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REVIEW

Clinical Utility of Long-Acting Injectable Risperidone in Schizophrenia and Bipolar I Disorder: A Review of Clinical Studies

Francesco Bartoli, Daniele Cavaleri, Ilaria Riboldi, Chiara Alessandra Capogrosso, Giuseppe Carrà

School of Medicine and Surgery, University of Milano-Bicocca, Monza, 20900, Italy

Correspondence: Daniele Cavaleri, School of Medicine and Surgery, University of Milano-Bicocca, via Cadore 48, Monza, 20900, Italy, Tel +39 02 6448 8326, Email d.cavaleri1@campus.unimib.it

Abstract: Risperidone was the first second-generation antipsychotic to be developed as a long-acting injectable (LAI). In the early 2000s, a risperidone microsphere formulation, intramuscularly administered every 2 weeks (BW-RLAI), was introduced. To date, five different risperidone LAI formulations have been marketed – including a second biweekly microsphere injection (LY03004), a newer monthly intramuscular formulation using in situ microparticles (ISM) technology that does not require an oral risperidone run-in, and two subcutaneous formulations (RBP-7000 and TV-46000). Understanding the advantages and limitations of each option is essential for tailoring treatment regimens based on clinical needs and patient preferences. In this review, with the aim of offering insights for clinical practice and future research, we provide a comprehensive synthesis of the currently available risperidone LAI formulations, examining their efficacy and safety for the treatment of schizophrenia and bipolar I disorder. While evidence supporting the efficacy, tolerability, and safety of risperidone LAI for schizophrenia is available for all marketed formulations to date, advantages for newer formulations, such as longer dosing intervals without oral supplementation, are also reviewed. In addition, although the Food and Drug Administration approved the biweekly LAIs for bipolar I disorder, there is no data on effectiveness of the other risperidone LAI formulations for this indication so far. The variety of the available risperidone LAI options is likely to enable a more personalized treatment approach. To facilitate this, healthcare providers should develop a comprehensive understanding of these formulations to select the most suitable option. While risperidone ISM, RBP-7000, and TV-46000 may enhance treatment feasibility and adherence, further research is needed to build an evidence base comparable to that available for BW-RLAI, particularly in the treatment of BD.

Plain Language Summary: Risperidone is a second-generation antipsychotic used to treat schizophrenia and bipolar I disorder. It was the first drug of its class to be made available as a long-acting injectable (LAI), offering continuous treatment without the need for daily pills. Over time, several risperidone LAI formulations have been developed, including biweekly and monthly intramuscular injections – such as risperidone microspheres and risperidone in situ microparticles (ISM) – as well as subcutaneous options available exclusively in the United States. This review provides an updated overview of the efficacy and safety of all currently available risperidone LAI formulations for the treatment of schizophrenia and bipolar I disorder.

Each formulation has distinct advantages and limitations: for instance, some require an initial period of oral risperidone supplementation, while others do not; some allow for longer dosing intervals, reducing the frequency of injections. Selecting the most appropriate option depends on both clinical needs and patient preferences.

While all approved risperidone LAI formulations have demonstrated their role in treating schizophrenia, only the biweekly risperidone microsphere formulation has been officially approved for bipolar I disorder. Further research is needed to assess the effectiveness of other formulations for this condition.

A thorough understanding of these options can help clinicians provide more personalized and effective treatment for individuals with schizophrenia and bipolar I disorder.

Keywords: bipolar disorder, effectiveness, long-acting injectables, RBP-7000, review, risperidone, risperidone ISM, risperidone microspheres, schizophrenia, TV-46000

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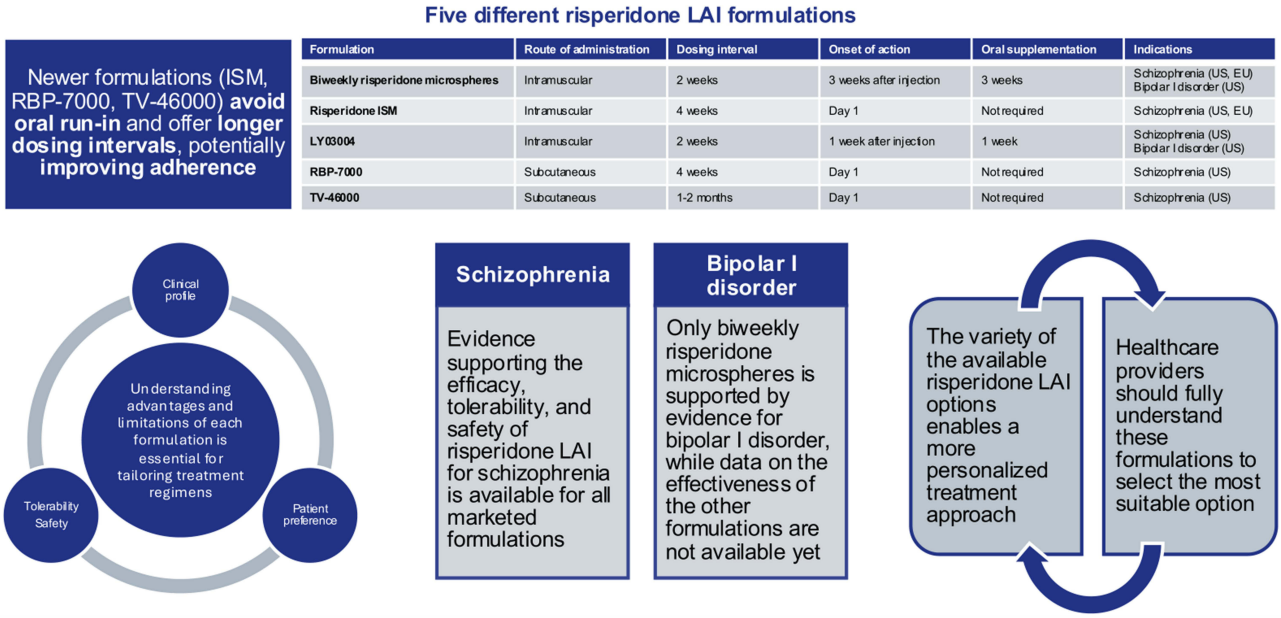
Graphical Abstract



