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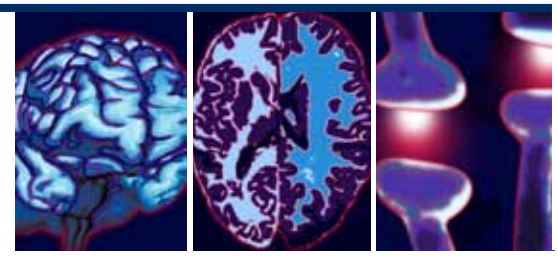

Comparison of long-acting antipsychotic injection and oral antipsychotics in schizophrenia

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Practice points

- Both oral and long-acting injectable antipsychotics have shown efficacy, tolerability and safety in the treatment of patients with schizophrenia.
- Second-generation oral antipsychotics have become the first line of treatment for schizophrenia.
- Nonadherence to treatment in patients with schizophrenia has been estimated in 40–60% of patients, and it has important clinical and social consequences for patients and carers, and accounts for 40% of health spending for the disease.
- Most of the effectiveness studies show a superiority of long-acting injectables, particularly in the case of risperidone, when compared with oral antipsychotics in relation to adherence, clinical improvement, reduction of relapses and hospitalizations, or cost–effectiveness.
- The disparity of methodological approaches used to compare different antipsychotic formulations, each one of them with important limitations, needs to be overcome with more accurate studies.
- The future development of new long-acting injectable antipsychotics will help tailor treatments to individual needs, particularly if these treatments are integrated into specialized mental health programs.

SUMMARY The aim of this article is to highlight objective differences between antipsychotic (both first generation and second generation) long-acting injections (LAIs) and typical and atypical oral antipsychotics, in terms of clinical outcomes. A systematic review of the literature has been performed. A total of 71 papers were selected for this article. Results are variable, mainly owing to methodological issues. For first-generation antipsychotic LAIs, randomized clinical trials and prospective observational studies show better outcomes for oral antipsychotics, while retrospective and mirror-image studies show the opposite. Most of the studies show a superiority for risperidone LAIs when compared with oral antipsychotics in relation to adherence, clinical improvement, reduction of relapses and hospitalizations, or cost–effectiveness. In the case of olanzapine pamoate and paliperidone palmitate there is not enough published evidence to draw conclusions. It seems that some evidence supports

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the advantages of LAIs over oral antipsychotics in clinical outcomes, at least for nonadherent patients. Methodological issues, as well as attitudes of patients, carers and healthcare practitioners towards LAI are discussed.

Schizophrenia is a chronic disease characterized by the occurrence of positive symptoms such as delusions and hallucinations, and negative symptoms such as lack of initiative, aboulia and cognitive impairment. It is a complex disorder that manifests with heterogeneous profiles across patients and variable psychotic episodes during a patient's lifetime. At present, no curative treatment for schizophrenia exists, but drugs that delay the occurrence of psychotic episodes and reduce the severity of symptoms are available [1].

The discovery of the sedative effects of chlorpromazine in 1952 and its effectiveness in controlling psychotic symptoms has resulted in it being considered as the first effective treatment in schizophrenia [2]. In the following 20 years, other similar neuroleptic agents with different chemical structures became available. All these drugs shared the property of being antagonists of dopamine, and their most common side effects are sedation, hypotension, parkinsonism, hyperprolactinemia and anticholinergic effects.

In 1966, the company ER Squibb & Sons Ltd (Uxbridge, UK) developed fluphenazine enanthate, the first long-acting injectable (LAI) antipsychotic. LAIs showed a number of potential advantages (ease of administration, monitoring of compliance, ensured regular contact with the patient, less risk of accidental or deliberate overdose, and better correlation between dose and plasma concentrations) and disadvantages (slow dose titration, longer time required to reach steady state levels, local side effects or prolonged side effects if they had to be discontinued for that reason) [3–7]. At that time, mainly under the influence of the spreading theoretical trends in the field of antipsychiatry, many psychiatrists refused LAI treatments, believing them to be 'coercive' [8,9]. However, the increasing number of studies demonstrating their efficacy and safety contributed to a progressive increase in use of LAIs [10–13]. The list of first-generation antipsychotic (FGA)-LAIs currently available include fluphenazine decanoate, haloperidol decanoate and zuclopenthixol decanoate, among others.

