	ns
					25mg (19.5)	12.9[b]	11.6A[b]	15.8A[b]	ns				
					50mg (37.1)	12.0[b]	12.6A[b]	15.1A[b]	ns				
					75mg (43.4)	4.8[b]	5.5A[b]	7.5A[b]	ns				
Gharabawi et al.[43]	614	50wk	Open, mc	AP (oral, depot)	25/50/75 mg/2wk	11.1[b]	ns	ns	ns	ns	ns	ns	Imp in 4 dmns
					No impairment (Insight Score 1–2) [48.9]	7.5[b]	ns	11.7A[b]	ns				$p > 0.05$[b] in 3 dmns
					Mild impairment (Insight Score 3–4) [40.2]	14.6[b]	ns	15.4A[b]	ns				Sig imp in 3 dmns
					Severe impairment (Insight Score 5–7) [10.9]	14.2[b]	ns	16.8A[b]	ns				ns
Chue et al.[44]	397	1y	Open, mc	AP (oral, depot)	25/50 mg/2wk	ns	ns	ns	ns	ns	ns	29	ns
Fleischhacker et al.[45]	615	1y	mc	AP (oral, depot)	25/50/75 mg/2wk	ns	ns	ns	ns	ns	ns	ns	$p > 0.01$[b] in 3 dmns
Gharabawi et al.[46]	614	50wk	Open	AP	Patients with dyskinesia Patients without dyskinesia	ns	ns	ns	40	ns	ns	ns	ns
Lindenmayer et al.[47]	439	12wk	db	Oral AP	25/50/75 mg/2wk	ns	ns	ns	ns	ns	ns	ns	ns
	725	50wk	Open	AP									
Lasser et al.[48]	336	50wk	Open	AP + 1mo oral RIS	25/50/75 mg/2wk	8.8/9.1[d]	ns	ns	12	49.7	34.3[d]	33.6	ns

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Lasser et al.[49]	110	50wk	Open, mc	AP	25/50/75 mg/2wk	14.4[d]	ns	ns	ns	57.7	24.3	32.7	ns
Leal et al.[50]	397	1y	Open, mc	AP	25/50 mg/2wk	ns	ns	ns	ns	ns	ns	29	ns
Lasser et al.[51]	57	50wk	Open, mc	AP	25/50/75 mg/2wk	14.4	ns	ns	ns	49	30.4	23	Sig imp in 4 dmns
van Os et al.[52]	46	50wk	Open, mc	AP (oral, cnv)	25/50/75 mg/2wk	11.8	ns	ns	ns	49	54.8	39	ns
Lasser et al.[53]	188	12mo	Open, mc	Depot with cnv AP	25/50/75 mg/2wk	9.3[b]	ns	ns	ns	51.5	ns	33.5	ns
Eerdekens et al.[28]	86	15wk	r, open, pros, mc	Oral RIS	25/50/75 mg/2wk	ns	ns	ns	ns	44–57	ns	10.5	ns
					25mg (28.0)	7.9	2.5A	9.5A	23.8				
					50mg (37.8)	4.7	1.8A	8.8A	0				
					75mg (34.2)	8.9	12.7A	6.3A	12				
Kane et al.[54]	554	12wk	db, pc, mc	Oral AP	25/50/75 mg/2wk	ns	ns	ns	ns	ns	ns	ns	ns
					25mg	7.6[d]	9.1A[d]	11.9A[d]	9.7[d]	47	27.8	51–52	
					50mg	10.3[d]	14.1A[d]	6.0A[d]	9.7[d]	48	2.3	51–52	
					75mg	9.2[d]	12.2A[d]	6.3A[d]	12.9[d]	39	0	51–52	
Ciliberto et al.[55]	439	12wk	r, db, pc	Oral AP	25, 50, 75 mg/2wk	ns	ns	ns	ns	ns	ns	ns	ns
					Caucasians (44%)	9.5[d]	ns	ns	ns				
					Afro-Americans (40)	13.8[d]	ns	ns	ns				
					Others (16)	14.2[d]	ns	ns	ns				
Lauriello et al.[56]	214	12wk	db, pc, mc	Oral AP	25/50/75 mg/2wk	11.1	ns	ns	ns	50	ns	65.4	ns
Nasrallah et al.[57]	369	12wk	r, db, pc, mc	Oral AP	25/50/75 mg/2wk	ns	ns	ns	ns	ns	ns	ns	$p > 0.05$[d] in 5 dmns
Lindenmayer et al.[58]	141	12wk	Open, mc	Oral AP	25/50/75 mg/2wk 25mg (23) 50mg (29) 75mg (48)	3.1	6.0	3.4	ns	37	ns	19	ns

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Simpson et al.[59]	324	52wk	r, db, pros, mc	Oral AP	25/50 mg/2wk	7.4[b]	7.6A[b]	10.7A[b]	ns	ns	25.6[b]		ns
					25mg (50.3)	6.6[b]	6.5A[b]	10.1A[b]	ns			47.9	
					50mg (49.7)	8.2[b]	8.2A[b]	11.4A[b]	ns			49.7	
Gefvert et al.[31]	13	44/71d	nr, open, PK study	ns	25/50/75 mg/2wk	11	23.3	9.4	ns	ns	ns	7.7	ns
					25mg (33.4)	3.9	6.7	14.5	ns				
					50mg (33.3)	20.7	44.3	7.8	ns				
					75mg (33.3)	10.7	22.9	4.6	ns				
Bai et al.[60]	50	12wk	r, sb	Oral AP	25/37.5/50 mg/2wk	0.2	−5.5	3.2	2.0	ns	ns	2	p > 0.017[d]
					25mg (14.6)	ns	ns	ns	ns				in 1 dmn
					37.5mg (8.3)	ns	ns	ns	ns				
					50mg (3.1)	ns	ns	ns	ns				
Taylor et al.[61]	250	6mo	Pros, f-up	Oral AP, cnv depot, untreated	25/37.5/50 mg/2wk	ns	ns	ns	18.9	ns	ns	52.8	ns
					25mg (51.2)	ns	ns	ns	ns				
					37.5mg (30.8)	ns	ns	ns	ns				
					50mg (17.6)	ns	ns	ns	ns				
					75mg (0.4)	ns	ns	ns	ns				
Young and Taylor[62]	250	1y	Non-p, f-up	Oral AP, cnv oral, CLZ	25–50 mg/2wk	ns	ns	ns	ns	ns	ns	67.6	ns

a Response definition: PANSS-Reduction ≥20%; A = PANSS symptom factor; C = of 166 patients/completers of the run-in phase; D = patients in 'remission' within the past 6mo.

b Significant vs baseline.

c Significant vs ZUC.

d Significant vs placebo.