Introduction

Schizophrenia and bipolar I disorder (BD-I) are severe mental disorders that require long-term treatment to manage symptoms, prevent relapse, and improve quality of life.[1,2] Despite the availability of several effective treatments, poor adherence to medications remains a critical challenge in individuals with schizophrenia and BD-I, leading to symptom recurrence and reduced functional recovery.[3,4]

Since the introduction of fluphenazine enanthate in the United States (US) market in 1967, several antipsychotics have been made available as long-acting injectable (LAI) formulations. Their use has increased significantly over the decades, mainly due to their evidence-based superior effectiveness in preventing relapse and rehospitalization in schizophrenia as compared with oral formulations in clinical practice.[5] Moreover, LAIs have been shown to be effective also in the management of BD-I, based on evidence demonstrating their benefit for short- and long-term outcomes, associated with the reduction of manic relapses.[6] Nonetheless, similar to oral formulations, the effectiveness of LAI first-generation antipsychotics is somewhat offset by their often-detrimental effects on negative symptoms, cognitive domains, and affective symptoms, as well as by relevant neuromotor side effects such as early and late-onset extrapyramidal symptoms, including the risk of tardive dyskinesia, which remains a significant concern with long-term exposure to first-generation agents.[7]

In the early 2000s, the first LAI formulation of a second-generation antipsychotic, a risperidone microsphere formulation to be administered biweekly (BW-RLAI), was introduced. Oral risperidone is widely used for the treatment of schizophrenia and has demonstrated efficacy also in managing manic and mixed episodes in BD-I:[8,9] similarly BW-RLAI has provided advantages for people with schizophrenia and BD-I in terms of both efficacy and all-cause discontinuation.[10]

In recent years, four additional LAI formulations have been developed and released for the treatment of schizophrenia. These include a different, more recently approved biweekly risperidone microsphere formulation (LY03004), two subcutaneous formulations (RBP-7000 and TV-46000), and an intramuscular formulation benefiting from an in situ microparticles (ISM, Laboratorios Farmacéuticos Rovi, Pozuelo de Alarcón, Madrid, Spain) technology, administered every 4 weeks. To date, BW-RLAI and risperidone ISM are approved both in the US and Europe, while the remaining formulations are available only in the US.[11]

The availability of different risperidone LAI options could enable the development of individualized treatment plans, allowing clinicians to choose formulations with various pharmacokinetics profiles and dosing intervals. However, robust clinical evidence of features mirroring pharmacokinetics differences has been poorly systematized so far. Moreover, how customizing regimens – to align with clinical history, symptom severity, and individual preferences – might actually support treatment adherence remains unclear. Indeed, the use of LAIs, including risperidone LAI formulations, in clinical practice remains hampered by a number of barriers that include perceived stigma and coerciveness, and clinicians' attitudes, also considering that LAIs use for BD in European countries is not approved and remains off-label.[12,13]

The recent regulatory approval of new risperidone LAI formulations marks a significant evolution in the treatment landscape. However, while BW-RLAI is supported by substantial scientific literature and clinical experience, the other formulations have been introduced so recently that relevant data are still at an early stage. In view of this, there is the need for an updated review to shed light on current evidence and to provide insight into the comparative features of available formulations so to inform clinical decision-making in this rapidly evolving field. The objective of this work was thus to provide a comprehensive overview of the different available formulations and their characteristics and utilization in the treatment of schizophrenia and BD-I. By synthesizing the existing evidence on all available formulations and outlining the advantages and limitations of each, we aimed at identifying specific needs and challenges, ultimately providing recommendations for clinical practice and future research.

Methods

Prescribing and technical information on available risperidone LAI formulations was retrieved from summaries of product characteristics provided by the US Food and Drug Administration (FDA) (https://www.fda.gov), the European Medicines Agency (EMA) (https://www.ema.europa.eu/en), and national registers, as well as data sheets supplied by drug manufacturers.

Then, main findings from trials and observational studies were reviewed and synthesized in order to summarize the available evidence on different risperidone LAI formulations for the management of both schizophrenia and BD-I.

Available Formulations

Biweekly Risperidone Microspheres

The first risperidone LAI was released in 2002 in Europe and in 2003 in the US, as a risperidone microsphere formulation to be administered biweekly (BW-RLAI) for the treatment of schizophrenia. Later, BW-RLAI received regulatory approval in the US also for the maintenance treatment of BD-I in adults, both as monotherapy and as adjunctive treatment to lithium or valproic acid. BW-RLAI relies on the Medisorb technology (Alkermes, Inc., Cambridge, Massachusetts, USA), made of polymeric microspheres, each consisting of a risperidone matrix encapsulated in polylactide-co-glycolide (a biodegradable polymer). Following an intramuscular injection, the polymer gradually breaks down releasing risperidone into the body at a controlled rate. The main release of risperidone begins at week 2 to 3 post-injection and increases during weeks 3 and 4, so the simultaneous administration of oral risperidone is recommended for the first 21 days. The release is maintained during weeks 4 through 6, and declines between weeks 6 and 7. Elimination is complete 7–8 weeks after the last injection of BW-RLAI. BW-RLAI is available at dosages of 12.5 mg, 25 mg, 37.5 mg and 50 mg to be administered every 2 weeks; the latter three doses roughly correspond to oral doses of 2–3 mg/day, 4 mg/day, and 5–6 mg/day, respectively. The recommended maintenance dosing for schizophrenia is 25 mg every 2 weeks, and higher dose adjustments should not be made more frequently than every 4 weeks.