In 1958, the search for new molecules similar to the recently introduced imipramine led to the synthesis of clozapine [14]. Subsequent studies in the 1970s demonstrated its antipsychotic properties, rather than the expected antidepressant effect [15]. While clozapine was not marketed in the USA because of the risk for agranulocytosis, it continued to be used in some European countries with success. Clozapine [16] became the first of the so-called atypical or second-generation antipsychotics (SGAs), a heterogeneous class of agents characterized by being serotonin/dopamine antagonists, D2 antagonists with rapid dissociation, D2 partial agonists, or serotonin partial agonists at 5-HT_{1A} receptors, sharing the property of being less likely to cause extrapyramidal motor control disabilities in patients than FGA **(Table 1)**.

Currently, oral SGAs are the first-line therapeutic agents of choice for patients with schizophrenia in most countries. However, oral SGAs have not improved patients' adherence to treatment [17]. The increasing concern about the lack of adherence to oral treatments in schizophrenia has led to the development of LAI formulations of these newer 'atypical' drugs **(Table 2)**.

Several studies directly relate nonadherence with higher rates of relapse, increased number of re-hospitalizations, increased dependence on families and the healthcare system, and worsening of long-term prognosis and functionality [18–20]. Nonadherence in schizophrenia also accounts for 40% of health spending for the disease [21]. The rate of patients with schizophrenia who are partially or totally noncompliant has been estimated at 40–60% of all patients [22–24]. Nonadherence patterns may vary between those with occasional failures in the treatment because of a mistake or by forgetting a dose, and those in which the refusal to take treatment is the result of a deliberate decision taken by the patient [25–27]. There are many factors involved in poor adherence to antipsychotic treatment. Some of them (e.g., complexity of regime, irregular daily routine, or lack of clinician awareness of nonadherence) can, theoretically, be surpassed by the use of LAIs.

Prescribing patterns depend on factors as diverse as clinical experience and beliefs, or health resources of the area or culture [28,29]. However, there are many authors who think LAIs are underused for maintenance treatment of schizophrenia [30,31].

Table 1. Oral second-generation antipsychotics.

Drug	Elimination half-life (h)	Receptor affinity (ordered from highest to lowest)	Most common side effects
Clozapine	12	5-HT_{2A}, H1, α1, α2, D1, D2, M1, 5-HT_{1A}	Sedation, hypotension, sialorrhea, weight gain, hyperglycemia, dyslipidemia
Risperidone	24	5-HT_{2A}, α1, D2, H1, α2	Parkinsonism, akathisia, hyperprolactinemia
Olanzapine	33	M1, 5-HT_{2A}, H1, D1, D2, α1	Sedation, weight gain, dyslipidemia
Quetiapine	6	H1, α1, 5-HT_{2A}, D2, α2, 5-HT_{1A}, D1	Sedation, hypotension, anticholinergic effects
Amisulpride	12	D2, D3	Parkinsonism, akathisia, hyperprolactinemia
Ziprasidone	7	5-HT_{2A}, 5-HT_{1A}, D2, α1, D1	Hypotension, anticholinergic effects
Aripiprazole	75	D2, 5-HT_{1A}, 5-HT_{2A}	Parkinsonism, akathisia, hypotension
Paliperidone	23	5-HT_{2A}, α1, D2, H1, α2	Parkinsonism, akathisia
Asenapine	24	5-HT_{2C}, 5-HT_{2A}, 5-HT_{7}, 5-HT_{2B}, 5-HT_{6}, D3, H1, D4, α1, α2, D2, D1, 5-HT_{5A}, 5-HT_{1A}, 5-HT_{1B}	Somnolence, dizziness, parkinsonism, oral hypoesthesia
Iloperidone	18–33	5-HT_{2A}, D2, D3	Hypotension, dizziness, somnolence
Lurasidone	18	5-HT_{2A}, 5-HT_{7}, D2, 5-HT_{1A}, α2C	Akathisia, somnolence, parkinsonism

5-HT: Serotonin.

