

LONG-ACTING INJECTABLE ANTIPSYCHOTICS IN FIRST-EPIISODE SCHIZOPHRENIA

GUEST EDITORS: EDUARD PARELLADA, DAWN I. VELLIQAN, ROBIN EMSLEY,
AND WERNER KISSLING





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Schizophrenia Research and Treatment

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Guest Editors: Eduard Parellada, Dawn I. Velligan,
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Editorial

Long-Acting Injectable Antipsychotics in First-Episode Schizophrenia

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Long-acting injectable antipsychotics (LAIAs) may improve adherence to treatment and reduce the rate of relapse and rehospitalization in first-episode or recent-onset schizophrenia (e.g., less than 2 years of illness duration). However, despite their potential advantages, LAIAs are underutilised in clinical practice and the place of LAIAs in the early phases of schizophrenia is still a controversial clinical issue. For example, negative attitudes toward LAIAs in first-episode schizophrenia among psychiatrists are common, and the place of LAIAs for first-episode psychoses (FEPs) remains uncertain in the current clinical guidelines for the pharmacological treatment of schizophrenia. Moreover, a recent paper published in the *New England Journal of Medicine* by Rosenheck et al. [1] reported negative results of LAI risperidone (RLAI) on relapse prevention, although this was in a multiepisode sample. The recent and forthcoming availability of additional second-generation LAIAs (SG-LAIAs), namely, olanzapine pamoate, paliperidone palmitate, aripiprazole, and iloperidone depot, will add interest to this clinical debate for practicing clinicians and researchers interested in this timely topic.

This special issue seeks to define the place of LAIAs in the treatment of first-episode or recent-onset schizophrenia.

S. Zhornitsky and E. Stip present a systematic review examining the efficacy and tolerability of LAIAs versus their oral equivalents in randomized and naturalistic studies. In

addition, they examine the impact of LAIAs on special populations at risk for treatment nonadherence such as patients with FEP, substance use disorders, and a history of violence or on involuntary outpatient commitment. Randomized studies suggest that not all LAIAs are the same in terms of side effects. They also suggest that LAIAs reduce risk of relapse versus oral antipsychotics in schizophrenia outpatients when combined with quality psychosocial interventions. Finally, large-scale naturalistic studies point to a larger magnitude of benefit for LAIAs, relative to their oral equivalent antipsychotics, especially among FEP patients.

One of the original studies (by A. Viala et al.) reports a naturalistic, open-label study of 25 patients in the early phases of schizophrenia treated with RLAI and followed up at least 18 months. The authors found that patients receiving RLAI had a favourable global outcome.

As already mentioned, although not found in all studies [1], there is growing evidence that the risk of relapse is lower with LAIA versus oral antipsychotics. In this sense, two recent studies published in 2011 deserve to be emphasized. First, a recent meta-analysis published by Leucht et al. [2] including all randomized controlled trials (RCTs) comparing LAIAs with oral formulations showed a reduced risk for relapse associated with LAIAs over oral antipsychotics. Second, the Tiihonen et al. [3] cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia in

2,588 FEP patients found that fewer than 50% of patients in the Finnish health care system continue treatment for the first 2 months after an initial hospitalization for schizophrenia. In this study, route of treatment administration also affected relapse rate. LAIAs had a 64% lower relapse rate than equivalent oral medication.

The paper published by R. Přikryl et al. in this special issue reviews the role of SG-LAIAs in treatment of first-episode schizophrenia patients and argues in favour of the use of LAIAs very convincingly in terms of clinical judgment. This paper also focuses on negative attitudes toward injectable medications among psychiatrists being one of the barriers that may explain the underutilization of LAIAs, especially in FEP patients, as reported by Heres et al. [4]. Other barriers to the use of LAIAs (negative attitudes among patients, reimbursement and logistical issues, etc.) should also be addressed. In this sense, some recent strategies for initiating a long-acting injection clinic in public health care centres and initiatives to provide education to prescribers and patients deserve mention: the ShoT At Recovery (A-STAR) program [5], the Munich Compliance Program, and the CERP Program [6]. The former is a LAIA program developed in Texas, based on a multidisciplinary treatment team to support adherence and recovery for patients on LAIAs. The Centres of Excellence for Relapse Prevention (CERP) in Schizophrenia Program is an international educational activity initiated by an international group of expert psychiatrists to address the worldwide issue of relapse among patients with psychotic disorders, especially schizophrenia. It is a new forum for education and information sharing around the topic of relapse and relapse prevention strategies including the early stages of illness.