Risperidone ISM

Risperidone ISM is a new intramuscular formulation of LAI risperidone indicated for the treatment of schizophrenia in adults. In December 2021, the Committee for Medicinal Products for Human Use recommended granting marketing authorization for this formulation, and, in early 2022, the European Commission authorized the commercialization of risperidone ISM for the treatment of schizophrenia in adults for whom the tolerability and effectiveness of oral risperidone have been established. The approval for schizophrenia in the US followed in Spring 2024. Risperidone

ISM is not approved for treating BD-I. The ISM technology is based on a solid and stable polymeric matrix system that contains risperidone. The product is reconstituted to an injectable fluid that precipitates in the muscle, resulting in the formation of solid or semisolid implants. As the implant erodes, risperidone is released over time in a controlled and sustained manner. Since risperidone ISM reaches the critical threshold of 65% dopamine D_2 receptor occupancy within the first hours after the first injection (ie, as fast as oral risperidone), neither loading doses nor oral supplementation are needed. In case stabilization is obtained with other oral antipsychotics, but risperidone tolerability was already established by previous trials, risperidone ISM administration is possible with a coverage period with oral risperidone of at least 6 days. Dopamine D_2 receptor occupancy remains above 65% during the whole 4-week treatment period, with less variability than oral risperidone. Risperidone ISM is available in two dosages – 75 mg (corresponding to oral risperidone 3 mg/day) and 100 mg (corresponding to oral risperidone 4 mg/day or higher) – and should be administered 24 hours after the last oral administration.

Other Formulations Approved in the United States

LY03004

A second microsphere formulation, LY03004, was approved for listing in the US in January 2023 with the same prescribing indications as BW-RLAI. Similarly to BW-RLAI, LY03004 is based on a polylactide-co-glycolide microsphere technology. Nonetheless, owing to different polymer formulation and manufacturing process, the drug is released faster, allowing an earlier onset of action: within 1 week after LY03004 administration, risperidone exposure is comparable or even superior to that guaranteed by BW-RLAI with a 3-week oral supplementation, allowing a shorter oral supplementation. Also, the steady state is reached approximately 2–3 weeks earlier than with BW-RLAI. Like BW-RLAI, LY03004 is manufactured at dosages of 12.5 mg, 25 mg, 37.5 mg, and 50 mg, and the recommended maintenance dose for schizophrenia is 25 mg every 2 weeks, and dose titration should not happen more frequently than every 4 weeks.

RBP-7000

In 2018, the first subcutaneous formulation of risperidone LAI, RBP-7000, was approved in the US for the treatment of acute schizophrenia in adults. RBP-7000 is a risperidone drug-device combination administered every 28 days that employs the ATRIGEL delivery system (Atrix Laboratories, Fort Collins, Colorado, USA), a polymeric solution of a biodegradable poly D,L(lactide co-glycolide) dissolved in a water-miscible, biocompatible solvent. Risperidone in RBP-7000 is both dissolved and suspended in this polymeric solution. After injection in the subcutaneous tissue in the abdomen or back of upper arm (with similar pharmacokinetics), the delivery system solidifies upon contact with bodily fluids, and the resulting biodegradable implant delivers risperidone for an extended period. RBP-7000 is available at dosages of 90 mg (equivalent to oral 3 mg) and 120 mg (corresponding to oral 4 mg), and it is designed so that the drug achieves clinically relevant therapeutic plasma concentrations on the first day of dosing, with no need for a loading dose or oral supplementation.

TV-46000

In 2023, another subcutaneous formulation of risperidone LAI, TV-46000, obtained the FDA approval for the treatment of schizophrenia in adults in the US. It is the first risperidone LAI formulation to be commercialized with a bi-monthly administration plan. TV-46000 consists of risperidone formulated within a matrix composed of a combination of diblock and triblock polyethylene glycol-polyester copolymers, namely BEPO (MedinCell, Jacou, France). This technology grants therapeutic blood concentrations of risperidone to be reached within 6–24 hours of a single dose, thus allowing for no oral supplementation. TV-46000 is available at doses of 50 mg, 75 mg, 100 mg, and 125 mg, 150 mg, 200 mg, and 250 mg, and is supplied in a prefilled syringe that does not require reconstitution but that must be kept refrigerated. TV-46000 can be administered monthly or every 2 months and should be initiated a day after the last dose of oral therapy.

Relevant features of each marketed risperidone LAI formulation, including country and year of approval, indications, storage requirements, administration methods, pharmacokinetics, dosing schedules, and safety recommendations are reported in Table 1.