The aim of this article is to highlight objective differences between LAI and oral antipsychotics through an extensive review of studies comparing them, in order to help clinicians to take evidence-based decisions, beyond habits or preconceptions.

Method

A systematic search of MEDLINE, EMBASE and PsycINFO was carried out to find comparative studies between oral and LAI antipsychotics with no limitations by date. Studies should include a group of patients with schizophrenia, schizoaffective disorder or schizophreniform disorders treated with LAIs, another group with an oral antipsychotic (typical or atypical) comparator, and provide data on efficacy or effectiveness. A total of 71 relevant studies were then selected for the review. Studies were divided into randomized controlled trials (RCTs) and observational (prospective, mirror-image and retrospective) studies and quantitative data were extracted in order to present descriptive information.

Results

■ First-generation LAI versus oral antipsychotics

Randomized controlled trials

The meta-analysis by Adams *et al.* found no differences in risk of relapse, extrapyramidal symptoms and need for anticholinergic drugs between LAI and oral antipsychotics studies **(Table 3)** [32]. Arango *et al.*, in a sample of patients with history of violence, found less violent behaviors in the zuclopenthixol LAI group than in the oral group in the follow-up, although no statistical differences were found in the Positive and Negative Syndrome Scale (PANSS) between groups [33]. Recently, Leucht *et al.* [34] have published a meta-analysis based on ten long-term

Table 2. Second-generation long-acting injectable antipsychotics.

Drug	Time to peak (days)	Plasma half-life (days)	Time to steady state (months)	Receptor affinity	Most common side effects†
Risperidone microspheres	28	4–6	2	5-HT_{2A}, α1, D2, H1, α2	Parkinsonism, akathisia, hyperprolactinemia
Olanzapine pamoate	2–4	14–28	2–3	M1, 5-HT_{2A}, H1, D1, D2, α1	Sedation, weight gain, dyslipidemia, PDSS‡
Paliperidone palmitate	13–17	25–49	0.5–1.0	5-HT_{2A}, α1, D2, H1, α2	Parkinsonism, akathisia

†All of them may cause local reactions at the site of the injection.
‡PDSS has been described 1–4 h after injection of olanzapine pamoate in 0.07% of cases, causing excesive sedation or delirium.
PDSS: Post-injection delirium sedation syndrome.

Table 3. First-generation long-acting injectable versus oral antipsychotics studies.

Study (year)	Selection criteria/variables	LAI group	Oral group	Follow-up	Principal findings	Ref.
RCTs						
Adams *et al.* (2001)	Meta-analysis based on 8 Cochrane reviews. 848 patients	Fluphenazine decanoate, fluspirilene decanoate, pipotiazine palmitate	Chlorpromazine, haloperidol, penfluridol, trifluoperazine	4 weeks to 2 years (mean time: 1 year)	No differences in risk for relapse, EPS and anticholinergic drugs	[32]
Arango *et al.* (2006)	Patients with history of violence	Zuclopenthixol decanoate (n = 26)	Zuclopenthixol (n = 20)	1 year	Less violent acts in LAI group. No differences in PANSS	[33]
Leucht *et al.* (2010)	Meta-analysis based on 10 long RCTs (7 of them first-generation LAIs vs oral FGA)	Fluphenazine decanoate vs oral fluphenazine [35–38], fluphenazine decanoate vs pimozide [39,40], haloperidol decanoate vs oral APS [41]		Variable	Depot APS reduce risk for relapse significantly. Methodological problems may bias the results of some studies	[34]
Prospective observational studies						
Conley *et al.* (2003)	Patients discharged from inpatient psychiatric units	Fluphenazine decanoate (n = 59), haloperidol decanoate (n = 59)	Clozapine (n = 41), risperidone (n = 149), OLZ (n = 103)	1 year	Risk to re-admission after 1 year for all oral SGAs was lower than for haloperidol decanoate and similar to fluphenazine decanoate	[42]
Tiihonen *et al.* (2006)	Outcome after first admission	Perphenazine LAI (n = 187)	Haloperidol, 10 APS cohorts (n = 107)	Mean 3.6 years	Perphenazine LAI was associated with lower relative risk of re-admission	[43]
SOHO study Haro *et al.* (2006, 2007)	Remission, relapse and discontinuation. All APS vs oral OLZ	Several FGA-LAIs (n = 348)	Several FGA or SGA (n = 4247)	3 years	Greater risk of relapse, discontinuation and no remission for FGA-LAI compared with oral OLZ	[44,45]
US-SCAP Zhu *et al.* (2008)	All-cause medication discontinuation in first year after initiation of an antipsychotic	Haloperidol decanoate (n = 47) or fluphenazine decanoate (n = 50)	Haloperidol (n = 109) or fluphenazine (n = 93)	1 year	LAI had longer mean time to all-cause discontinuation. LAI were twice as likely to continue taking the medication	[46]
Retrospective observational studies						
Devito *et al.* (1978)	Outpatients. Groups were not matched	Fluphenazine decanoate (n = 61)	Several (n = 61)	1 year	Lower hospitalization rates for fluphenazine decanoate	[47]
Marchiaro *et al.* (2005)	Patients who had completed treatment for 2 years. Groups matched for demographic and clinial variables	Several FGA-LAIs (n = 30), mostly haloperidol decanoate	Several SGA (n = 30)	2 years	No statistical differences in hospitalization rates Greater anticholinergic drug prescription in the FGA-LAI group	[48]