One additional paper (see B. Kim et al.) reviews clinical trials, survey studies, and current international guidelines on the use of LAIAs in first-episode schizophrenia and considers the pros and cons of this treatment option. The paper presents a brief overview of a few preliminary naturalistic and randomized clinical studies primarily designed to evaluate SG-LAIAs in first-episode schizophrenia. Published clinical guidelines reflect uncertainties in the use of LAIAs in the critical early period of the illness. With some exceptions, the majority of treatment guidelines limit the use of LAIAs to multiple-episode patients and to openly nonadherent patients [7]. Clearly, the current clinical guidelines regarding LAIAs use are too conservative.

The objective of the original research paper published by Ch. Asseburg et al. is to quantify changes in hospital resource use in a naturalistic clinical setting in schizophrenia patients in Finland following initiation of RLAI. Although not primarily focusing on FEP, the study found that consistent reductions in resource use are associated with the initiation to RLAI in Finland. These results agree with several recent studies exploring the issue of health resource utilization and cost-effectiveness [8, 9].

Finally, we would like to outline three unmet research needs concerning LAIAs in FEP for the future.

First, there is a need for better designed RCTs in FEP. There is an absence of long-term RCTs comparing LAIAs with oral medication after FEP regarding efficacy, tolerability,

relapse prevention, and global outcomes. We also need studies examining patient preferences, acceptability, and attitudes toward LAIAs in early phases of the illness, as well as data about nonadherence rates of SG-LAIAs in early phases of the schizophrenia. There is also a lack of cost-effectiveness studies comparing LAIAs with oral antipsychotic treatments specifically focusing on first-episode schizophrenia patients.

Second, the question of whether effective early intervention positively influences long-term outcome needs to be more effectively addressed. We need to know whether we are able to alter disease trajectory to clinical and neurological deterioration that mainly occurs within the first 3–5 years following the onset of the illness. Although there is some evidence to suggest a better global outcome using LAIAs as compared to oral antipsychotics with a reduced risk of relapse and rehospitalization [10, 11], it is still not clear whether these agents can improve biological and clinical outcomes by reducing early relapse and loss of function in first-onset patients. A positive answer for benefits on disease progression would provide support to an emerging literature regarding the neuroprotective effects of the antipsychotics, especially SG antipsychotics [12–14].

Third, we need increased availability of additional SG-LAIAs and to develop more reliable methods of antipsychotic delivery. Given the failure of the long-term oral treatments and keeping in mind that relapse can lead to serious consequences from all perspectives (biological and psychosocial), the future of the schizophrenia pharmacotherapy will hopefully evolve to include better long-term delivery systems such as longer extended release injectable formulations, transdermal patches, subcutaneous implants of antipsychotics, and other long-acting devices like antipsychotic pumps to more effectively address the high risk of relapse due to nonadherence early in the course of illness. Antipsychotic release of skin implants containing risperidone and biodegradable polymers has been already assessed *in vitro* and *in vivo* in animal models [15, 16]. Such devices could however raise concerns regarding the therapeutic alliance and obvious issues of medical ethics that should be appropriately addressed.

To summarize, considering that poor adherence to oral antipsychotic treatments and the very high relapse rates early in the illness due to nonadherence are the rule rather than an exception, from the clinical point of view, psychiatrists should think in terms of relapse prevention from the outset of the illness, identify and overcome local barriers to use LAIAs, and consider the option of SG-LAIAs to all patients with first-episode or recent-onset schizophrenia in a shared decision-making approach. The success of such pharmacological intervention would of course be enhanced by combining with appropriate psychosocial interventions within a relapse prevention program. In this sense, the current clinical guidelines regarding LAIA use in FEP are much too conservative and need to be updated. However, it needs to be remembered that there is still a need for more open-label or double-blind RCTs in early phases of schizophrenia, regarding the long-term efficacy, safety, global functional outcome, and cost-effectiveness of SG-LAIAs compared to oral antipsychotics in order to obtain a more

robust clinical database for evidence-based medicine. Such studies will also define whether or not LAIAs introduced early in the course of the schizophrenia illness can alter the disease trajectory.