Table 1 Main Characteristics of Available Long-Acting Injectable Risperidone Formulations

	BW-RLAI	Risperidone ISM	LY03004	RBP-7000	TV-46000
Regional agency (year) of approval	EMA (2002) FDA (2003)	EMA (2022) FDA (2024)	FDA (2023)	FDA (2018)	FDA (2023)
Clinical target	Schizophrenia in adults. Bipolar I disorder maintenance therapy both as monotherapy or adjunctive treatment to lithium and valproic acid in adults (FDA only).	Schizophrenia in adults.	Schizophrenia in adults. Bipolar I disorder maintenance therapy both as monotherapy or adjunctive treatment to lithium and valproic acid in adults (FDA only).	Schizophrenia in adults.	Schizophrenia in adults.
Dosing interval	2 weeks	4 weeks	2 weeks	4 weeks	1 month or 2 months
Switch from oral	Subjects originally on oral risperidone 3 mg/day or less receive BW-RLAI 25 mg. Subjects originally on oral risperidone > 3 mg but < 5 mg/day receive 37.5 mg. Subjects originally on oral risperidone 5 mg/day or higher receive 50 mg.	Subjects originally on oral risperidone 3 mg/day receive risperidone ISM 75 mg. Subjects originally on oral risperidone 4 mg/day (or higher) receive risperidone ISM 100 mg.[a]	As BW-RLAI.	Subjects originally on oral risperidone 3 mg/day receive RBP-7000 90 mg. Subjects originally on oral risperidone 4 mg/day receive RBP-7000 120 mg. Subjects who are on stable oral risperidone doses < 3 mg/day or > 4 mg/day may not be candidates for RBP-7000.	Subjects originally on oral risperidone 2 mg/day receive TV-46000 50 mg monthly or 100 mg bimonthly. Subjects originally on oral risperidone 3 mg/day receive TV-46000 75 mg monthly or 150 mg bimonthly. Subjects originally on oral risperidone 4 mg/day receive TV-46000 100 mg monthly or 200 mg bimonthly. Subjects originally on oral risperidone 5 mg/day receive TV-46000 125 mg monthly or 250 mg bimonthly.
Onset of action	3 weeks after injection	Day 1	1 week after injection	Day 1	Day 1
Steady state	4 injections	1 injection	2 injections	2 injections	2 months
Oral supplementation	3 weeks	Not required	1 week	Not required	Not required
Storage/ preparation	Store at 2° to 8° C; room temperature for at least 30 minutes prior to mixing contents.	Store below 30°C.	Store at 2° to 8° C; room temperature for at least 30 minutes prior to mixing contents.	Store at 2° to 8° C; room temperature for at least 15 minutes prior to mixing contents.	Store at 2° to 8° C; room temperature at least 30 minutes prior to administration (prefilled syringe) and for up to 90 days.

(*Continued*)

Table 1 (Continued).

	BW-RLAI	Risperidone ISM	LY03004	RBP-7000	TV-46000
Volume	Vial containing the risperidone microspheres + pre-filled syringe containing diluent 2 mL	Powder pre-filled syringe + solvent pre-filled syringe containing solvent 0.383 mL (for 75 mg dosage) or 0.490 mL (for 100 mg dosage)	Vial containing the risperidone microspheres + pre-filled syringe containing diluent 2 mL	90 mg: 0.6 mL 120 mg: 0.8 mL	50 mg: 0.14 mL 75 mg: 0.21 mL 100 mg: 0.28 mL 125 mg: 0.35 mL 150 mg: 0.42 mL 200 mg: 0.56 mL 250 mg: 0.7 mL
Administration	Intramuscular (gluteal or deltoid)	Intramuscular (gluteal or deltoid)	Intramuscular (unspecified)	Subcutaneous (abdomen or upper arm)	Subcutaneous (abdomen or upper arm)
Needle	2″ 20-G (gluteal) 1″ 21-G (deltoid)	2″ 20-G (gluteal) 1″ 21-G (deltoid)	2″ 20-G (gluteal)	5/8″ 18-G	5/8″ 21-G
Renal/hepatic impairment	Carefully titrate with oral risperidone prior to initiating treatment with BW-RLAI. A lower starting dose of BW-RLAI of 12.5 mg may be appropriate in some subjects.	Titrate with oral risperidone (up to at least 3 mg) before initiating treatment with risperidone ISM at a dose of 75 mg. Not recommended if creatinine clearance <60 mL/min.	Titrate with oral risperidone (up to at least 2 mg) prior to initiating treatment with LY03004.	Titrate with oral risperidone (up to at least 3 mg) prior to initiating treatment with RBP-7000 at a dose of 90 mg.	Titrate with oral risperidone (up to at least 2 mg daily) prior to initiating treatment with TV-46000 at a dose of 50 mg.

Note: [a]EMA indications.
Abbreviations: BW-RLAI, biweekly risperidone microspheres long-acting injectable; EMA, European Medicines Agency; FDA, US Food and Drug Administration.

Risperidone LAI in the Treatment of Schizophrenia

Risperidone Microspheres

The available clinical evidence supporting the effectiveness of risperidone microsphere formulations – and risperidone LAI in general – primarily derives from studies on BW-RLAI, as it has been available for more than 20 years.

A first 12-week double-blind, placebo-controlled trial analyzing 400 subjects with schizophrenia showed that BW-RLAI was effective and well tolerated, also for inpatient treatment.[14] These findings were reinforced by a long-term extension study.[15] A subsequent randomized, double-blind, placebo-controlled trial reported clinically meaningful improvements in all mental-health domains as well as in health-related quality of life.[16] Further, a randomized, double-blind trial including clinically stable outpatients with schizophrenia or schizoaffective disorder confirmed that BW-RLAI was associated with low relapse and rehospitalization rates over a 1-year follow-up.[17]