APS: Antipsychotic; EPS: Extrapyramidal side effect; FGA: First-generation antipsychotic; LAI: Long-acting injectable; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized controlled trial; SCAP: Schizophrenia Care and Assessment Program; SGA: Second-generation antipsychotic; SOHO: Schizophrenia Outpatient Health Outcomes.

Table 3. First-generation long-acting injectable versus oral antipsychotics studies.

Study (year)	Selection criteria/variables	LAI group	Oral group	Follow-up	Principal findings	Ref.
Mirror-image studies						
Denham and Adamson (1971)	Days of hospitalization and number of admissions before and after receiving FGA-LAI in comparable periods of time	Fluphenazine decanoate or enanthate (n = 103)	Entry criteria: >1 year duration of LAI treatment Mean time: 2 years		In each study, total inpatient days and number of admissions were lower after receiving FGA-LAI than during the preceding oral treatment period	[49]
Gottfries and Green (1974)		Flupentixol decanoate (n = 58)	No minimum period of treatment required Mean duration of LAI treatment: 3 years			[50]
Morritt (1974)		Fluphenazine decanoate (n = 33)	Entry criteria: 1 year duration of LAI treatment Mean duration of LAI treatment: 1 year			[51]
Johnson (1975)		Fluphenazine decanoate (n = 140)	Entry criteria: >1 year duration of LAI treatment Mean duration of LAI treatment: 1.5 years			[52]
Lindholm (1975)		Perphenazine enanthate (n = 24)	Entry criteria: >1 year duration of LAI treatment Mean duration of LAI treatment: 2.5 years			[53]
Marriott and Hiep (1976)		Fluphenazine decanoate (n = 131)	Entry criteria: >1 year duration of LAI treatment Mean duration of LAI treatment: 2 years			[54]
Polonowita and James (1976)		Fluphenazine decanoate (n = 35)	No minimum period of treatment required Mean duration of LAI treatment: 1 year			[55]
Freeman (1980)		Fluphenazine decanoate (n = 143)	Entry criteria: >12 years duration of LAI treatment			[56]
Tan *et al*. (1981)		Fluphenazine decanoate (n = 127)	Entry criteria: 2 years duration of LAI treatment Mean duration of LAI treatment: 2 years			[57]
Tegeler and Lehmann (1981)		Fluphenazine and flupentixol decanoate, penfluridol, fluspirilene (n = 76)	Entry criteria: >1 year duration of LAI treatment Mean duration of LAI treatment: 5 years			[58]

APS: Antipsychotic; EPS: Extrapyramidal side effect; FGA: First-generation antipsychotic; LAI: Long-acting injectable; OLZ: Olanzapine; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized controlled trial; SCAP: Schizophrenia Care and Assessment Program; SGA: Second-generation antipsychotic; SOHO: Schizophrenia Outpatient Health Outcomes.