AP = antipsychotics; **CGI** = Clinical Global Impression; **CLZ** = clozapine; **cnv** = conventional; **db** = double-blind; **dd** = double-dummy; **dmn** = dimension; **ESRS** = Extrapyramidal Symptom Rating Scale; **ext** = extension; **f-up** = follow-up; **imp** = improvement; **mc** = multicentre; **med** = medication; **neg** = negative; **non-i** = non-inferiority; **non-p** = non-parallel; **nr** = nonrandomised; **ns** = not specified; **OLA** = olanzapine; **PANSS** = Positive and Negative Symptoms Scale; **pc** = placebo-controlled; **PK** = pharmacokinetic; **pos** = positive; **pros** = prospective; **QOL** = quality of life; **r** = randomised; **RIS** = risperidone; **sb** = single-blind; **SF-36** = Medical Outcomes Study 36-item short-form health survey; **sig** = significant; **ZUC** = zuclopenthixol.

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The 12-month, open-label trial of long-acting injectable risperidone also achieved positive results, although open-label studies are difficult to interpret. It included patients with schizophrenia (n = 615) and schizoaffective disorder (n = 110).[42,51] The findings in the patients with schizophrenia were published by Fleischhacker et al.,[42] who reached positive conclusions about the efficacy, tolerability and utility of long-acting injectable risperidone. After a 2-week run-in period, during which symptomatically stable patients with Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV schizophrenia received flexible doses of 1–6mg of oral risperidone, patients received an injection of 25, 50 or 75mg of long-acting risperidone every 2 weeks for 12 months. The dose levels of long-acting risperidone were selected according to the level of the oral pre-treatment: patients receiving up to 2mg of oral risperidone were started on 25mg of long-acting risperidone, patients receiving >2mg up to 4mg of the oral drug were started on 50mg, and patients receiving >4mg up to 6mg were started on 75mg. The investigator was allowed to adjust the dose of long-acting risperidone whenever deemed necessary. Patients received supplementary oral risperidone (1–6mg, as determined by the investigator) for the first 2 or 3 weeks of the 12-month study period. Temporary oral supplementation was also permitted when considered by the investigator to be clinically necessary for treatment of breakthrough psychosis; 615 patients were included and had at least one injection of long-acting risperidone. The 12-month trial was completed by 65% of patients. Treatment was discontinued because of adverse events in 5% of patients. A substantially higher proportion of patients in the 75mg group discontinued because of insufficient response: 15% versus 2% in the 25mg group and 3% in the 50mg group. Symptom severity (PANSS total scores) and severity of positive and negative symptoms were reduced from baseline to endpoint in each of the dose groups. According to both the last-observation-carried-forward analysis and observed case analysis, the improvements were significant in each group. Greater improvements were seen in the 25 and 50mg groups than in the 75mg group. The change at endpoint for the PANSS total scores was −6.1 ± 0.7 for the total group, −8.0 ± 1.3 for the 25mg group, −8.3 ± 1.1 for the 50mg group and −3.3 ± 1.1 for the 75mg group. EPS were reported as adverse events by 25% of the patients. Severity of EPS (according to Extrapyramidal Symptom Rating Scale[63] [ESRS] scores) was low at baseline (total ESRS scores at baseline 5.1 ± 0.7 in the 25mg group, 8.3 ± 0.6 in the 50mg group and 7.4 ± 0.5 in the 75mg group) and decreased in each of the groups during the 12 months of treatment (change at endpoint −1.8 ± 0.4, −3.3 ± 0.4 and −2.1 ± 0.4, respectively). The other most common adverse events were anxiety in 24%, insomnia in 21%, psychosis in 17% and depression in 14% of the patients. Injection was tolerated very well in terms of local pain or discomfort. The authors summarised that in terms of both efficacy and safety, symptomatically stable patients with schizophrenia benefit from being switched to long-acting injectable risperidone.

A special analysis of this study focused on emergent tardive dyskinesia and existing dyskinesia.[46] Of 530 individuals in this analysis without dyskinesia at baseline, 5 (0.94%) met the predefined criteria for emergent persistent tardive dyskinesia during therapy. When adjusted for duration of exposure to study medication, the annualised rate was 1.19%, as was the 1-year rate assessed by Kaplan-Meier survival analysis. Among the 132 individuals with dyskinesia at baseline, the mean score on the ESRS physician's exam for dyskinesia improved significantly at endpoint (−2.77), regardless of anticholinergic drug use. The authors conclude that the tardive dyskinesia rate reported in this study is consistent with other reports of atypical antipsychotics and substantially lower than with conventional antipsychotics.

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The recently proposed remission criteria for schizophrenia were applied *post hoc* to the whole sample of the open-label study.[41] Groups were identified by initial remission status. Although considered clinically stable, 68.2% did not meet the symptom-severity component of remission criteria at baseline. Following long-acting injectable risperidone treatment, 20.8% of nonremitted patients at baseline achieved symptom remission for at least 6 months. Among 31.8% of patients meeting the symptom-severity component of remission criteria at baseline, 84.8% maintained these criteria at endpoint. Significant improvements were also found in QOL dimensions on the Medical Outcomes Study 36-item short-form health survey (SF-36) mental component summary score and vitality and social functioning scales.[45]

Several other subanalyses of the study were performed: (i) on elderly patients;[51] (ii) on those patients who were receiving conventional depot antipsychotic therapy at study entry;[53] (iii) on patients switched from oral conventional antipsychotic therapy to long-acting risperidone;[52] and (iv) on the subgroup of patients who changed from oral to long-acting risperidone.[48] These subgroup analyses found positive efficacy and tolerability results.

The evaluation of a new galenic formulation of a drug follows different principles from those of the evaluation of a new molecule. A restricted clinical programme is necessary to demonstrate in a proof-of-concept approach that short- and long-term efficacy and safety are not changed by the new formulation and that the new formulation achieves an adequate pharmacokinetic result that is sufficient to obtain the license. The studies reported in this section were part of the core programme for long-acting injectable risperidone in the sense of proof of concept. However, a relapse-prevention, control group study comparing the long-acting formulation and oral risperidone was not performed because of the principal methodological problems and pitfalls of such a comparison. It does not seem possible to demonstrate, in the context of a controlled clinical trial, the superiority of long-acting risperidone because the study procedure itself would overestimate the compliance with the oral formulation, while at the same time underestimating the advantages of the long-acting formulation. For this reason, such a study was not performed, although, of course, many clinicians would have been interested in the results. However, based on experience with the depot formulations of classical antipsychotics, it can be expected that the outcome under the conditions of a controlled clinical trial would be similar to that of the old studies on depot formulations of classical antipsychotics; i.e. it would not be possible to prove adequately the superiority of the depot in comparison to the oral counterpart. Even so, on the basis of their clinical experience most psychiatrists agree that the depot formulation has its advantages, especially in patients who are difficult to treat and have a high risk of noncompliance.

