

Treatment-completion rates with olanzapine long-acting injection versus risperidone long-acting injection in a 12-month, open-label treatment of schizophrenia: indirect, exploratory comparisons

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Background: Little is known about the comparative effectiveness of atypical antipsychotics in long-acting injection formulation. Due to the absence of head-to-head studies comparing olanzapine long-acting injection and risperidone long-acting injection, this study was intended to make exploratory, indirect, cross-study comparisons between the long-acting formulations of these two atypical antipsychotics in their effectiveness in treating patients with schizophrenia.

Methods: Indirect, cross-study comparisons between olanzapine long-acting injection and risperidone long-acting injection used 12-month treatment-completion rates, because discontinuation of an antipsychotic for any cause is a recognized proxy measure of the medication's effectiveness in treating schizophrenia. Following a systematic review of the literature, two indirect comparisons were conducted using open-label, single-cohort studies in which subjects were stabilized on an antipsychotic medication before depot initiation. The first analysis compared olanzapine long-acting injection (one study) with pooled data from nine identified risperidone long-acting injection studies. The second analysis was a "sensitivity analysis," using only the most similar studies, one for olanzapine long-acting injection and one for risperidone long-acting injection, which shared near-identical study designs and involved study cohorts with near-identical patient characteristics. Pearson Chi-square tests assessed group differences on treatment-completion rates.

Results: Comparison of olanzapine long-acting injection data (931 patients) with the pooled data from the nine risperidone long-acting injection studies (3950 patients) provided almost identical 12-month treatment-completion rates (72.7% versus 72.4%; $P = 0.87$). When the two most similar studies were compared, the 12-month completion rate for olanzapine long-acting injection was significantly higher than for risperidone long-acting injection (81.3% versus 47.0%; $P < 0.001$). However, any conclusions drawn from this comparison may be limited by differences in the studies' geographic catchment areas.

Conclusion: Using treatment-completion rates as a proxy measure of medication effectiveness, olanzapine long-acting injection did not differ significantly from risperidone long-acting injection when including all eligible studies. However, the findings of this exploratory analysis should be interpreted with caution, considering the methodological limitations of these indirect, cross-study comparisons.

Keywords: antipsychotic drugs, intramuscular injection, olanzapine, risperidone, schizophrenia

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Introduction

Nonadherence to medication is a major risk factor contributing to relapse and hospitalization among patients with schizophrenia.^{1,2} Treatment with antipsychotics in long-acting injection formulations (depot) is recognized as a safe and effective strategy for improving medication adherence^{3,4} and appears to benefit patients with schizophrenia who are nonadherent to medications.⁵ Currently, several atypical antipsychotics are available in long-acting “depot” injections: a microsphere formulation of risperidone⁶ (risperidone long-acting injection), a pamoate salt of olanzapine⁷ (olanzapine long-acting injection), and a palmitate ester of paliperidone,⁸ the major metabolite of risperidone. Still other long-acting injectable formulations are in development, such as a cholesterol-based, implantable preparation of aripiprazole.⁹ The earliest of these formulations to receive marketing approval in the United States, risperidone long-acting injection and olanzapine long-acting injection, have been available for several years. However, the comparative effectiveness of these two medications is unclear, as they have not been compared yet in any head-to-head study. The aim of this analysis was to compare the effectiveness of olanzapine long-acting injection and risperidone long-acting injection in the long-term, open-label treatment of patients with schizophrenia, using 12-month treatment-completion rates as a proxy measure of treatment effectiveness. Treatment-completion rate is considered a proxy measure of treatment effectiveness, as it reflects both patients’ and physicians’ judgments of the efficacy, safety, and tolerability of a medication.^{10,11} In previous head-to-head research of olanzapine and risperidone in standard oral tablet formulation in the treatment of schizophrenia, olanzapine-treated patients were found to stay on therapy significantly longer and have significantly lower treatment-discontinuation rates compared with risperidone-treated patients.^{10–22} It is currently unknown whether findings from studies of the oral formulations of olanzapine and risperidone would extend to their depot formulations, as there are no head-to-head studies comparing the long-acting injectable formulations of these two medications.