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Review Article

Long-Acting Injectable Antipsychotics for First-Episode Schizophrenia: The Pros and Cons

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Clinical and psychosocial deterioration associated with schizophrenia occurs within the first few years following the onset of the illness. Therefore, to improve the long-term prognosis, it is important to provide schizophrenia patients with intensive treatment following their first episode. Relapse is highly associated with partial medication adherence or nonadherence in patients with first-episode schizophrenia. Recent studies suggest that long-acting injectable (LAI) antipsychotics compared with oral antipsychotics are more effective for medication adherence and relapse prevention. Moreover, some clinical guidelines for the treatment of schizophrenia suggested that LAI antipsychotics should be considered when patients are nonadherent “at any stage.” Decreased compliance is a common cause of relapse during the initial stages of the disease. Therefore, LAI antipsychotics should be highly considered when treating patients with first-episode schizophrenia. In the present paper, clinical trial data and current guidelines on the use of LAI antipsychotics for first-episode schizophrenia are discussed as well as the pros and cons of this treatment option.

1. Introduction

Schizophrenia is a chronic disorder characterized by periods of illness alternating with periods of full or partial remission. Previous studies [1, 2] suggest that schizophrenia is a neurodegenerative disease associated with frequent relapses. This alternating nature of the illness causes neurotoxicity in the brain, thereby resulting in structural abnormalities, including ventricular enlargement and cortical atrophy. Recent evidence further suggests that progressive structural changes in the brain occur within the initial years following a diagnosis [3–5]. Moreover, with each subsequent relapse after the first episode, it usually takes longer time to reach remission [6]. The primary clinical and psychosocial deterioration associated with schizophrenia occurs within the first 5 years following the onset of the illness, called the

critical period [7, 8]. Therefore, it is important to provide intensive biopsychosocial interventions during the critical period in an effort to improve the long-term prognosis.

The primary goal of treatment during the critical period is to prevent a subsequent relapse and to restore socio-occupational functioning to the premorbid level. The relapse rate in patients with first-episode schizophrenia is relatively low during the first year of the illness but substantially rises to rates of 53.7% and 74%–81.9% after 2 and 5 years, respectively [9, 10]. The most common cause of relapse in patients with schizophrenia is a lack of adherence to oral medication [11, 12]. The discontinuation of antipsychotics in patients with first-episode schizophrenia or schizoaffective disorder increases the risk of relapse by approximately five times [9]. The rate of medication discontinuation in individuals with first-episode psychosis ranges from 26% [13] to 44% [14]

during the first year. Coldham et al. [15] reported a 59% rate of poor adherence (39% nonadherent and 20% inadequately adherent) within the year after the first episode. None of the interventions currently used to improve adherence have been completely reliable in the treatment of schizophrenia. Long-acting injectable (LAI) antipsychotics, however, may improve medication adherence and possibly reduce relapse in patients with schizophrenia [16]. The Texas Medication Algorithm Project Antipsychotic Algorithm for schizophrenia [17] recommended that clinicians should assess contributing factors and consider LAI antipsychotic preparations in patients who are inadequately adherent at any stage. Previous studies have suggested that LAI antipsychotics may be more effective for maintaining medication adherence [18] and preventing relapse [19] in first-episode schizophrenia compared with oral antipsychotics. Clinically, however, the majority of psychiatrists use LAI antipsychotics very conservatively [20, 21]. Moreover, very few psychiatrists offer LAI antipsychotics after a patient's first psychotic episode [22]. Recently, Osborne et al. (2012) reported that society associates a higher utility with increasing time between injections, with 4-weekly and 3-monthly administration of an antipsychotic LAI representing an advance over 2-weekly administration in the health-related quality of life (HRQoL) of patients with schizophrenia [23]. They discussed that participants from the general population preferred less frequent injections given the psychological stress and pain associated with injections as well as the burden related to the requirement of travel to outpatient clinics for their administration. In this regard, currently available option of LAI antipsychotic with one month injection interval would add substantial value to the improvement of quality of life in patients with schizophrenia and their family members. Optimal therapeutic outcomes associated with first-episode psychosis are often compromised by early treatment discontinuation and poor treatment adherence; therefore, LAI antipsychotics should be more actively considered with first-episode schizophrenia.

The present paper reviews the relevant literature including clinical drug trials, survey studies, and clinical guidelines on the use of LAI antipsychotics in patients with first-episode or recent-onset schizophrenia. Moreover, the pros and cons of LAI antipsychotic used with first-episode schizophrenia are discussed.