Instead of proceeding in this direction, an attempt was made to collect as much clinical data as possible from observational studies that investigated practically relevant questions, such as the transition from different kinds of antipsychotics as pre-treatment to long-acting risperidone. Among other aspects investigated was whether it is necessary to have an intermediate phase with oral risperidone, as was the case in the core studies already discussed, when switching from a pre-treatment antipsychotic to long-acting risperidone or whether it is possible to switch directly from the pre-treatment antipsychotic to long-acting risperidone. Rather than review all these observational studies here in detail, they are described in table I, and one is described here as an example.

The study investigated the efficacy and safety of direct transition to long-acting injectable risperidone in patients pre-treated with various antipsychotic therapies (StoRMi [Switch to Risperidone Micro-

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spheres] study).[33] Schizophrenia patients who were symptomatically stable, but considered to require a treatment change, received long-acting risperidone 25mg, which was increased to 37.5 or 50mg, if necessary, every 2 weeks for 6 months. The recommended starting dose was 25mg, but patients with persistent symptoms or who were known to respond only to higher doses of antipsychotics could receive initial doses of either 37.5 or 50mg. Subsequently, the doses could be adjusted according to the patients' symptoms and response to treatment. The most frequent indications for treatment change were noncompliance (38%), insufficient efficacy (33%) and adverse effects (26%). The study was performed to investigate the maintained antipsychotic efficacy and safety of long-acting risperidone. A total of 1876 patients were included in this study and received at least one dose of long-acting risperidone. Patients were transitioned from their previous antipsychotic agent(s) to long-acting risperidone without an oral risperidone run-in. Patients who were treated previously with an oral antipsychotic continued to receive that agent at the same dose for 21 days after the first injection of long-acting risperidone, after which it was stopped or tapered off over 3 days. The treatment regimen of patients who changed their medication from conventional depot antipsychotics depended upon the injection regimen of the previous medication. Patients who received medication every 2 weeks had an injection of depot antipsychotic 7 days before the first long-acting risperidone injection and a final injection of depot antipsychotic 7 days after the first long-acting risperidone injection; patients who received a depot antipsychotic every 3 weeks had an injection 21 days before the first long-acting risperidone injection, plus a final injection of depot agent on the same day as the first long-acting risperidone injection, administered in the other buttock; and patients who received a depot antipsychotic every 4 weeks had an injection of that drug 7 days before the first long-acting risperidone injection. A total of 1378 patients completed the 6-month treatment period (73.5% of the original sample). The most common reasons for dropout were withdrawal of consent (8.7%), adverse events (5.7%), insufficient response (4.4%) and noncompliance (2.9%). The majority of patients (83%) received an initial dose of long-acting risperidone 25mg, whereas the remainder received the 37.5mg (11%) or 50mg dose (6%). At endpoint, 44% of patients were receiving the 25mg dose, whereas 26% and 30% were receiving 37.5 and 50mg, respectively. During the 6-month study period, 22% of patients received oral risperidone supplementation at a mean modal dose of 3.2mg for a mean duration of 43 days. At baseline the mean PANSS total score for the study population was 73.4 and this was significantly reduced at endpoint to 63.1. A significant improvement was apparent after 1 month of treatment, and further improvements were observed with continued treatment during the 6 months of the study. At endpoint, 38% of patients had a ≥20% improvement in the PANSS total score compared with baseline. *Post hoc* analysis revealed that 30% and 20% of patients had improvements of ≥30% and ≥40%, respectively. Significant improvements from baseline to endpoint were observed in all the subscores for the PANSS positive, negative and general psychopathology subscales (table I). There was an overall improvement in health-related QOL during the 6-month treatment period, with significant improvements from baseline to endpoint reported for all factors of the SF-36 ($p \leq 0.001$). Despite a withdrawal rate of 26.5% in the open-label study, among the completers, patient satisfaction improved significantly with treatment. Scores on ESRS showed significant, sustained improvements during the study period. Overall, the study showed that long-acting risperidone is appropriate for the treatment of a wide range of patient types, including those deemed clinically stable, to further improve symptom control and the tolerability of treatment, as

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well as the patients' QOL. Furthermore, direct initiation of long-acting risperidone in patients receiving oral or depot preparations of the conventional antipsychotics or novel antipsychotics was effective and well tolerated.

A subgroup of the StoRMi study was treated beyond the 6-month timeframe for up to 12 months (715 patients entered this extension phase and 508 completed the 12-month study).[36] The PANSS total score was significantly reduced during the 12 months up to 59.7 at treatment endpoint. The proportion of patients who met the PANSS severity criteria for remission[64] increased from 29% at day 0 to 60% at treatment endpoint after 12 months. The proportion of patients who met these criteria for >6 months increased from 24% at month 6 to 45% at endpoint. A subgroup analysis of the younger patients (aged ≤45 years) of the StoRMi study presented similar results.[34]

Other studies also demonstrated positive results with long-acting risperidone in terms of efficacy and tolerability. For example, a 6-month study focused on patients pre-treated orally with olanzapine and then switched to risperidone 25mg every 2 weeks;[38] in a 12-week, open-label study 166 patients were switched from their pre-treatment with conventional depot antipsychotics to long-acting risperidone every 2 weeks for 12 weeks at an initial dose of 25mg;[39] and a 12-week study in stable patients switched from typical and atypical oral antipsychotics.[58]

Another 6-month study included 100 patients who were switched from orally administered antipsychotics to long-acting risperidone.[65] In comparison with the other studies described here, this study was not well designed and only Clinical Global Impressions (CGI) scores were applied as the efficacy measurement; it comes to the somewhat critical conclusion that risperidone was moderately effective in clinical practice as judged by attrition from treatment (51% of the patients discontinued treatment within 6 months), and also the CGI score changes suggest moderate effectiveness. Risperidone was also well tolerated in this study. Patients receiving a preceding oral antipsychotic were more likely to discontinue long-acting risperidone than those receiving a preceding depot. Treatment refractoriness weakly confounded this relationship. After adjusting for preceding antipsychotic type, patients with treatment refractoriness were no more likely to discontinue than those without.[66]