RCTs, seven of them comparing first-generation LAIs versus oral FGAs [35–41], and conclude that the currently available evidence suggests a clinically meaningful superiority of depot medication compared with oral antipsychotic drugs in outpatients with schizophrenia.

Prospective observational studies

Five studies were analyzed. Four of them showed a lower risk of relapse or re-admission for oral antipsychotics [42–45]. One showed lower discontinuation rates and greater mean time to discontinuation for any cause for LAIs compared with oral antipsychotics studies [46].

Retrospective observational studies

One study showed lower hospitalization rates for fluphenazine LAIs when compared with several oral antipsychotics [47]. Another study concludes that there were no statistical differences in hospitalization rates for FGA-LAI when compared with oral SGA, but more prescriptions for anticholinergic drugs were needed in the FGA-LAI group [48].

Mirror-image studies

In mirror-image studies, a cohort of patients receiving LAIs is compared with that during an equal time period immediately preceding LAI initiation. All the studies analyzed showed that total inpatient days and number of admissions were lower after receiving FGA-LAI than during the preceding oral treatment period [49–58].

■ Risperidone LAI versus oral antipsychotics

Randomized controlled trials

One study comparing risperidone LAI (RLAI) and olanzapine concluded that both treatments were efficacious and well tolerated **(Table 4)** [59]. In a review of 12 RCTs assessing psychomotor and cognitive functioning in patients taking RLAI or oral risperidone, olanzapine, quetiapine or olanzapine, RLAI was associated with improved functioning in the domains of attention/vigilance, verbal learning and memory, reasoning and problem solving, as well as psychomotor functioning [60]. In one study in first episode patients, most of them accepted the recommendation for RLAI, and those who received RLAI had significantly better adherence status after 12 weeks [61]. Finally, an open-label, randomized, active-controlled study, showed better adherence and delayed time to relapse after 2 years for RLAI compared with oral quetiapine [62].

Prospective observational studies

In five studies [63–67], the RLAI group resulted in higher levels of treatment adherence and/or was more effective in variables such as treatment retention, improvement in clinical symptoms and functioning, and reduction in hospital stays and days in hospital than oral SGA. One study comparing RLAI with oral risperidone showed similar efficacy for both treatments after 12 weeks [68]. However, another study found that patients on RLAI were more likely to discontinue treatment than those on oral SGA (except ziprasidone and aripiprazol) [69].

Two studies comparing cost–effectiveness of RLAI versus oral SGA showed that RLAI is more cost effective than oral SGA [64,70].

Other observational studies

Other observational studies are open-label studies in which patients are switched from their original medication to RLAI. Four studies showed a decrease in the number of hospitalizations or days hospitalized after initiating RLAI [71–74]. A total of 14 studies showed an improvement in clinical outcomes, such as symptom improvement, quality of life, or reduction in side effects after switching to RLAI [75–88].

Only a few of this type of study made mirror-image comparisons: five of them showed that RLAI reduced hospital admissions [89–93], while two studies concluded that RLAI did not decrease [94] or even increased [95] days of hospitalization or healthcare costs.

■ Olanzapine pamoate studies

Olanzapine pamoate (OLZ-P) is a novel injectable depot formulation of the atypical antipsychotic olanzapine, which has been licensed for the maintenance treatment of schizophrenia [96,97]. Two double-blind randomized clinical trials of OLZ-P have been conducted. In an 8-week, randomized double-blind study [98] in 404 patients acutely ill with schizophrenia, OLZ-P demonstrated significant antipsychotic efficacy (vs placebo). In a 24-week, randomized, double-blind, active-controlled study [99] in 1065 schizophrenia patients stabilized with oral olanzapine, OLZ-P delayed exacerbation of positive symptoms or hospitalization: the majority of oral olanzapine-treated patients (93%), as well as most OLZ-P patients receiving high (95%), medium (90%), low (84%) and very low doses (69%), remained exacerbation free, demonstrating efficacy similar to that of oral olanzapine

Table 4. Risperidone long-acting injectable versus oral antipsychotics studies: randomized, controlled trials and observational controlled studies.