Materials and methods

Data used in this analysis were identified via a systematic search of the published and unpublished literature. A search of the Embase® (Elsevier BV, Amsterdam, The Netherlands) and Medline® (National Library of Medicine, National Institutes of Health, Bethesda, MD) databases was conducted to identify relevant studies of olanzapine long-acting injection and risperidone long-acting injection using the following search

terms: “olanzapine pamoate depot”, “olanzapine depot”, “olanzapine long-acting”, or “long-acting olanzapine”, “Risperdal Consta”, “risperidone depot”, “risperidone long-acting”, and “long-acting risperidone”. In addition, potentially relevant olanzapine long-acting injection trials were identified via a search of the Eli Lilly internal database, and from the reference lists of identified studies and reviews.

Studies were eligible for inclusion in the analysis if they met the following criteria: an open-label design (ie, patients and investigators were aware of what treatment they were assigned to); patients received either olanzapine long-acting injection or risperidone long-acting injection (ie, only a “single cohort” was involved); age \geq 18 years; inclusion of patients with a diagnosis of schizophrenia or a related disorder (for example, schizoaffective disorder); and availability of data reporting the proportion of patients completing at least 12 months of treatment with olanzapine long-acting injection or risperidone long-acting injection. In addition, studies had to include patients who were symptomatically stable at baseline. The latter criterion was included to increase comparability between the olanzapine long-acting injection and risperidone long-acting injection studies, because there has been only one olanzapine long-acting injection open-label, single-cohort study, F1D-MC-HGKB (referred to hereafter simply as HGKB),²³ and this study included patients who were stable at baseline.

Data regarding study and patient characteristics, as well as 12-month completion rates, were extracted from the included studies. Two comparisons of 12-month completion rates were made. The first analysis compared data from the olanzapine long-acting injection study (HGKB) and all identified risperidone long-acting injection studies that met the inclusion criteria. The second analysis was conducted as a form of sensitivity analysis, comparing olanzapine long-acting injection data with that from the risperidone long-acting injection study that was most similar in design and patient characteristics. Group comparisons of 12-month treatment-completion rates were conducted using Fisher’s exact test.

Results

The literature search resulted in the identification of 10 studies with 4901 patients (olanzapine long-acting injection, $n = 931$; risperidone long-acting injection, $n = 3970$; Table 1). Of the 10 studies, one was presented as an unpublished study report²³ (F1D-MC-HGKB) providing effectiveness data on olanzapine long-acting injection and in two published articles,^{24,25} and nine publications provided effectiveness data on risperidone long-acting injection.^{26–34} The HGKB olanzapine long-acting injection study^{23,25} was