A recent study presented by Rubio and colleagues[37] provided evidence for a beneficial role of long-acting risperidone in patients with schizophrenia and a comorbidity of substance abuse. Under randomised, controlled, open conditions, 115 patients with schizophrenia and concomitant substance abuse disorder were treated with either long-acting risperidone or zuclopenthixol-depot over 6 months. Patients who received long-acting risperidone presented significantly fewer positive urine tests (8.67 compared with 10.36; $p = 0.005$), better amelioration of clinical signs as measured by the PANSS scale and a higher degree of adherence to a psychotherapeutic treatment regimen (92.91% attended >75% of the sessions compared with 67.79%; $p = 0.001$) [table I]. Thus, in this study, long-acting risperidone improved substance abuse in patients with schizophrenia and efficacy of a cognitive-behavioural programme for managing substance abuse.

3.3 Tolerability

Tolerability is an important factor when determining antipsychotic therapy, since it affects patients' well-being, QOL and adherence to medication.[67] Atypical antipsychotics are generally regarded as having more favourable tolerability profiles than conventional antipsychotics, especially in terms of EPS.[68-70] Other adverse effects such as weight gain[71,72] are increasingly becoming a focus of attention, although they were already a relevant

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issue with classical antipsychotics. Differences between specific atypical drugs are important when tailoring treatment to the individual.

The results of the studies discussed in section 3.2 suggest that, when patients are switched to long-acting risperidone directly or indirectly from another antipsychotic agent, it is associated with a low incidence of EPS and may even improve the frequency and severity of movement disorders. Moreover, long-acting risperidone had a favourable weight-gain profile of 1–2kg in the short-term studies and around 3kg over 1 year's treatment, with no further weight gain for up to 4 years; it did not appear to negatively affect lipid and glucose metabolism. Although long-acting risperidone was associated with elevations in serum prolactin in 2–7% of patients, these decreased over time and were not necessarily manifested as symptomatic adverse effects.[73]

Altogether, the adverse effects are similar to those associated with oral risperidone treatment. There are some indications that tolerability may even be better with long-acting than with oral risperidone. For example, Bai et al.[60] found that, at the end of their 12-week, single-blind, randomised study of oral versus long-acting risperidone in 50 patients, the long-acting risperidone group had a significantly decreased total score on the Udwalg for Kliniske Undersogelser Side Effect Rating Scale[74] ($p = 0.037$). Furthermore, the long-acting risperidone group also had a significantly lower prolactin level than that of the oral risperidone group at weeks 4 ($p = 0.009$) and 12 ($p = 0.001$). The use of long-acting risperidone also seems to be safe in special subgroups such as elderly, young or first-episode patients and patients with schizoaffective disorder.[73] A summary of the main tolerability results is presented in table II.

Because the overall general tolerability profile of long-acting risperidone appears to be similar to that of oral risperidone, injection site reactions and pain as a specific component of tolerability of long-acting risperidone are addressed here in detail (see also table III).

Two 12-week studies evaluated pain at the injection site following administration of long-acting risperidone.[47,54,58] In a double-blind, randomised, placebo-controlled study (n = 400), injection site pain (measured with a 100mm visual analogue scale [VAS]) was mild throughout the study and diminished from the first injection to the last in all long-acting risperidone treatment groups (25, 50 or 75mg intramuscularly every 2 weeks). In addition, according to investigator assessments, most patients had no pain or swelling after each of the six injections.[54] A further analysis of injection site pain from this study revealed comparable pain rating scores among patients receiving placebo and long-acting risperidone. Mean ± SD VAS scores at first and final injections were 15.6 ± 20.7 and 12.5 ± 18.3 for placebo; for long-acting risperidone, scores were 11.8 ± 14.4 (first) and 10.0 ± 12.4 (final) for 25mg, 16.3 ± 21.9 (first) and 13.6 ± 21.7 (final) for 50mg, and 16.0 ± 17.9 (first) and 9.6 ± 16.0 (final) for 75mg. Investigators rated redness, swelling and induration after the first injection as absent in 96–100% of assessments, and pain as absent in 79–85% of assessments.[47] Furthermore, in a multicentre, open-label trial in 141 patients who were switched from therapy with oral haloperidol, quetiapine or olanzapine to long-acting risperidone (25, 37.5 or 50mg intramuscularly every 2 weeks), only one patient reported pain at the injection site after the first injection. For the remainder of the 12-week study, no further injection site reactions were reported.[58]

Injection site pain with long-acting risperidone has also been evaluated in the longer term in four studies.[42,47,48,53] In a 1-year, open-label study (n = 615), little pain at the injection site was reported by patients, and pain ratings decreased during treatment with long-acting risperidone (25, 50 or 75mg intramuscularly every 2 weeks). On the investiga-

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Table II. Overview of studies that have examined the tolerability profile of long-acting risperidone (LAR) in patients with schizophrenia or schizoaffective disorder (data partially taken from Möller[73])