2. Overview of Clinical Studies on the Effectiveness of Long-Acting Injectable Risperidone Treatment for First-Episode or Recent-Onset Schizophrenia (Table 1)

In a study by Parellada et al. [24], 382 patients received long-acting injectable risperidone (RLAI) treatment during the early stages of their disease (i.e., within 3 years of diagnosis). The study, conducted in Europe, evaluated the efficacy and safety of RLAI. It was an open-label, nonrandomized, and single-arm, multicenter study that consisted of a 6-month treatment period. Significant improvements in total Positive and Negative Syndrome Scale (PANSS) scores were noted at the first visit and continued to improve through the end of

the study. At the end of the study, 148 patients (40%) displayed an improvement in total PANSS and subscale scores. Functioning is also improved from baseline to endpoint, with a mean Global Assessment of Functioning (GAF) score of 57.6 (± 6.5) at baseline and a mean GAF score of 65.3 (± 18.3) at the end of the study. Adverse events were reported by 263 patients (69%), including extrapyramidal symptoms. These symptoms, however, improved significantly over the 6-month treatment period. Parellada [25] also reported that individuals treated with RLAI, including patients with first-episode schizophrenia, demonstrated improvement in symptom severity and compliance as well as a reduction in the rate of relapse and a favorable tolerability profile.

According to a study that compared RLAI and oral risperidone for the treatment of first-episode schizophrenia [19], significant improvements in PANSS, GAF, and Clinical Global Impression (CGI) were noted in the RLAI group compared with the oral risperidone group. No significant differences in extrapyramidal symptoms or frequency of prolactin-related adverse effects were noted in either group. Moreover, medication adherence was higher, and the relapse rates at 1 and 2 years were significantly lower in the RLAI group. The oral risperidone group showed significantly greater nonadherence. In the study, the amount of time to nonadherence predicted the relapse in patients with first-episode schizophrenia. The authors proposed that RLAI may be effective in preventing relapse through maintaining medication adherence. The authors [30] also emphasized that psychosocial interventions for relapse prevention may be effective for maintaining medication compliance in patients with schizophrenia who receive RLAI.

A single-site open-label study of 50 patients with first-episode schizophrenia who were treated with RLAI [26] found that 32 patients (64%) achieved remission. Of the 32 patients, 31 (97%) maintained remission throughout the study. The remission and nonremission groups were compared based on clinical, functional, and quality-of-life outcome measures. The remission group showed significantly greater improvements on the CGI-Severity (CGI-S) scale and PANSS total score and also displayed improvements in extrapyramidal symptoms. Remission patients received lower doses of RLAI and showed greater improvement in social functioning compared with the nonremission group in the study. Multivariate level analyses showed that the chance of remission increased in females. Early symptom improvement was also significantly associated with remission. Moreover, less decline in the PANSS score was associated with a reduced likelihood of remission. The remission rate in this study compared favorably with that reported in previously published studies could be benefit of assured antipsychotic delivery and better adherence of treatment of RLAI. In another study conducted at the same site [26], compared with patients treated with oral risperidone or haloperidol, RLAI-treated patients had significantly fewer all-cause discontinuations (26% versus 70% at 24 months), greater symptom reduction according to PANSS total score (-39.7 versus -25.7), higher remission rates (64% versus 40%), lower relapse rates (9.3% versus 42%), and lower extrapyramidal symptoms [27].

TABLE 1: Overview of clinical studies on the effectiveness of long-acting injectable antipsychotics for the treatment of first-episode or recent-onset schizophrenia.