Since then, a large body of evidence has been accumulating. Several open-label trials with both short- and long-term follow-ups have demonstrated the efficacy of BW-RLAI in schizophrenia spectrum disorders without particular safety concerns,[18–20] even without an oral risperidone run-in, showing that its direct initiation was effective in sustaining positive and negative symptom control, achieving remission, and reducing relapse rates as well as number and length of hospitalizations at different time points and up to over 1 year,[15] with good safety and tolerability. A strong benefit of the direct transition to BW-RLAI was highlighted also in clinically stable individuals with schizophrenia, pre-treated with oral antipsychotics other than risperidone, such as olanzapine.[21] Predictors of remission at 6 months seem to include baseline symptom severity and functioning, while male gender may be a risk factor for relapse.[22] Regarding side effects, a reduction in movement disorders and extrapyramidal symptoms was observed.[18,21]

Consistently with trials, observational studies also support the utility of BW-RLAI in people with schizophrenia, especially for those with adherence issues. Both in retrospective[23] and prospective studies[24] its use for schizophrenia was associated with early and late improvements in symptom severity as well as decreased hospitalizations and emergency room visits, despite differences in health care delivery systems. Additionally, mirror-image studies, understood to be particularly appropriate to assess the clinical utility of LAIs[25,26] suggest a strong superiority of BW-RLAI as compared with oral antipsychotics in reducing severity, remissions, and hospitalizations.[27]

Based on a large body of evidence from both open-label and observational studies, BW-RLAI also seems guarantee improvements in cognition,[28] functioning and personal and social performance,[22,24] subjective well-being and quality of life, attitudes toward medication, and treatment satisfaction.[16,19,22] Younger age, longer duration of illness, inpatient status at initiation,[29] and a history of previous treatment failure with at least two antipsychotics[30] seems to predict higher likelihood of BW-RLAI discontinuation. Moreover, in real-world settings, its early discontinuation in subjects with schizophrenia or schizoaffective disorder seems strongly associated with the absence of oral supplementation during the first 21 days of treatment.[31] Even dosages of 75 mg or higher every 14 days seem to be well tolerated.[32]

However, the superiority of BW-RLAI over oral antipsychotics in people with schizophrenia has been questioned. Indeed, some efficacy trials comparing BW-RLAI with oral antipsychotics in individuals with schizophrenia showed no superiority of the LAI formulation both in the short-[33,34] and long-term.[34,35] Nonetheless, even if BW-RLAI is not more effective than oral risperidone, it may offer the advantage of an improved tolerability profile, with fewer extrapyramidal side effects and better prolactin control.[35] Notwithstanding these issues, structural differences between the controlled setting of trials and real-world environments should always be taken into account.[36] Evidence from naturalistic, long follow-ups shows that BW-RLAI is associated with greater symptom improvement, larger reduction in hospitalization rates and length, improved functioning, more days until medication discontinuation, and reduced risk of medication switching compared to oral antipsychotics.[23]

As regards recent-onset schizophrenia, evidence from both trial and naturalistic settings suggests that BW-RLAI may be a feasible and beneficial option,[37,38] guaranteeing significantly lower relapse rates, improvements in global, social, and occupational functioning, fewer treatment discontinuations due to inadequate clinical response, and higher medication adherence, with better patient satisfaction and quality of life, without negative impacts on attitudes towards medication. Notably, the early initiation of RLAI in recently diagnosed subjects appears to yield better outcomes than in those with a longer duration of illness.[39]

BW-RLAI seems effective on positive and negative symptoms, movement disorder severity, functioning, and patient satisfaction also in elderly subjects with schizophrenia[40–42] by allowing the dosage of concomitant medications to be reduced.[42] BW-RLAI can be considered even if not preceded by oral risperidone treatment[41] and may be safely increased from the recommended dose of 25 mg every 2 weeks up to 37.5 mg or even 50 mg.[43]

Evidence suggests that BW-RLAI may be effective in treatment-resistant and treatment-refractory schizophrenia, also with good tolerance, reduced extrapyramidal side effects, and low dropout rates, even at high dosages.[39] Augmentation with BW-RLAI has shown potential benefits in case of clozapine non-adherence, though high doses may be required.[44]

BW-RLAI may offer advantages over oral treatment in case of comorbid alcohol or substance use,[45,46] appearing preferable over oral risperidone[47] and demonstrating good efficacy in improving both schizophrenia symptoms and substance use outcomes in people with co-occurring disorders,[48] albeit associated with early discontinuation.[31]

In terms of cost-effectiveness, the higher initial acquisition cost of BW-RLAI seems offset by its effectiveness on several clinical domains – leading to reduced hospitalization costs – in a wide, international array of different healthcare systems, but not all studies show a clear benefit:[49] some highlighted that, notwithstanding shorter lengths of hospital stay[50] and decreased service use in general,[51] individuals treated with BW-RLAI posed higher overall medical costs. However, since BW-RLAI must be administered as frequently as every 2 weeks, the higher costs may be due, at least partly, to increased utilization of outpatient services.[50,51] Additionally, the need for an initial 3-week oral supplementation, along with storage and administration costs, contribute to the overall expense linked to BW-RLAI treatment.[49]

Regarding LY03004, while pharmacokinetic and safety studies have been conducted,[52] evidence supporting its clinical efficacy is not yet available.