Study and description	AEs	Effects on metabolic parameters	Effects on movement disorder parameters
Kane et al.[54] 12wk, db, pc study in pts with schizophrenia Doses of other antipsychotic medications reduced and discontinued; run-in with oral RIS LAR 25mg (n = 99) LAR 50mg (n = 103) LAR 75mg (n = 100) Placebo (n = 98)	Incidence of AEs in respective treatment groups: 80%, 83%, 82% and 83%; incidence of serious AEs: 13%, 14%, 15% and 24% Withdrawals due to AEs: 11%, 12%, 14% and 12% AEs occurring in ≥5% of pts – LAR (all doses): headache (20%), agitation (15%), insomnia (15%), psychosis (12%), anxiety (9%); placebo: agitation (26%), psychosis (24%), anxiety (15%), insomnia (14%), headache (12%)	Change in mean bodyweight: LAR 25mg +0.5kg; LAR 50mg +1.2kg; LAR 75mg +1.9kg; placebo −1.4kg	Mean (±SD) change in total ESRS at endpoint: LAR 25mg −1.5 (4.0); LAR 50mg +0.1 (3.6); LAR 75mg +0.0 (5.3); placebo −0.1 (4.8) Incidence of EPS: LAR 25mg 10%; LAR 50mg 24%; LAR 75mg 29%; placebo 13%
Lauriello et al.[56] Hospital inpatients (subanalysis of Fleischhacker et al.[42]) LAR 25mg (n = 52) LAR 50mg (n = 57) LAR 75mg (n = 52) Placebo (n = 53)	Withdrawals due to AEs: LAR (all doses) 14%, placebo 11% Most common AEs (LAR, all doses): headache (25%), agitation (22%), psychosis (17%), insomnia (17%), dyspepsia (15%)	Change in mean bodyweight: LAR (all doses) +2.3kg; placebo −0.4kg	Change in mean pt-rated ESRS (items 1–11) at endpoint: LAR (all doses) −0.24; placebo −0.73 Change in mean investigator-rated ESRS (items 13–30) at endpoint: LAR (all doses) −0.75; placebo −1.8
Lindenmayer et al.[58] 12wk open-label study in pts with schizophrenia switched from oral haloperidol (n = 46), oral quetiapine (n = 45) or oral olanzapine (n = 50) LAR 25, 37.5 and 50mg (n = 141)	Incidence of AEs: 81% (all doses), 83% (previous haloperidol), 84% (previous quetiapine), 76% (previous olanzapine) Withdrawals due to AEs: 4% (all doses), 7% (previous haloperidol), 2% (previous quetiapine), 2% (previous olanzapine) AEs occurring in ≥10% of pts: insomnia (16%), headache (15%), agitation (11%), psychosis (11%), anxiety (9%)	Change in mean bodyweight: +0.4kg (all doses), +1.4kg (previous haloperidol), +0.3kg (previous quetiapine), −0.5kg (previous olanzapine) Change in glucose levels (all doses): from 6.2 mmol/L at baseline to 5.8 mmol/L at endpoint Change in triglycerides (all doses): from 2.3 mmol/L at baseline to 2.0 mmol/L at endpoint	Incidence of EPS: 8% (all doses), 15% (previous haloperidol), 4% (previous quetiapine), 4% (previous olanzapine)
Turner et al.[39] 12wk open-label study in pts with schizophrenia switched from depot conventional antipsychotics: flupenthixol (n = 41), fluphenazine (n = 33), haloperidol (n = 50) and zuclopenthixol (n = 42) No run-in with oral RIS LAR 25, 37.5 and 50mg (n = 166)	Incidence of AEs: 58% (all doses), 68% (previous flupenthixol), 52% (previous fluphenazine), 54% (previous haloperidol), 57% (previous zuclopenthixol); incidence of serious AEs (all doses): 8% Withdrawals due to AEs (all doses): 1% AEs occurring in ≥10% of pts: psychosis (13%), hyperprolactinaemia (11%), insomnia (10%), headache (7%), rhinitis (7%)	Change in mean bodyweight (all doses): +1.0kg; change in BMI (all doses): +0.3 kg/m^2	Median change in total ESRS at endpoint (all doses): −2.0 Incidence of EPS (all doses): 3%

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Table II. Contd

Study and description	AEs	Effects on metabolic parameters	Effects on movement disorder parameters
Chue et al.[40] 12wk db study in pts with schizophrenia taking oral RIS who either continued oral RIS or switched to LAR Oral RIS 2, 4 and 6 mg/day (n = 321) LAR 25, 50 and 75mg (n = 319)	Incidence of AEs: oral RIS 60%, LAR (all doses) 61% AEs occurring in ≥5% of pts: oral RIS (all doses): insomnia (9%), anxiety (7%), headache (7%), psychosis (5%); LAR (all doses): anxiety (10%), insomnia (10%), headache (8%), psychosis (5%)	Change in mean bodyweight: oral RIS (all doses) +0.3kg; LAR (all doses) +0.5kg	Incidence of EPS: oral RIS (all doses) 6%; LAR (all doses) 7%
Möller et al.[33] 24wk open-label study in pts with schizophrenia switched directly from other oral or long-acting antipsychotics; no run-in with oral RIS LAR 25, 37.5 and 50mg (n = 1876)	Incidence of AEs (all doses): 72% Withdrawals due to AEs (all doses): 6% Most common AEs: anxiety (7%), insomnia (7%), exacerbation of disease (6%)	Change in mean bodyweight (all doses): +0.9kg Glucose-related AEs (all doses): 5 (0.3%) pts; 3 (0.2%) cases of new-onset diabetes mellitus	Mean change in total ESRS at endpoint: −1.5 (pts switched from atypical antipsychotic); −4.8 (pts switched from long-acting conventional agent); −2.5 (pts switched from oral conventional agent); $p < 0.001$ Incidence of EPS (all doses): 12%
Parellada et al.[34] Pts in the early phases of schizophrenia or schizoaffective disorder (subanalysis of Möller et al.[33]) LAR 25, 37.5 and 50mg (n = 382)	Incidence of AEs (all doses): 69%; incidence of serious AEs (all doses): 14% Withdrawals due to AEs (all doses): 6% AEs occurring in ≥3% of pts: LAR (all doses): insomnia (7%), exacerbation of disease (6%), depression (5%), anxiety (5%), weight increase (4%), relapse (3%), headache (3%)	Change in mean bodyweight (all doses): +1.8kg Change in BMI (all doses): +0.6 kg/m^2	Mean total ESRS score at endpoint: from 5.2 to 2.6 ($p \leq 0.001$)
Gastpar et al.[38] Pts previously stabilised on olanzapine (subanalysis of Möller et al.[33]) LAR 25, 37.5 and 50mg (n = 192)	Incidence of AEs (all doses): 72% Withdrawals due to AEs (all doses): 6% Most common AEs: LAR (all doses): anxiety (12%), exacerbation of disease (10%), insomnia (9%), depression (6%), akathisia (5%)	Bodyweight and BMI remained unchanged from baseline to endpoint (all doses)	Mean change in total ESRS at endpoint (all doses): $p = 0.0001$ Mean change in ESRS subscales at endpoint (all doses): subjective parkinsonism symptoms −0.6, $p = 0.003$; CGI of clinical severity of parkinsonism −0.3, $p = 0.0006$; hyperkinesias −0.4, $p = 0.0005$; hypokinesia −0.8, $p = 0.0001$
Kissling et al.[36] 1y open-label extension of the study by Möller et al.[33] LAR 25, 37.5 and 50mg (n = 715)	Incidence of AEs (all doses): 72%; incidence of serious AEs (all doses): 20% Withdrawals due to AEs (all doses): 3% LAR (all doses): anxiety (12%), insomnia (10%), weight increase (8%), depression (7%), headache (5%)	Change in mean bodyweight (all doses): +1.4kg Change in BMI (all doses): +0.5 kg/m^2	No data given