Study (year)	Selection criteria/variables	RLAI group	Comparison group	Follow-up	Principal findings	Ref.
RCTs						
Keks *et al.* (2007)	377 patients Efficacy Tolerability	RLAI (25–50 mg every 14 days)	Olanzapine (5–20 mg/day)	1 year	Both treatments were efficacious and well tolerated	[59]
Houthoofd *et al.* (2008)	Review of 12 RCTs Cognitive and psychomotor functioning	RLAI	Risperidone, clozapine, quetiapine, olanzapine	Variable	RLAI seemed to be associated with improved functioning in the domains of attention/vigilance, verbal learning and memory, and reasoning and problem solving, as well as psychomotor functioning	[60]
Weiden *et al.* (2009)	First-episode patients Acceptance and initial adherence Outcomes	RLAI (n = 26; only 19 accepted treatment)	Oral atypical antipsychotics (n = 11)	12 weeks	Most first-episode patients will accept RLAI therapy. Recommendation did not affect adherence. Acceptance of RLAI was associated with significantly better adherence	[61]
Gaebel *et al.* (2010)	710 patients Time to relapse	RLAI (n = 329)	Quetiapine (n = 337)	2 years	Time to relapse was significantly longer in patients randomized to RLAI	[62]
Prospective observational studies						
De Graeve *et al.* (2005)	Efficacy and costs	RLAI	Oral olanzapine, haloperidol decanoate depot	2 years	RLAI more effective and less costly than comparators	[63]
Edwards *et al.* (2005)	Cost–effectiveness	RLAI	Risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole (and haloperidol decanoate depot)	1 year	RLAI is predicted to result in better clinical outcomes and lower total healthcare costs	[64]
Chue *et al.* (2005)	640 patients Efficacy	RLAI	Oral risperidone	12 weeks	Both treatments showed comparable efficacy	[68]
Kim *et al.* (2008)	First-episode schizophrenia Adherence Time to nonadherence Relapse rates	RLAI (n = 22)	Oral risperidone (n = 28)	2 years	RLAI group showed significantly lower relapse rate and higher medication adherence	[65]
Olivares *et al.* (2009)	Long-term treatment outcomes	RLAI (n = 1345)	SGA (n = 277)	2 years	RLAI got better treatment retention, greater improvement in clinical symptoms and functioning, reduction in hospital stays and days in hospital	[66]
Yang *et al.* (2009)	Cost–effectiveness	RLAI	Olanzapine, quetiapine	2 years	RLAI was more cost effective	[70]
Mohamed *et al.* (2009)	11,821 patients Likelihood of discontinuing medications as compared with RLAI	RLAI (n = 283)	Oral SGA (clozapine, olanzapine, risperidone and aripiprazol), oral FGA	2 years	Patients who were initiated RLAI were more likely to discontinue (except ziprasidone and aripiprazole)	[69]
Gutierrez-Casares *et al.* (2010)	1848 outpatients Adherence (assessed by MEMS™)	RLAI (n = 219) FGA-LAI (n = 161)	Oral SGA (n = 1073), oral FGA (n = 286)	3 months	RLAI showed more adherence	[67]

FGA: First-generation antipsychotic; LAI: Long-acting injectable; RCT: Randomized controlled trial; RLAI: Risperidone long-acting injectable; SGA: Second-generation antipsychotic.

as well as to each other. Long-term open-label studies provide additional information [100]. The overall tolerability profile for OLZ-P is similar to that for the oral formulation; however, postinjection delirium sedation syndrome [101,102], which resembles an overdose of oral olanzapine, has been described in 0.07% of injections of OLZ-P, requiring patients to be observed for 3 h after injection. At present, there are no studies available that directly compare OLZ-P with other antipsychotics other than oral olanzapine.

■ Paliperidone palmitate studies

Intramuscular paliperidone palmitate (PAL-P) is a long-acting, atypical antipsychotic that is indicated in the USA for the acute and maintenance treatment of adult patients with schizophrenia [103,104]. In an open-label study [105], PAL-P was effective at reducing PANSS total scores in patients with acute schizophrenia, in addition to demonstrating a good safety and tolerability profile. In a randomized, double-blind, long-term clinical trial, time to recurrence of symptoms was significantly longer in patients receiving PAL-P than in those receiving placebo [106–110]. In addition, in another randomized double-blind study [111], PAL-P was noninferior to risperidone long-acting injection, and both compounds showed similar tolerability and safety. At this time, there are no studies comparing effectiveness of PAL-P versus oral antipsychotics.