Table 1 Baseline patient characteristics for each study included

Study (sample size)	Male n (%)	Caucasian n (%)	Schizophrenia n (%)	Inpatients n/N (%)	Age at entry years, mean (SD)	Age at onset years, mean (SD)	PANSS total mean (SD)	CGI-S mean (SD)
HGKB								
Overall ¹³⁻²⁵	621 (66.7)	629 (67.6)	909 (97.6)	93/931 (10.0)	39.3 (11.7)	25.3 (8.6)	54.5 (17.7)	2.9 (0.9)
(n = 931)								
HGKA subgroup ^{24,25}	414 (64.5)	445 (69.3)	642 (100.0)	18/642 (2.8)	39.3 (11.6)	25.8 (8.4)	50.1 (14.5)	2.7 (1.0)
(n = 642)								
Chue et al ²⁶	249 (62.7)	(nr)	329 (82.9)	96 (24.2)	43.6 (15.2)	(nr)	(nr)	(nr)
(n = 397)								
Fleischhacker et al ²⁷	422 (68.6)	564 (91.7)	615 (100.0)	(nr)	42.0 (0.6) ^a	(nr)	67.1 (0.8) ^a	(nr)
(n = 615)								
Gharabawi et al ²⁸	58 (66.7)	35 (40.2)	68 (78.2)	(nr)	39.8 (10.3)	(nr)	65.4 (13.5)	(nr)
(n = 87)								
Kissling et al ²⁹ (StoRMi extension)	450 (62.9)	(nr)	579 (81.0)	244 (34.1)	39.9 (11.8)	25.5 (8.5)	74.9 (22.7)	(nr)
(n = 715)								
Lee et al ³⁰	25 (62.5)	(nr)	34 (85.0)	4 (10.0)	37.0 (10.5)	26.1 (6.5)	84.7 (19.1)	4.2 (0.9)
(n = 40)								
Lindenmayer et al ³¹	67 (67.0)	48 (48.0)	100 (100.0)	(nr)	45.4 (12.9)	(nr)	(nr)	2.2 (0.7)
(n = 100)								
Olivares et al ³² (eSTAR Spain)	855 (63.6)	(nr)	1145 (85.1)	118 (8.8)	38.4 (11.2)	(nr)	(nr)	4.6 (0.9)
(n = 1345)								
Rossi et al ³³	215 (62.0)	(nr)	260 (74.9)	0 (0.0)	44.2 (11.4)	26.9 (9.4)	88.4 (22.1)	(nr)
(n = 347)								
Simpson et al ³⁴	202 (62.3)	160 (49.4)	258 (79.6)	0 (0.0)	40.9 (11.0)	25.4 (9.4)	66.5 (16.4)	(nr)
(n = 324)								

Note: ^aStandard error.

Abbreviations: eSTAR, electronic Schizophrenia Treatment Adherence Registry; CGI-S, Clinical Global Impressions-Severity scale; n, number of patients with identified characteristic; HGKA, study FID-MC-HGKA; HGKB, study FID-MC-HGKB; nr, not reported; N, total number of patients in study sample; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; StoRMi, Switch to Risperidone Microspheres.

an open-label, single-cohort extension study that enrolled patients from 128 sites in 25 countries in North and South America, Europe, Asia, Africa, the Middle East, and Australia who completed one of three previous clinical trials (“feeder studies”). The three trials included an 8-week randomized, double-blind, placebo-controlled inpatient study³⁵ of olanzapine long-acting injection (F1D-MC-HGJZ), a maintenance study^{36,37} in which patients stabilized on oral olanzapine for 4–8 weeks were randomly assigned to oral olanzapine or olanzapine long-acting injection for 24 weeks of double-blind treatment (F1D-MC-HGKA), and a pharmacokinetic study³⁸ of olanzapine long-acting injection (F1D-EW-LOBS). The 12-month treatment-completion rate on olanzapine long-acting injection was calculated twice, for two populations in the HGKB study: all HGKB patients, regardless of which feeder study they came from,^{23–25} and only patients who entered HGKB after completing HGKA, a randomized, controlled trial comparing olanzapine long-acting injection with oral olanzapine in patients with schizophrenia who were first stabilized on oral olanzapine (data on file, Eli Lilly and Company and/or one of its subsidiaries^{31,36}).

The nine risperidone long-acting injection studies, with one exception, were single-cohort, open-label studies involving male or female adult (aged ≥ 18 years) patients. The one study that was an exception to the “single cohort” inclusion criterion³⁴ had randomized patient treatment assignments to one of two dosing regimens of open-label risperidone long-acting injection, and as such, was considered a single treatment cohort of risperidone long-acting injection. Of special interest was the study by Lindenmayer et al,³¹ which reported 12-month treatment-completion rates for two cohorts of patients being treated with open-label, flexible-dose risperidone long-acting injection in an extension study of two previous “feeder” studies: study A, which included patients from 41 sites in the United States who had either completed or been withdrawn from a 12-week, double-blind, randomized, controlled trial of inpatients comparing risperidone long-acting injection and placebo,³⁹ and study B, which included patients from 28 sites in the United States who had completed a 12-week, open-label outpatient study of risperidone long-acting injection.⁴⁰ Unlike study B, study A did not include all patients who had completed the feeder study, and it is unclear whether study A participants were stable when enrolled in the extension study by Lindenmayer et al.³¹ The 12-month treatment-completion rate for patients in study A was reported in the text³⁹ to be 55%. However, other information reported for patient disposition (as represented in a figure of the published report of study A) indicated a 12-month completion rate of 50%.