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Table II. Contd

Study and description	AEs	Effects on metabolic parameters	Effects on movement disorder parameters
Fleischhacker et al.[42] 1y open-label study in pts with schizophrenia switched from other oral or long-acting antipsychotics; run-in with oral RIS LAR 25mg (n = 120) LAR 50mg (n = 228) LAR 75mg (n = 267)	Incidence of AEs in respective treatment groups: 82%, 84% and 87% Withdrawals due to AEs: 4%, 6% and 5% Most common AEs: anxiety (24%), insomnia (21%), psychosis (17%), depression (15%), headache (12%)	Change in mean bodyweight: LAR 25mg +1.7kg; LAR 50mg +2. kg; LAR 75mg +1.9kg	Mean (±SE) change in total ESRS at endpoint (all doses): −2.5 (0.2) Incidence of EPS: LAR 25mg 21%; LAR 50mg 27%; LAR 75mg 25% 4 pts (0.7%) reported tardive dyskinesia
van Os et al.[52] Pts switched from oral conventional antipsychotics (subanalysis of Fleischhacker et al.[42]) LAR 25mg (n = 18) LAR 50mg (n = 16) LAR 75mg (n = 12)	Incidence of AEs (all doses): 54% Most common AEs: anxiety (26%), insomnia (22%), hyperkinesia (17%), depression (15%), psychosis (15%)	No data given	Mean (±SD) subjective ESRS pt rating at endpoint: from 73.1 (0.7) to 1.4 (2.2) [$p < 0.018$] Mean (±SD) objective ESRS physician rating of parkinsonism at endpoint: from 7.8 (9.9) to 3.8 (5.7) [$p < 0.003$]
Lasser et al.[53] Pts switched from depot conventional antipsychotics (subanalysis of Fleischhacker et al.[42]) LAR 25mg (n = 35) LAR 50mg (n = 80) LAR 75mg (n = 73)	Incidence of AEs (all doses): 90% Most common AEs: anxiety (29%), psychosis (19%), headache (18%), insomnia (18%)	Change in mean bodyweight (all doses): +2.4kg; change in BMI (all doses): +1.2 kg/m^2	Mean (±SD) subjective ESRS pt rating at endpoint: from 4.9 (4.2) to 2.8 (3.8) [$p < 0.001$] Mean (±SD) objective ESRS physician rating of parkinsonism at endpoint: from 10.4 (1.0) to 5.3 (7.2) [$p < 0.001$] Mean (±SD) objective ESRS physician rating of dyskinesia at endpoint: from 2.8 (4.6) to 1.5 (3.2) [$p < 0.001$] Incidence of EPS (all doses): 9%
Lasser et al.[48] Pts switched from oral RIS (subanalysis of Fleischhacker et al.[42]) LAR 25mg (n = 79) LAR 50mg (n = 125) LAR 75mg (n = 132)	Incidence of AEs (all doses): 81% Most common AEs: insomnia (24%), anxiety (22%), depression (19%), worsening of psychosis (18%)	Change in mean bodyweight (all doses): +2.51kg; change in BMI (all doses): +0.83 kg/m^2	Mean (±SD) subjective ESRS pt ratings at endpoint: from 2.7 (3.1) to 1.8 (2.4) [$p < 0.001$] Mean (±SD) objective ESRS physician rating of parkinsonism at endpoint: from 5.9 (7.3) to 4.8 (7.4) [$p < 0.005$] Incidence of EPS at months 10–12 (all doses): 4%
Lasser et al.[51] Elderly pts (≥65y) [subanalysis of Fleischhacker et al.[42]] LAR 25, 50 and 75mg (n = 57)	Incidence of AEs in respective treatment groups: 74%, 71% and 78% AEs occurring in ≥10% of pts: insomnia (14%), constipation (12%), bronchitis (12%), psychosis (11%), rhinitis (11%)	No data given	Mean (± SD) change in total ESRS at endpoint: LAR (all doses), −3.1 ± 0.8 ($p < 0.001$ vs baseline) No cases of emergent tardive dyskinesia
Gharabawi et al.[46] Emergent tardive dyskinesia (subanalysis of Fleischhacker et al.[42]) LAR 25, 50 and 75mg (n = 662)	No data given	No data given	Mean (±SD) physician score for dyskinesia at endpoint: from 6.9 (4.6) to 4.1 (4.3) [$p < 0.001$] Incidence of emergent tardive dyskinesia in respective treatment groups: 0.88%, 1.04% and 0.89%

AEs = adverse events; **BMI** = body mass index; **CGI** = Clinical Global Impression; **db** = double-blind; **EPS** = extrapyramidal symptoms; **ESRS** = Extrapyramidal Symptom Rating Scale; **pc** = placebo-controlled; **pt** = patient; **RIS** = risperidone.

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Table III. Overview of patients' evaluation of injection site pain and investigators' ratings[a] of pain, redness, swelling and induration at injection site after administration of placebo or long-acting risperidone (LAR)

Study (for description see table II)	Pts' evaluation of injection site pain	Investigators' ratings[a] of pain/redness/swelling/induration at injection site
Kane et al.[54]	Pts' perception of injection site pain was low at the 1st injection, and decreased during treatment. Mean ± SD VAS[b] ratings of injection site pain: 1st injection: LAR 25mg 12.0 ± 15.8; LAR 50mg 18.2 ± 24.0; LAR 75mg 16.7 ± 20.0; placebo 16.7 ± 20.7 6th injection: LAR 25mg 9.0 ± 10.3; LAR 50mg 11.8 ± 21.2; LAR 75mg 8.5 ± 14.4; placebo 12.6 ± 17.4	Percentage of pts with pain or swelling rated as absent after the 6th injection: Pain: LAR 25mg 80%; LAR 50mg 81%; LAR 75mg 84%; placebo 90% Swelling: LAR 25mg 100%; LAR 50mg 100%; LAR 75mg 100%; placebo 100%
Lauriello et al.[56]	Pt-reported injection site pain low in both groups; VAS[b] ratings at endpoint, mean (±SD): LAR (all doses) 12.3 ± 20.01; placebo 6.71 ± 12.81 VAS scores declined from baseline to endpoint in both groups but not significantly so	No data given
Lindenmayer et al.[58]	1 pt reported mild injection site pain after the first injection. No other injection site adverse reactions were reported	No injection site adverse reactions reported
Turner et al.[39]	No data given	No data given
Chue et al.[40]	Pain at injection site low (mean scores of 18–20 on a VAS[b]) and similar after injections containing active risperidone and placebo	Pain rated as absent or mild in most pts Redness at injection site was mild, reported in 3.7–6.8% of pts in the LAR group and reported less frequently after the 3rd injection Swelling mild or absent and induration absent in almost all pts in both groups
Möller et al.[33]	No data given	No data given
Parellada et al.[34]	6 pts (2%) reported injection site pain	No data given
Gastpar et al.[38]	No data given	No data given
Kissling et al.[36]	9 pts (1%) reported adverse events associated with the injection site, of which 8 were reported as injection pain	No data given