Study	No. of patients (female/male)	No. of previous episodes	Duration of illness	Study duration	Design	Dosage	Reduction of total PANSS (%)	Reduction of CGI-S (%)	Functional improvement (%)	Tolerability	Adherence	Long-term outcome
Parellada et al. [24]	382 (117/265)	ns	1.5 (1.1) yr	6 mo	Open, 1-arm, mc	25–50 mg	18.3%	ns	GAF 13.4%	ESRS 53.8% ↓ PRL-related 0.3% wt gain 4%	ns	ns
Kim et al. [19]	RLAI: 22 (14/8) Oral: 28 (17/11)	1	1.5 (1.5) yr	2 yr	Open, C	25–50 mg	RLAI: 10.0% Oral: 2.0%	RLAI: 10.0 Oral: 2.5	GAF RLAI: 26.9% Oral: 0.5%	ns	RLAI: GA (>70%) 68% Oral: GA 32%	2-yr relapse RLAI: 23% Oral: 75%
Emsley et al. [26]	50 (18/32)	1	≤1 yr	2 yr	Open, 1-arm	25–50 mg	Remission: 45.0% No remission: 29.7%	Remission: 73.1% No remission: 34.4%	SOFAS remission: 85.2% No remission: 43.2%	ESRS 53.3% ↓ in remission; 55.0% ↓ in no remission	ns	2-yr remission 62%
Emsley et al. [27]	RLAI: 50 (18/32) Oral: 47 (20/27)	≤2 adm	≤1 yr	2 yr	Open, 1-arm Oral: R, C (ris versus hal)	25–50 mg	RLAI: 44.0% Oral: 28.8%	ns	ns	Total maximum changes of ESRS RLAI: 1.40 (2.60) Oral: ris 5.61 (5.22) hal 9.04 (6.21)	ns	2-yr remission RLAI: 64.0% Oral: 40.4%
Weiden et al. [18]	RLAI: 19 Oral: 11	1	≤16 wk of lifetime AP exposure	12 wk	Open, R, C	25–37.5 mg	ns	ns	ns	ns	RLAI: 89% Oral: 59%	ns
Napryeyenko et al. [28]	294 (116/178)	2.4 (0.7)	≤2 yr	26 wk	Open, 1-arm, mc	25–50 mg	18.6%	20.5%	GAF 16.9%	EPS 5.6% PRL-related 4.3% wt gain 3.0%	NC, n = 3	1-yr remission 59.5%
Dubois et al. [29]	105 (79/26)	<4	3.0 (3.92) yr	12 mo	Open, 1-arm, mc	25–50 mg	ns	43.4%	GAF 71.1%	EPS 3.8% PRL-related 9.5% wt gain 18.1%	>80%	1-yr remission 34.1%

PANSS: Positive and Negative Syndrome scale; CGI-S: Clinical Global Impression-Severity scale; GAF: Global Assessment of Functioning; SOFAS: Social Occupational Functioning Assessment scale; ESRS: Extrapyramidal Symptom Rating scale. adm: hospital admissions for psychosis; AP: antipsychotics; C: controlled study; EPS: extrapyramidal symptoms; GA: good adherence (>70%) group; hal: haloperidol; mc: multicenter; mo: month; NC: non-compliance; ns: not specified; open: open-label; oral: oral risperidone; PRL: prolactin; pts: patients; R: randomized; ris: risperidone; RLAI: long-acting injectable risperidone; wk: week; wt: weight; yr: year; 1-arm: single arm.

A randomized controlled trial reported on acceptance and initial adherence outcomes with RLAI treatment in patients with first-episode schizophrenia [18]. According to the results, 73% of subjects (19 out of 26) randomly assigned to receive RLAI accepted. Individuals who took RLAI were significantly more likely to remain adherent at 12 weeks compared with patients treated with oral antipsychotics. The authors suggested that better adherence was achieved in patients who received RLAI through two possible explanations. One is that starting treatment with RLAI might have direct adherence benefits in preventing or delaying nonadherence in some individuals. The other one is that refusal of the RLAI recommendation is a sign that the patient plans to stop oral medication in the very near future, which means that the more important thing is not so much the RLAI itself but the will to stay on treatment with any antipsychotics. The researchers anticipated that some patients would refuse the RLAI recommendation; however, they found that about 73% of subjects accepted the recommendation for treatment with RLAI. This suggests the feasibility and acceptability of LAI antipsychotics as a treatment strategy during the early stages of schizophrenia.

According to an open-label noncomparative study of recent-onset schizophrenia [28], patients showed good progress as indicated by symptom reduction, improved functional outcomes, and improved health-related quality of life. Rabinowitz et al. [31] also demonstrated that improved premorbid functioning in patients with schizophrenia is predictive of increased treatment response with RLAI as measured by clinical rating scales of symptoms and functioning, health care-related quality of life, and remission.

A multicenter, nonintervention, observational study on the clinical effectiveness of RLAI administration was published in 2011 [29]. Treatment with RLAI for 12 months during the early stages of schizophrenia was associated with significant improvements in clinical and functional outcomes in patients. This investigation suggested the effectiveness of RLAI for treatment of patients early in the course of schizophrenia in a similar vein to previous studies [19, 26] with the result from relatively large subjects ($n = 105$).