Baseline characteristics of participants in each of the 10 included studies are presented in Table 1. The majority of patients were male (62% to 69%) and had a diagnosis of schizophrenia (75% to 100%). Racial origin varied widely among the studies reporting racial origin, with Caucasians constituting as few as 40.2% of the patients in the Gharabawi et al study²⁸ and as many as 92% of the patients in the study by Fleischhacker et al.²⁷ Five studies did not report racial origin. Study participants also differed with regard to their baseline symptom severity, with mean baseline total scores on the Positive and Negative Syndrome Scale⁴¹ (PANSS) ranging from 54.5 (mildly ill⁴²) in the HGKB study to 88.4 (moderately to markedly ill⁴²) in the study by Rossi et al,³³ while baseline Clinical Global Impressions-Severity scale⁴³ (CGI-S) scores ranged from 2.2 (borderline mentally ill to mildly ill) in study B of the Lindenmayer study³¹ to 4.6 (moderately to markedly ill) in the Olivares electronic Schizophrenia Treatment Adherence Registry (e-STAR) study.³² Baseline PANSS scores were not provided for three of the 10 studies, and baseline CGI-S scores were not provided for six of the studies.

In the HGKB study, 90% of all patients treated with olanzapine long-acting injection were outpatients at baseline, and 10% were inpatients.²⁴ In the HGKA subgroup of the HGKB study,²⁵ 97% were outpatients at baseline, while 3% were inpatients (data on file). Information about outpatient and inpatient status at baseline was not reported in all risperidone long-acting injection studies. Studies reporting status indicated that the proportion of inpatients ranged from 0% in the studies by Rossi et al³³ and Simpson et al³⁴ to 34% in the Switch to Risperidone Microspheres (StoRMi) extension study by Kissling et al.²⁹

As presented in Table 2, a comparison of data from all 10 studies (analysis 1) showed nearly identical 12-month treatment-completion rates for patients treated with olanzapine long-acting injection or risperidone long-acting injection (72.7% versus 72.4%, respectively; $P = 0.87$). Completion rates for risperidone long-acting injection ranged from 47.0% for study B conducted by Lindenmayer et al in the United States³¹ to 86.1% for the Olivares eSTAR study conducted in Spain.³²

Due to the disparity between the included studies in their designs and patient baseline characteristics, a second analysis (analysis 2) was conducted between the two most similar studies as a form of sensitivity analysis. For olanzapine long-acting injection, this was the HGKA cohort from the HGKB study²⁵ ($n = 642$; data on file), and for risperidone long-acting injection, it was the study B cohort ($n = 100$) from the study by Lindenmayer et al.³¹ There were

Table 2 Twelve-month completion rates for olanzapine long-acting injectable or risperidone long-acting injectable (analysis 1)

Study	Baseline medication(s)	OLAI n/N (%)	RLAI n/N (%)
HGKB ²³⁻²⁵	OLAI	677/931 (72.7)	
Chue et al ²⁶	Any antipsychotic		281/397 (70.7)
Fleischhacker et al ²⁷	Any antipsychotic		400/615 (65.0)
Gharabawi et al ²⁸	Oral risperidone		33/67 ^b (49.3)
Kissling et al ²⁹ (StoRMi extension)	RLAI		508/715 (71.0)
Lee et al ³⁰	Oral antipsychotic		25/40 (62.5)
Lindenmayer et al ³¹ (study B)	RLAI		47/100 (47.0)
Olivares et al ³² (eSTAR Spain)	Any antipsychotic		1158/1345 (86.1)
Rossi et al ³³	Any antipsychotic		243/347 (70.0)
Simpson et al ³⁴	Any antipsychotic		166/324 (51.2)
Overall 12-month completion rate ^a		677/931 (72.7)	2861/3950 (72.4)

Notes: ^a $P = 0.87$, olanzapine-LAI versus pooled nine studies of risperidone-LAI, per Pearson Chi-square test; ^bintent-to-treat population only.