Discussion

The first comparative studies between LAI and oral antipsychotics were made in the 1960s and 1970s, immediately after the introduction of these drugs [112,113]. Those studies were generally made with inpatients, using a wide disparity of methodological approaches, and making it very difficult to draw conclusions [114–117]. In subsequent studies, methodological approaches can be divided into: RCTs – good to assess efficacy – and; observational (prospective, retrospective and mirror-image) studies – better to address effectiveness. The diverging results obtained from efficacy and effectiveness studies may be explained by a number of reasons. Efficacy studies are usually short-term studies (i.e., 8 weeks), low and/or fixed drug doses are used, and they have very strict inclusion and exclusion criteria; therefore, the results are difficult to generalize (owing to the lack of representivity of samples, clinical settings and treatment conditions). On the contrary, effectiveness studies are more capable of answering the interesting questions both from clinicians and health authorities, as they include representative samples of patients, use pragmatic variables, reproduce routine treatment conditions, and are done in representative clinical settings [118,119]. The strict selection of patients for the RCTs may lead to exclusion of patients who do not adhere to treatment, and this may bias the generalization of the results. This may bias the interpretation of the results of the RCTs comparing FGA-LAI versus oral FGA antipsychotics studies that showed no differences between both groups of treatments. By contrast, observational studies involving 'real' patients, with long periods of follow-up, trying to use relevant clinical measures (such as re-hospitalization rates) also have important limitations. For example, the fact that patients are not randomized may bias the LAI group, including a greater proportion of patients with low adherence (i.e., treatment failures by previous history and comorbidity) since this type of patient is more likely to receive a LAI.

In the mirror-image studies analyzed, the results of the FGA-LAI are better than oral antipsychotics in terms of re-hospitalization. Although these results are replicated in a wide range of studies in diverse populations with very different conditions, these type of studies can be confounded by independent events, such as a reduction of hospital beds [3], and some authors have highlighted that this methodological strategy has an 'inherent bias towards improvement' for several reasons that have been discussed elsewhere [120]. Finally, the few studies that report tolerability data [32,44,48] did not use direct measures (i.e., rating scales) but clinical observations or the use of anticholinergic drugs. This also limits the interpretation of the results.

Regarding the SGA-LAI studies, both for OLZ-P and PAL-P, more studies are needed comparing these formulations with oral antipsychotics, in order to be able to make conclusions regarding their differences in clinical outcomes. For the case of RLAI, an important number of studies have already been published. Safety, tolerability and efficacy of RLAI in the maintenance treatment of schizophrenia has been clearly established [121–127]. In addition, RLAI has been proven to be well tolerated in special population groups [128] such as the elderly [129] or pregnant women [130]. However, there are still only a few RCTs comparing RLAI and oral antipsychotics. In general, these studies show a superiority

of RLAI compared with oral antipsychotics in relation to adherence, clinical improvement and reduction of relapses and hospitalizations. Moreover, as is the case for the FGA-LAI, RLAI tends to be used by clinicians in chronic patients with a history of poor adherence and multiple relapses, so the results of the studies (especially in observational studies) should be assessed under this potential bias. However, most of the observational studies also show favorable results for RLAI, although the methodology used to analyze the events following the change of treatment in a patient stabilized to RLAI has serious limitations when interpreting the results. Few of these studies can be considered strictly mirror-image studies, since in many cases, the characteristics and length of the prior treatment are not specified, so it is not possible to do a correct mirror-image comparison after receiving RLAI. In any case, these studies are appropriate to evaluate the efficacy, safety and tolerability of RLAI, but it is risky to extrapolate findings on other variables such as cost–effectiveness or adherence.