Continued next page

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Table III. Contd

Study (for description see table II)	Pts' evaluation of injection site pain	Investigators' ratings[a] of pain/redness/swelling/induration at injection site
Fleischhacker et al.[42]	Little pain reported, and pain ratings decreased during the trial. The median VAS[b] score was 10 at the first injection and 5 at the 25th	Percentage of pts with pain, redness, swelling or induration rated as absent after the 6th injection: Pain: first injection 68%; last injection 80% Redness: first injection 95%; last injection 100% Swelling: first injection 98%; last injection 100% Induration: first injection 100%; last injection 93%
van Os et al.[52]	Injection site pain consistently rated as low, and decreased significantly ($p = 0.042$) over the study: Mean ± SD VAS[b] ratings (all doses): First injection: 14.93 ± 19.59 Endpoint: 6.44 ± 14.72	No data given
Lasser et al.[53]	Pain assessments low throughout the trial in all dose groups and decreased significantly ($p < 0.001$) over the study Mean ± SD VAS[b] ratings of injection site pain (all doses): First injection: 21.42 ± 23.3 Endpoint: 13.9 ± 20.8	Redness, swelling and induration absent in 98–99% of pts
Lasser et al.[48]	Self-ratings of pain low throughout the trial in all dose groups and decreased over the study Mean ± SD VAS[b] ratings (all doses): First injection: 18.0 ± 1.9 Endpoint: 11.0 ± 1.6	Percentage of pts with redness, swelling or induration over the course of the study: Mild reactions: LAR 25mg 17.3%; LAR 50mg 10.3%; LAR 75mg 8.2% Moderate reactions: LAR 25mg 0.9%; LAR 50mg 0.3%; LAR 75mg 0.6% Severe reactions: 0% (all doses)
Lasser et al.[51]	Self-ratings of pain low throughout the trial in all dose groups and decreased significantly over the study ($p < 0.01$) Mean ± SD VAS[b] ratings of injection site pain (all doses): First injection: 8.6 ± 2.2 Endpoint: 2.3 ± 0.6	First injection: pain reported by 8 pts (mild in 5, moderate in 3), induration in 2 (mild in 1, moderate in 1), swelling in 1 (mild) and redness in no pts At week 48, mild pain reported in 5 pts, with no induration, swelling or redness
Gharabawi et al.[46]	No data given	No data given

a Rated on a categorical scale (absent, mild, moderate or severe).

b 100mm VAS, where 0 = no pain and 100 = unbearably painful.

pt = patient; **VAS** = visual analogue scale.

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tors' ratings, none of the parameters (injection site pain, redness, swelling or induration) increased from baseline to endpoint.[42] A further analysis of injection site pain from this study revealed that mean VAS scores at the first and last injections were 17.9 ± 22.2 (first) and 9.5 ± 16.7 (final; $p < 0.0001$) for 25mg, 18.1 ± 19.7 (first) and 10.4 ± 14.8 (final; $p < 0.0001$) for 50mg, and 18.5 ± 21.6 (first) and 13.6 ± 19.9 (final; $p = 0.0001$) for 75mg of long-acting risperidone.[47] Furthermore, treatment satisfaction increased during the study as indicated on the 10-point Drug Attitude Inventory scale (baseline 7.30; endpoint 7.70; $p < 0.0001$ vs baseline).

In addition, in a subset of patients from the 1-year study who had received therapy with long-acting conventional antipsychotics (n = 188), mean VAS ratings of injection site pain significantly decreased from 21.42 ± 23.3mm at baseline to 13.9 ± 20.8mm at endpoint ($p < 0.001$) with long-acting risperidone (25, 50 or 75mg intramuscularly every 2 weeks).[53] Finally, patients in the 1-year study who had switched from oral risperidone (n = 366) to long-acting risperidone (25, 50 or 75mg intramuscularly every 2 weeks) also experienced decreased injection site pain from baseline to endpoint (from 18.0 ± 1.9mm to 11.0 ± 1.6mm).[48]

3.4 Pharmacoeconomic Considerations

The advent of new atypical antipsychotics with their higher acquisition costs than conventional antipsychotics primarily raised concerns from health insurance companies and prescribing doctors. This prompted pharmacoeconomic evaluations of their costs and benefits. This article addresses these issues only very briefly.

Some of the studies focused on risperidone in comparison with haloperidol or other second-generation antipsychotics, especially olanzapine.[75-80] In their review published in 1998, Foster and Goa[81] stated that, in terms of pharmacoeconomic parameters, the use of risperidone in preference to conventional antipsychotics in patients with (chronic) schizophrenia has been supported by several model studies.

Reductions in hospitalisation rates would be expected to reduce treatment costs.[81] Long-acting risperidone 25 or 50mg once every 2 weeks reduced hospitalisation and partial hospitalisation rates over 1 year in patients with schizophrenia or schizoaffective disorder.[82,83] The 1-year re-hospitalisation rates were 17.6% overall, 15.9% for outpatients and 25.0% for inpatients.[84] Significant reductions in the number of hospitalisations (36% vs 53% of patients; $p = 0.02$), the number of episodes of institutional care (85 vs 136; $p = 0.0005$) and the cumulative duration of hospitalisation (2404 vs 6635 days; $p = 0.006$) occurred in patients receiving long-acting risperidone 25–75mg every 2 weeks for 2–5 years compared with the corresponding period before treatment with long-acting risperidone.[85] Long-acting risperidone was the dominant strategy compared with intramuscular haloperidol decanoate or oral olanzapine over a 2-year period in patients with schizophrenia, according to a binary decision tree model from a French payer's perspective.[86] Incremental cost-effectiveness ratios, i.e. cost per responder over 2 years, for long-acting risperidone were −€1418 versus oral olanzapine and −€14 732 versus intramuscular haloperidol decanoate.[86] Effectiveness data were from clinical trials with oral haloperidol,[26] oral[87] and long-acting risperidone[42,83] and oral olanzapine.[87] Cost analyses using a discrete event model found that long-acting risperidone produced cost savings over 5 years relative to both depot haloperidol and oral olanzapine in The Netherlands as first-line therapy in patients with schizophrenia at high risk of noncompliance (€5005 and €16 066 per patient)[88] and relative to oral olanzapine and depot haloperidol in Germany as first-line therapy in patients with schizophrenia (€2192 and €131).[89] A subgroup analysis of noncompliant patients in the German model found