Abbreviations: eSTAR, electronic Schizophrenia Treatment Adherence Registry; n, number of patients completing 12 months of treatment; N, total number of patients treated; HGKB, study FID-MC-HGKB; OLAI, olanzapine long-acting injectable; RLAI, risperidone long-acting injectable; StoRMi, Switch to Risperidone Microspheres.

notable similarities between the two treatment groups that were compared in analysis 2:

- Both studies enrolled patients who had completed a previous “feeder” study of the corresponding depot medication and then continued into an extension period. These patients were likely similarly satisfied with their favorable response to treatment and thus willing to continue into the extension phase.
- Both studies included a single cohort of patients with schizophrenia.
- Both studies were open label, with flexible dosing of the medication.
- Both studies included chronically ill but stabilized patients with schizophrenia.
- Both studies included patients who were mildly ill, per mean PANSS total score or CGI scores.
- Both studies used identical prespecified inclusion criteria for baseline PANSS Positive scores (a score ≥ 4 on each of the following four PANSS positive items: conceptual disorganization, hallucinatory behaviors, suspiciousness, and unusual thought content).
- Both studies used a lead-in period of at least 4 weeks on the corresponding oral formulation prior to switching to the depot formulation.
- Participants in both studies had a similar mean age at study entry.

- Participants in both studies had a similar mean age at illness onset.
- Participants in both studies had a similar proportion of males and females.

Importantly, these patient characteristics (age at study entry, age at illness onset, and sex) have been previously found to be significant predictors of discontinuation on antipsychotic medications in the long-term treatment of patients with schizophrenia.⁴⁴⁻⁵⁰ However, the two comparison groups did differ in one important characteristic: geographic catchment area. Patients in the HGKA entry cohort of the olanzapine long-acting injection study represented 25 countries around the globe, whereas patients from the study B group of the risperidone long-acting injection trial were exclusively from the United States. The results of analysis 2 (Table 3) showed significantly higher 12-month treatment-completion rates for the HGKA cohort of the olanzapine long-acting injection trial compared with the study B group of the risperidone long-acting injection study (81.3% versus 47.0%, respectively; $P < 0.001$). It is noteworthy that, for study B, Lindenmayer et al³¹ reported two different treatment-completion rates, 52% in the text and 47% in a figure in the report; the correct rate is 47%, per personal communication from the principal author.

Discussion

This exploratory analysis made an indirect comparison between olanzapine long-acting injection and risperidone long-acting injection for 12-month treatment-completion rates using open-label, flexible-dose, single-cohort, prospective, observational studies conducted in the usual care of patients with schizophrenia. However, the findings from indirect cross-study comparisons are susceptible to selection bias and other confounding variables. To help minimize potential bias, we conducted two separate analyses. The first analysis used all

Table 3 Twelve-month completion rates for olanzapine long-acting injectable or risperidone long-acting injectable (analysis 2)

Study	Baseline medication(s)	OLAI n/N (%)	RLAI n/N (%)
HGKB ^{24,25} (HGKA subgroup, data on file, Eli Lilly and Company and/or one of its subsidiaries)	OLAI	522/642 (81.3)	
Lindenmayer et al ³¹ (study B)	RLAI		47/100 (47.0)
Overall 12-month completion rate ^a		522/642 (81.3)	47/100 (47.0)

Notes: ^a $P < 0.001$, olanzapine-LAI versus risperidone-LAI, per Pearson Chi-square test.