Risperidone ISM

The efficacy and safety of risperidone ISM was evaluated in the PRISMA-3 study, a phase-3, double-blind, randomized, placebo-controlled trial recruiting 438 subjects with acute and severe exacerbation of schizophrenia at 26 centers in the US and Ukraine between June 2017 and December 2018.[53] Participants received once-monthly intramuscular injections of risperidone ISM (75 or 100 mg) or placebo for 12 weeks. Compared to placebo, risperidone ISM was associated with a significant decrease in schizophrenia symptom severity at study endpoint with both dosages, with no significant differences in the magnitude of overall symptom score change from baseline to day 85 between the 75 mg group and the 100 mg group. Risperidone ISM was effective in significantly decreasing symptom severity at 12 weeks even in the more severely ill participants at both dosages, with the 100 mg dose providing a slightly greater improvement than the 75 mg dose. Similarly, both dosages led to a significantly greater reduction in clinical global severity compared to placebo from day 8 onward, and the clinical global improvement associated with both dosages was significantly superior to that observed with placebo from as early as day 8. The overall response rate improved over placebo from day 8 with risperidone ISM 100 mg and from day 15 for risperidone ISM 75 mg, and these differences remained significant until the end of the study. More specifically, significant improvements versus placebo were observed since day 8 for positive symptoms and day 15 for negative symptoms in both risperidone ISM groups, as well as since day 8 for general psychopathology symptoms for the 100 mg dose. At study endpoint, the overall response rate in subjects receiving risperidone ISM was 39.2% higher than placebo for the 75 mg dose and 33.8% higher for the 100 mg dose, meaning that the number-needed-to-treat was about 3 for both dosages. The first significant difference from placebo in overall response rate was observed after 1 week for risperidone ISM 100 mg and after 2 weeks for risperidone ISM 75 mg. Both doses were well tolerated: even though more than half of the participants experienced at least one treatment-emergent adverse event, most of these were mild (68%) or moderate (28%), and serious ones were reported in just 12 subjects, with no clear differences across the three groups. In general, the adverse events observed were those expected for oral as well as other risperidone LAI formulations, ie, blood prolactin increase and hyperprolactinemia, akathisia, and headache (though the latter was observed also in the placebo group). Concerning extrapyramidal symptoms, treatment groups were comparable and no relevant changes from baseline to end of treatment were observed in any group. Similarly, akathisia, and dyskinesia were not different between either dose of risperidone ISM and placebo. Injection site reactions such as redness, swelling, or induration were mild and not frequent – ranging from 6.1% with placebo to 9.6% with risperidone ISM 100 mg – and associated with low pain. The study completion was highest in the risperidone ISM 75 mg group (74%) and lowest in the placebo group (60%). Both risperidone ISM groups were associated with a lower rate of discontinuation owing to treatment-emergent adverse events (4.2% with the 75 mg dose and 6.2% with the 100 mg dose) compared to placebo (7.5%).

In addition, a 12-month, open-label, extension study of the PRISMA-3 study was conducted among 215 adults with schizophrenia. This study included 55 placebo (unstable) and 119 risperidone ISM (stabilized) rollover participants from the previous 12-week double-blind phase[53] as well as 41 *de novo* stable subjects.[54,55] Participants received monthly injections of risperidone ISM 75 or 100 mg in the gluteus maximus or deltoid muscles for 12 months. Three out of four recruited subjects completed the follow-up, with no differences across the subgroups; most discontinuations were due to withdrawal of consent. Overall psychotic symptom severity – as well as positive, negative, and general psychopathology symptoms severity – decreased significantly from baseline to endpoint in all groups, regardless of the initial disease severity. However, the greatest reductions were observed in unstable participants (who had a more severe clinical condition at baseline) and those previously stabilized on risperidone ISM, but also stable subjects had a slight decrease in psychotic symptom severity from baseline to endpoint. Similarly, risperidone ISM led to a significantly greater reduction in the clinical global severity of unstable and stabilized participants, also being maintained in the *de novo* participants throughout the study. At approximately 4 months, clinical global severity in rollover subjects reached levels comparable to those shown by the *de novo* participants at baseline, and this improvement was maintained until the end of the 12-month follow-up for both risperidone ISM 75 mg and 100 mg. Consistently, both the unstable and stabilized groups showed a significant clinical global improvement. Clinical response was achieved by 69% of participants in the unstable group and by 45% of subjects in the stabilized group. Notably, also an additional 12% of participants in the stable group

could be labeled as responders at the end of the open-label study. Relapse rate at 1 year was as low as 10.7%, and just nine patients (4.2%) were rehospitalized for psychotic symptoms during the study. As in the 12-week, double-blind study, both dosages (75 and 100 mg) appeared safe and well-tolerated in the long-term as well. Altogether, 84 (39%) patients reported at least one treatment-emergent adverse event, with a comparable incidence between the two risperidone ISM dosages. Nonetheless, most treatment-emergent adverse event were of mild (26%) or moderate (12%) in severity. The most common treatment-emergent adverse events were comparable to those observed in the 12-week, double blind study.[53] The incidence of serious treatment-emergent adverse events was low (7%), and led to treatment discontinuation in just seven cases, with no differences between the risperidone ISM 75 mg and 100 mg. Only 4.2% of participants showed extrapyramidal symptoms (akathisia, extrapyramidal disorder, tremor, or restlessness) after 1 year of treatment with risperidone ISM, with no clinically relevant changes from baseline to end of treatment with either dose. Such conditions required treatment with anticholinergic agent[56] or beta-blocking medications in less than 7% of subjects and lead to treatment discontinuation in just two individuals. Blood prolactin increases were observed as expected, but only two participants stopped treatment with risperidone ISM because of hyperprolactinemia symptoms. On the other hand, a decrease in prolactin levels in participants already stabilized on risperidone ISM at study entry was observed at endpoint. Over the 12 months, the mean increase from baseline in bodyweight was 1 kg, being significant in 12 patients (5.6%) and leading to treatment discontinuation in a single subject. Injection site reactions were limited in frequency and severity, and generally associated with low pain.