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cost savings with long-acting risperidone relative to depot haloperidol and oral olanzapine (€1442 and €9082).[89,90]

4. Clinical Perspectives on the Use of Long-Acting Risperidone

Schizophrenia is a disease with a generally early onset and very often a poor outcome.[1] The lifelong nature of schizophrenia requires long-term treatment in most patients, usually with a combination of pharmacological and psychological strategies.[2,69,70] One of the main problems in long-term treatment is the high noncompliance and high relapse rates. Apparently, atypical antipsychotics, although advantageous in several respects in terms of broader efficacy and fewer EPS, were not able to overcome this problem to a satisfactory degree.[6-8] Even clozapine, which is seen to have advantages, especially in patients who are difficult to treat and have a chronic disease course, cannot solve the compliance problem satisfactorily. Therefore, the advent of long-acting injectable atypical agents, starting with the introduction of long-acting risperidone, might represent an important opportunity to improve the treatment of patients with schizophrenia.

As described in section 3, the efficacy and safety data of long-acting risperidone are positive. Clinicians would be even more convinced if data from a long-term, randomised, controlled trial comparing long-acting injectable risperidone with oral risperidone were available. Preliminary data from pharmacoeconomic studies suggest that long-acting injectable risperidone may be more cost effective and offer cost savings relative to other options such as treatment with haloperidol depot or oral atypical antipsychotics. Given the advantages of both atypical antipsychotics and depot formulations in general, long-acting injectable risperidone, and possibly also long-acting formulations of other atypical antipsychotics that are currently in phase III development, will find their place in the treatment of schizophrenia and be less restrictively prescribed than the classical depot antipsychotics, which were increasingly prescribed for only a small subgroup of noncompliant patients with chronic unstable disease with a poor prognosis.

The recently published results of a huge North American multicentre effectiveness trial on antipsychotic treatment[91] demonstrated the high proportion of discontinuation under maintenance treatment with oral atypical antipsychotics, even under clinical trial conditions. This problem of a high discontinuation rate, even with atypical antipsychotics, has to be answered by alternative treatment strategies. In this context, the niche indication of classical depot antipsychotics might possibly be replaced by the broader indication of long-acting atypical agents. When considering broadening the indication of long-acting injectable atypical antipsychotics, even first-episode patients – who are also known to have a high degree of noncompliance – should be included.[92,93]

In order to really benefit from the potential of a long-acting atypical antipsychotic it also seems worthwhile to think about starting treatment with a long-acting formulation earlier than used to be the rule. Especially in countries where the duration of hospital stay for the treatment of acute schizophrenic episodes is comparatively short, it might make sense to start the long-term treatment at a very early stage before discharge, to guarantee compliance after discharge from hospital. But such a strategy might even be meaningful under other conditions, i.e. in countries where the hospital stay for a schizophrenic episode is quite long, potentially also with the goal to achieve an earlier discharge from hospital, knowing that compliance is guaranteed. More data are required that support this early treatment strategy with long-acting formulations of atypical antipsychotics.

Despite the high incidence of medication noncompliance, many clinicians may be reluctant to

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consider administering long-acting injectable antipsychotics.[7] Owing to the traditional situation with depots of classical antipsychotics, long-acting antipsychotics may be perceived as a treatment of last resort that is to be given only after multiple relapses. Clinicians may fear that adverse effects, such as acute dystonia or neuroleptic malignant syndrome, which were common in the period when the classical antipsychotics were used, may be prolonged and difficult to manage with long-acting agents. However, the good tolerability of the atypical agents has changed the situation. Physicians have to learn that long-acting injectable atypical antipsychotics offer more treatment opportunities than the classical depots, and they should consider this potential when making their treatment decisions. Long-acting injectable atypical agents should not be restricted to the indication of patients with a history of poor adherence or to minimise covert noncompliance. They might offer the opportunity to achieve better treatment outcome in a much larger group of patients. The recent evidence about efficacy of long-acting risperidone in patients with schizophrenia and a comorbidity of substance abuse[37] serves as a valuable example for a beneficial broader application of long-acting second-generation antipsychotics. The high prevalence of co-occurring substance abuse or addiction in schizophrenia (15–65%[94]), the lack of data about the use of depot formulations in this indication, and the negative implications for the course of schizophrenia should stimulate researchers to conduct further trials using long-acting second-generation antipsychotics in this population.

The patient's subjective dimension of clinical decision making also deserves consideration. There are various pros and cons for a patient's decision about treatment with a depot antipsychotic. These include a fear of stigmatisation associated with depots of classical antipsychotics, which are seen as being a treatment for poor-outcome patients. On the other hand, the fact that only one injection is required every 2 weeks, instead of taking a pill once or several times a day, is seen as a pragmatic advantage.

The recommended dosage of long-acting risperidone is 25mg every 2 weeks (maximum 50mg) by intramuscular gluteal injection. Patients who have not been previously treated with oral risperidone should receive a test dose of oral risperidone as a hypersensitivity challenge. During the first 2 weeks of long-acting risperidone treatment, patients should receive supplemental oral risperidone or an alternative antipsychotic at an adequate dose. A change in dose of injectable risperidone should be considered only a minimum of 4 weeks after the previous dose adjustment.[90]

Specific dosage recommendations, warnings, precautions and drug interactions are contained in the manufacturer's prescribing information. Principally, the same rules can be applied as for oral risperidone. The manufacturer's instructions for storage of injectable risperidone, and for preparing and performing the injection, should be followed carefully. Of special importance is the finding that the risk of local adverse effects at the injection site is very low. The general monitoring of treatment is the same as with other antipsychotics.

In addition, clinical guidelines for dose administration and switching strategies for long-acting risperidone are available.[95-97] Of special importance is the fact that patients taking oral second-generation antipsychotics or even depot formulations of classical antipsychotics can be switched directly from the previous treatment to long-acting risperidone.

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