Abbreviations: HGKA, study FID-MC-HGKA; HGKB, study FID-MC-HGKB; n, number of patients completing 12 months of treatment; N, total number of patients treated; OLAI, olanzapine long-acting injectable; RLAI, risperidone long-acting injectable.

eligible studies reporting 12-month treatment-completion rates and found no significant difference between the two depot drugs on treatment-completion rates. However, because medication discontinuation rates tend to be influenced by study design, country of study sites, study burden, and patients' clinical and demographic characteristics, we also attempted to conduct an additional sensitivity analysis by selecting the risperidone long-acting injection study most similar to the single olanzapine long-acting injection study that was available. This was done due to the marked heterogeneity among the nine available risperidone long-acting injection studies and the need to compare "like with like." The second analysis, which compared results from two studies that were most similar in both their methodology and patient characteristics, found a significantly higher treatment-completion rate for olanzapine long-acting injection compared with risperidone long-acting injection. Results from the second analysis are consistent with those from head-to-head comparative studies of oral olanzapine and risperidone,¹⁰⁻²² as well as the results of two other recent and similarly designed studies in the treatment of patients in the United States with schizophrenia.^{51,52} One study⁵² was a randomized, open-label, 2-year study that compared risperidone long-acting injection and oral atypical antipsychotics and reported a high rate of discontinuation (approximately 80%) of risperidone long-acting injection for any cause over the 2-year study. The other study⁵¹ was also a randomized, open-label, 2-year study comparing olanzapine long-acting injection and oral olanzapine, and that study found a relatively lower 2-year discontinuation rate (54.9%) for any cause on olanzapine long-acting injection. However, it is notable that the "most similar" risperidone long-acting injection study used in our second analysis reported a considerably lower treatment-completion rate compared with the other eight risperidone long-acting injection studies.^{27,29,30,32,33,53-55} Moreover, the two studies in analysis 2 differed with respect to their catchment areas, in that the risperidone long-acting injection study B was conducted exclusively in the United States, while the olanzapine long-acting injection study was conducted more globally, outside the United States. This may account in large part for the observed disparity in discontinuation rates, because regional differences may lead to differences in study discontinuation rates.⁵⁶ A recent paper about a 2-year, single-cohort, open-label study⁵⁶ of risperidone long-acting injection found the 2-year treatment-completion rates for risperidone long-acting injection to differ markedly among the four countries studied, ranging from 39.3% in the United States to 62.7% in Spain. The authors noted that, "variation in discontinuation among the four countries may be due to differences in access to treatment,

social support (for example, in patients who live alone), and cost (for example in Spain, RLAT [risperidone long-acting injection] is free to most patients)." This information strongly suggests that the present exploratory comparison would require more definitive proof in the form of a direct, head-to-head comparison under essentially identical study conditions and in the same geography/country to clarify the validity of the current findings.

The current analyses are the first to compare the effectiveness of olanzapine long-acting injection and risperidone long-acting injection side by side and are preliminary and exploratory in nature. Therefore, there is a need to interpret the findings cautiously in the context of their limitations. As noted previously, these analyses were carried out using data from open-label, single-cohort studies, which are susceptible to selection bias and other confounding variables, including the country or countries where the study was conducted. Moreover, there is an imbalance in study representation, with just a single olanzapine long-acting injection study being compared with multiple risperidone long-acting injection studies, the latter being associated with a greater pooled variation in the total patient sample. While every effort was made in our study to ensure comparability of the data used by comparing the two studies most similar in study design and patient baseline characteristics, the differences between olanzapine long-acting injection and risperidone long-acting injection in the 12-month treatment-completion rates could have been an artifact due to differences in the studies' geographies, which often reflect differences in health care practices, social supports, and medication costs. Therefore, the current findings should be interpreted cautiously with these limitations in mind. There is a clear need for comparative head-to-head studies of olanzapine long-acting injection and risperidone long-acting injection in the long-term treatment of patients with schizophrenia, to help accurately delineate the comparative effectiveness of these two atypical antipsychotics in depot formulations.

Disclosure

HA-S, WSM, DPM, and PDF are employees of, and minor shareholders in, Eli Lilly and Company. KAC is an employee of OptumInsight.

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