Conclusion & future perspective

Schizophrenia is a disorder in which adherence to treatment represents a major challenge [131]. Almost half of all patients with schizophrenia do not comply with their treatment at any given time [132]. The negative consequences of medication nonadherence in patients with schizophrenia are substantial. This concerns the rate of relapse and re-admission, morbidity and mortality, in particular suicide, as well as the economic burden to society [133]. Nonadherence to treatment may explain in part why schizophrenia is one of the major contributors to the global burden of disease, being the fifth and sixth leading cause of disability among males and females, respectively [201]. According to the recommendations of clinical guidelines, LAI would be especially suitable in cases in which adherence is a problem [30], and we support that recommendation, even after seeing the difficulties in extracting the evidence-based indications from the reviewed literature. The periodic mode of administration of LAI (1–6 weeks) ensures that the patient receive the antipsychotic medication and favors a reasonable frequency of visits and interviews with the patient by the medical team [134]. Furthermore, the patient attendance to the depot clinic can be monitored, which allows early interventions tailored to each case to prevent relapse [135]. The issue of nonadherence is of particular significance to patients in the early phases of psychosis, as they have poor insight into the disease. Several authors propose the use of LAIs at the first psychotic episode, as prognostic divides emerge early and chronicity in individual patients may be determined very early in the course of the disease [136]. There is some evidence of good results in acceptance and adherence rates in early diagnosed patients [61,137,138].

The economic implications of the different types of treatment must also be considered: several studies have shown RLAIs to be more cost effective than SGA [79,92,139]. However, prescription of LAIs is much lower than oral antipsychotics [140,141]. LAIs represent 20–40% of all antipsychotic treatments [142]. The percentage varies between countries, from the UK figures (28–36%) [143–145] to those of Switzerland (5%) [146]. The differences between potential and actual rates of prescription of LAIs trigger us to think about the attitudes of doctors, patients and carers towards LAIs. It seems that there are misconceptions and prejudices [32] against LAIs, by both patients and their caregivers and psychiatrists, many of them believing that LAIs are old fashioned, stigmatizing, associated with side effects and costly, or that they should be reserved for chronic patients [147–149]. For example, less than 10% of psychiatrists prescribe LAIs in first episode patients, despite the data on the effectiveness of these drugs in this patient group [61,65,150]. In one study addressing patients' treatment preferences after hospital discharge, patients who had received or were receiving injectable treatment showed a predominantly positive attitude towards LAIs (45 and 75%, respectively), but these positive attitudes reached only 23% in the oral treatment group [151]. The overall positive attitude to oral medication in this study was 88 versus 40% for LAIs. It is believed that patients tend to prefer the route of administration commonly used, and that LAIs generate greater feelings of shame or stigma [148]. A recent systematic review indicates a predominantly positive attitude (four positive studies, one neutral and two negative) among psychiatrists and nurses to LAIs [152]. However, in one study, psychiatrists admitted they had not ever offered this type of treatment to 65% of their patients with schizophrenia because they thought they achieved satisfactory adherence rates with oral treatment [7]. It appears that prescribing patterns of LAIs tend to create a vicious cycle that begins with the therapist's assumption that the patient will refuse LAI treatment [147], so this type of treatment is reserved for those cases

resistant or when there is some sort of judicial involvement that requires compliance, contributing to worsening the image of these treatments compared with new patients, thus encouraging attitudes of rejection towards the LAI. The future development of other new LAIs (i.e., aripiprazol and iloperidone) will help to individualize LAI treatments to suit patient preferences and/or tolerability to side effects. There are some studies comparing FGA-LAI, showing few differences among them [153–159]. Several studies have shown benefits in changing FGA-LAI to RLAI in terms of effectiveness and tolerability [160–163], while others show better adherence for FGA-LAI than for RLAI [164], although the authors recognize that there may be a bias sample, because more severe patients may be more represented in the RLAI group. Future head-to-head studies comparing LAI treatments (both FGA and SGA) are needed, owing to the scarcity of the published evidence available to date.

Obviously, the success in compliance that may be achieved with LAI is not a unique or definitive solution to the problem of lack of adherence to treatment. To develop specific management programs for LAI integrated into mental health programs [165], together with improvements in therapeutic alliance, patients and carers education and counseling, and community support, may enable continuous patient care by qualified personnel and will help to maximize the potential of these treatments to improve adherence and, therefore, clinical outcomes.

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- ▪ of interest
- ▪▪ of considerable interest

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