As regards personal and social functioning, compared to placebo, risperidone ISM also provided a rapid and sustained enhancement at the end of the 12-week, double-blind study. The significantly greater functional improvement for the risperidone ISM group compared to placebo in the 12-week, double-blind phase was observed as early as 4 weeks after starting the treatment. Early improvements were observed in all evaluated domains but self-care: participants showed better personal and social relationship as well as higher social integration and more socially useful activities (such as work and study), also with a reduction of disturbing and aggressive behaviors. Such improvements were maintained at the end of the 12-month extension study, which demonstrated long-term benefits of risperidone ISM, particularly on domains of personal and social functioning and perception of well-being. Participants who were clinically stable with oral risperidone at study entry maintained the same level of functioning and perception of well-being throughout the 12-months open-label phase.[55]

Given that risperidone ISM was only recently marketed, no real-world data is available yet.

Subcutaneous Formulations

The clinical efficacy and tolerability of RBP-7000 was established in a phase-3, short-term, randomized, placebo-controlled trial in 354 subjects with acute schizophrenia.[57–59] Both dosages tested – 90 mg and 120 mg monthly – were superior to placebo in reducing the severity of positive, negative (though not for the 90 mg dosage), and general psychopathology symptoms at each time point, from day 15 to week 8.[58,59] Dose-dependent responses were observed for specific symptom subdomains, suggesting that subjects with higher baseline severity may benefit from initiation of treatment at the 120 mg dose.[59] There were improvements also in quality of life, patient well-being, and satisfaction for RBP-7000- versus placebo-treated patients, especially with 120 mg.[57] A subsequent 52-week, open-label study of RBP-7000 120 mg monthly, including both rollover participants from the double-blind trial by Nasser et al[58] and stable *de novo* participants, demonstrated favorable safety and tolerability profiles (similar to oral risperidone), also with further symptom improvement for rollover participants and relevant clinical stability without apparent safety concerns for the *de novo* participants.[60] Quality of life, well-being, and patient satisfaction were maintained over the year.[61] A higher dose was explored by a subsequent study in clinically stable participants with schizophrenia[62] which supported the use of RBP-7000 180 mg monthly in individuals stable on oral risperidone 6 mg/day. No data from real-world studies is available to date.

Concerning TV-46000, its efficacy and tolerability were investigated in a phase-3, randomized, double-blind, placebo-controlled trial conducted in adult and adolescent outpatients with schizophrenia, stabilized with oral risperidone for 12 weeks.[63] The study showed that TV-46000 delays psychotic relapse and helps maintaining stability if administered both

monthly and once every 2 months, with a tolerability similar to that of oral and other LAI risperidone formulations at both dosages. No further clinical evidence on TV-46000 is available at present.

Risperidone LAI in the Treatment of Bipolar I Disorder

Although BW-RLAI was initially approved only for schizophrenia, its potential as a valuable therapeutic option for BD quickly became apparent. Early studies about the possible utility of risperidone LAI in the treatment of BD were observational investigations with very small sample sizes.[64,65] These studies preliminarily indicated that BW-RLAI, alone or in combination with standard oral treatment, may decrease severity in the maintenance phase of BD,[64] reducing manic symptoms, the mean number of manic and mixed episodes, and hospitalization number and length, thus increasing time to relapse, with improvements in treatment adherence.[65] Since then, BW-RLAI has been more systematically investigated as both monotherapy or adjunctive therapy in people with BD.

Considering BW-RLAI monotherapy, an open-label trial by Quiroz et al evaluated 303 adults with BD-I who had been stabilized on BW-RLAI for 26 weeks.[66] Participants were then randomly assigned to either continuing BW-RLAI or switching to placebo injections for up to 24 months. The study found that BW-RLAI significantly prolonged the time to recurrence of any mood episode and manic episodes as such, though not depressive episodes.[66] Similarly, a randomized, double-blind, placebo-controlled trial including 560 BD-I subjects stabilized on BW-RLAI for 12 weeks who were randomized to BW-RLAI monotherapy, placebo, or oral olanzapine monotherapy for 18 months showed that BW-RLAI significantly delayed the recurrence of any mood episode and manic episodes, though not depressive ones.[67] Additionally, BW-RLAI demonstrated significant improvements in global clinical status compared to placebo, with no evidence of worsening depression.[66,67]

Used as an adjunctive treatment in BD, the utility of BW-RLAI is similarly supported by several studies. Macfadden et al conducted a randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive BW-RLAI in frequently relapsing subjects with BD-I.[68] After a 16-week, open-label stabilization phase, with BW-RLAI in addition to treatment-as-usual, 124 remitted participants entered a 52-week, double-blind, placebo-controlled, relapse-prevention phase with either BW-RLAI (25–50 mg every 2 weeks) + treatment-as-usual or placebo + treatment-as-usual. This study found a relative relapse risk 2.3-fold higher with adjunctive placebo, showing higher completion rates, longer time to relapse, and significant improvements in functioning among participants receiving adjunctive BW-RLAI.[68] Open-label investigations further substantiated the utility of adjunctive BW-RLAI in BD: a 6-month, randomized, open-label comparison of continuation of oral second-generation antipsychotic therapy or switch to BW-RLAI in 49 outpatients with BD who were concomitantly taking a mood stabilizer showed similar effectiveness, safety, and tolerability between BW-RLAI and oral second-generation antipsychotics.[69] Further data emerged from a subgroup analysis of participants of the StoRMi trial diagnosed with BD-I: 16 subjects requiring a change of antipsychotic medication received BW-RLAI injections while allowed to continue taking mood stabilizers or anticonvulsants and showed a significant symptom reduction from baseline to endpoint, along with increased subjective satisfaction.[70]