A recent study by Bartzokis et al. [32] compared RLAI and oral risperidone treatment in subjects with first-episode schizophrenia. The study focused on changes in frontal lobe myelination and cognitive functioning. White matter (WM) volume remained stable in the RLAI group and decreased significantly in the oral risperidone group, resulting in a significant difference on the effects of treatment. RLAI seems to promote myelination and stabilizes frontal lobe WM volume compared with oral risperidone. Moreover, the changes in frontal lobe WM volume were positively associated with higher-order executive functioning, working memory, and mental flexibility. No significant volume changes were noted in the frontal lobe. The authors suggested that the changes in WM and gray matter (GM) represent a myelination-driven shift of the GM/WM boundary into or out of the cortex. The myelination trajectory was significantly quadratic (inverted U) and peaked at 1 year of antipsychotic treatment. This was followed by a premature decline compared with healthy subjects who do not decline until after the fifth decade of

life. The nonsignificant increase in WM volume observed with RLAI suggests that the trajectory defined by oral antipsychotic treatment may be modifiable with RLAI. Therefore, the consistent medication levels that are achieved with RLAI may result in a higher WM volume, which may subsequently impact cognitive performance.

Although favorable results of LAI antipsychotics have been reported for patients with first-episode or recent-onset schizophrenia, the effectiveness of LAI treatment for patients with chronic schizophrenia remains controversial. A meta-analysis of depot antipsychotics was conducted in 2001 [33]. This report suggested that depot antipsychotics were statistically better for global improvements compared with oral antipsychotics. However, relapse, attrition, and adverse effects were not significantly different. In addition, a recent long-term randomized controlled trial that included patients with unstable schizophrenia [34] demonstrated that RLAI was not superior to oral treatment in terms of duration of adherence, time to rehospitalization, clinical symptoms, or improvement in functional outcome. Moreover, this study reported that RLAI treatment was associated with more local injection site and extrapyramidal adverse effects. On the other hand, the recent meta-analysis [35] comparing LAI with oral antipsychotics showed that a reduced risk for relapse was associated with LAI over oral antipsychotics. To clarify clinical issue related to the use of LAI antipsychotics in first-episode or recent-onset schizophrenia, further studies, especially randomized controlled trials, are warranted especially with regard to the effectiveness on relapse or rehospitalization.

3. The Pros and Cons of LAI Antipsychotics (Table 2)

The general attitude of psychiatrists toward depot antipsychotics is negative. Depot antipsychotics are considered old-fashioned, stigmatized, and less acceptable to patients. Many psychiatrists stated that first-generation depots are avoided because of the threat of extrapyramidal side effects, whereas second-generation LAI drugs are associated with high treatment costs [20]. It is of interest to see two opposing opinions about the use of LAI drugs in first episode of psychosis in the recent surveys. Over half of the psychiatrists in the UK who participated in a survey agreed that LAI drugs can be used in patients with first-episode psychosis [21]. In contrast, Heres et al. [20] reported that the majority of psychiatrists (64–71%) applied the “no depot in first-episode psychosis” rule. They also recently investigated factors associated with psychiatrist’s negative attitude toward offering depot treatment to first-episode patients and found that three factors, limited availability of different second-generation antipsychotic depot drugs, the frequent rejection of the depot offer by the patients, and the patients’ skepticism based on the lack in experience of a relapse, were of marked influence [36]. In a study conducted in Switzerland, fewer than 10% of psychiatrists offered depot treatments in response to the first psychotic episode [22]. Given that psychiatrists are relatively conservative in offering

TABLE 2: The pros and the cons of using long-acting injectable (LAI) antipsychotics for the treatment of first-episode schizophrenia.

Pros	Cons
High relapse caused by poor compliance could be prevented	Because of uncertainty of diagnosis for those in first-episode psychosis, prescribing LAI drugs may be stigmatizing and may hamper therapeutic relationships
Some high-functioning individuals may prefer depot formulations	Discourage patient's motive to recover because of the general perception that an injectable treatment means a more severe condition with respect to the illness
Favorable side effect profile due to low variation in the peak and trough levels would have positive effects on drug compliance	For those with first-episode schizophrenia showing a positive outcome, the goal of treatment is to gradually reduce the dosage of antipsychotics, which does not fit the traditional goals of LAI drugs
Best time to prescribe LAI drugs may be just before discharge	It is difficult to adjust the dosage of LAI drugs quickly in response to side effects; therefore, LAI treatment may negatively affect subsequent treatment compliance during the critical period