Further evidence arises from observational studies. Retrospective cohort studies from Taiwan suggested that BW-RLAI is superior to both oral antipsychotics[71] and LAI first-generation antipsychotics[72] as regards rates of psychiatric hospitalization (regardless of episode polarity) and emergency room visit.[71] Further, a 1-year mirror-image study[73] showed that, in subjects with BD, BW-RLAI use decreased emergency room visits, hospital admissions, length of hospital stays, and non-medication costs (with savings attributed to lower hospitalization costs notwithstanding higher shares for medication), also reducing the concomitant use of other antipsychotics, lithium, and antidepressants.[73]

BW-RLAI may also be useful in rapid cycling BD, as shown by a 12-month, randomized, open-label comparison, reporting no significant difference in relapse rates between subjects treated with BW-RLAI + treatment-as-usual compared to those taking treatment-as-usual alone.[74] Moreover, compared to their non-rapid counterpart, rapid cycling individuals showed greater reduction in emergency room visits and inpatient service utilization with BW-RLAI.[73]

As for BD with psychotic features, a 3-year treatment with BW-RLAI seemed to reduce psychotic symptoms, along with manic and depressive ones as well as the number of mood episodes and hospitalizations, with improved functioning as compared with an equivalent pre-treatment period.[75]

In pediatric BD, although data is limited, the use of BW-LAI seems to favor treatment adherence and mood stabilization,[76] thus possibly representing a useful option, especially for those subjects failing to respond to prior medication trials or with adherence problems.[77]

No evidence regarding the efficacy and safety of the other available risperidone LAI formulations in clinical populations suffering from BD-I is available.

Discussion

Non-adherence to treatment in people with schizophrenia and BD-I keeps representing a major barrier to achieving optimal clinical and functional outcomes.[78,79] Despite robust evidence supporting the use of LAIs for both conditions, they are still underutilized.[12,13]

The range of available risperidone LAI formulations has recently broadened with new options that differ in diverse characteristics including available dosages, route of administration, need for eventual oral risperidone supplementation, and dosing intervals but also regional approval and indications. Since the comparative features of these formulations are only relatively known by clinicians, understanding the advantages and limitations of each option is essential for selecting the most suitable individual treatment.

As regards approved indications, although all available risperidone LAI formulations are approved for the treatment of schizophrenia, only BW-RLAI is approved for BD-I, specifically as monotherapy or as adjunctive therapy to lithium or valproate for maintenance treatment; still limited to the US and not authorized in Europe. Additionally, only BW-RLAI and risperidone ISM are approved by the EMA, while all the other formulations are not available in Europe so far.

A key difference across available risperidone LAI formulations is the route of administration: BW-LAI and the much similar LY03004, as well as risperidone ISM, are all intramuscularly administered, whereas RBP-7000 and TV-46000 are delivered subcutaneously. While prior studies have found that many patients prefer subcutaneous rather than intramuscular medication administration,[80] a recent survey did not show any clear preference between the two routes, with the majority of respondents reporting no strong inclination toward either option.[81]

It is certainly beneficial not to require oral supplementation when LAI treatment is started,[81] likely mirroring the desire to simplify treatment supporting LAI options for people with severe mental disorders.[3,4] Consistently, early discontinuation of risperidone LAI treatment has been closely linked to the requirement for oral risperidone supplementation during the initial 21 days of therapy with BW-RLAI,[31] contributing to reduced treatment adherence and subsequent higher risk of relapse.[41] Therefore, formulations that necessitate a shorter duration of concomitant oral treatment (LY03004) or eliminate the need for it altogether, ie, risperidone ISM and the subcutaneous formulations, may offer significant advantages in routine clinical practice.

Similarly, patients seem to prefer the lower treatment burden offered by longer dosing intervals.[82] In this perspective, newer risperidone LAI formulations administered once monthly or even once every 2 months may be preferable over BW-LAI. Furthermore, the tighter administration schedule of BW-LAI, together with logistics and costs related to refrigerated storage and reconstitution, increases the burden on outpatient services as well as overall treatment costs.[49,50] On the other hand, higher medication costs of newer formulations may limit their use in certain contexts.[83]

Conclusions

Evidence supporting the efficacy, tolerability, and safety of risperidone LAI is available for all marketed formulations to date. However, while substantial data from both clinical trials and real-world studies supporting the use of BW-RLAI has accumulated, the evidence for the newer formulations is more limited. Thus, there is a clear need for additional research to better understand the efficacy and safety profiles of latest risperidone LAI formulations and subsequently their role in the clinical management of schizophrenia and BD-I.

The diversity of the available risperidone LAI options enables a more personalized treatment approach by potentially accommodating both clinician preferences and patient needs. To facilitate personalized care, healthcare providers should develop a comprehensive understanding of these formulations, allowing them to guide patients in selecting the most suitable option in the context of shared decision-making. Moreover, further research is needed to explore additional strategies and products that ensure the effective and satisfactory delivery of risperidone. New LAI formulations,

including implants – such as the DLP-114 implant, a subcutaneous titanium rod designed for continuous risperidone delivery over 6 to 12 months[84] are currently in clinical development. These ongoing advancements highlight the continued effort to optimizing the treatment of schizophrenia and BD-I in clinical practice.

Abbreviations

BW-RLAI, biweekly risperidone microsphere long-acting injectable; EMA, European Medicines Agency; FDA, Food and Drug Administration; LAI, long-acting injectable; US, United States.

Ethics Approval and Informed Consent

This research did not involve humans or animals.

Author Contributions

All authors made a significant contribution to the conception, study design, execution, and interpretation of data; took part in drafting the article; gave final approval of the version to be published; have agreed on submitting the article to this journal; and agree to be accountable for all aspects of the work.

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