information about depot antipsychotics [22] and that some patients feel positively toward treatment with depot medication [37, 38], more patients with first-episode psychosis may accept LAI medication if psychiatrists provided them with adequate information. The best rationale for using LAI antipsychotics in first episode of psychosis comes from the fact that frequent relapses occur during first few years of the illness, and there is evidence for decreased rate of relapse with LAI medication compared to oral antipsychotic drug in first-episode schizophrenia [19, 30, 39]. Another advantage may be that LAI antipsychotics can improve patient's quality-of-life overtime with more possibilities to meet friends and family, to live a more stable and independent life, outside the psychiatric hospital [40]. Patients with schizophrenia are more sensitive to adverse drug effects during the first few years of the illness [41–43]; therefore, the low incidence of adverse events caused by low variation in peak and trough levels of LAI antipsychotics may have additional benefits for pharmacological compliance during the critical period. Some people argued that the best time to prescribe LAI antipsychotics is just prior to discharge. One argument against the use of LAI antipsychotics for the treatment of first-episode psychosis may be related to the uncertainty of the diagnosis. If brief psychotic disorder, not otherwise specified (NOS) psychotic disorder, or schizophreniform disorder is suspected, the recommended duration of treatment should be much shorter, and a greater portion of patients may have a chance of recovery than in case of schizophrenia. For such cases, the patient's autonomy is even more important in the process of treatment decision. Because of negative association of injection with coercion, recommending LAI antipsychotics by treating doctors would hamper therapeutic relationship. Moreover, it would discourage patient's motive to recover because of the general perception that injection treatment option usually means severe condition of the illness. Moreover, due to the difficulty of adjusting the dose of LAI drugs quickly in response to side effects, treatment compliance may be negatively affected during the critical period. To improve the conservative attitude of psychiatrists with respect to LAI antipsychotic treatment for patients with first-episode schizophrenia, several issues must be tackled. First, the development of more accurate subjective or

objective measures that predict or detect drug compliance in patients with first-episode schizophrenia should be pursued. Second, more diverse second-generation depot formulations should be available for the current clinical practice, like paliperidone palmitate, olanzapine pamoate, aripiprazole, or iloperidone depot. The development of completely different formulae, such as a patch drug containing olanzapine [44] or risperidone [45], would have wide applicability for patients with first-episode schizophrenia because one of the primary reasons why individuals reject LAI drugs is the fear of needles. Third is about using financial incentives may improve adherence to antipsychotic maintenance medication [46]. This applies not only to first-episode schizophrenia but also to multiple-episode chronic schizophrenia and raises its ethical issues [47]. In Japan, counseling and management fees have been used for depot antipsychotics since 1990 to promote the use of depot antipsychotics for schizophrenia (personal communication). It remains to be seen how financial incentives will unfold especially in relation to first-episode schizophrenia.

4. Guidelines for the Treatment of First-Episode Schizophrenia with LAI Antipsychotics

According to the American Psychiatric Association [48], LAI antipsychotic medication is recommended for patients with recurrent relapses related to partial or full nonadherence. Also, the Canadian clinical practice [49] recommends LAI formulations to reduce nonadherence in multiple-episode patients or patients with persistent positive symptoms. The International Psychopharmacology Algorithm Projects (IPAPs) schizophrenia algorithm (<http://www.ipap.org/schiz/>) suggested that depot antipsychotics were recommended in patients with partial or complete non-compliance. However, there was no mention of LAI for the treatment of first-episode schizophrenia. These guidelines, therefore, limit the use of LAI to patients characterized as multiple episodes or noncompliance.

However, there have been subtle changes in more recent guidelines. For example, the procedural manual by the Texas Medication Algorithm Project [17] recommends

that the clinicians assess contributing factors and consider LAI antipsychotics in patients who are inadequately adherent “at any stage.” It means that LAI could be used even in first-episode schizophrenia if the patients are not enough adherent to their medications. Similarly, in 2009, the National Institute for Health and Clinical Excellence (NICE) guidelines regarding schizophrenia (<http://www.nice.org.uk/CG82>) stated that clinicians should consider offering depot/LAI antipsychotic medications to patients with schizophrenia who would “prefer such treatment after an acute episode and where avoiding covert non-adherence to antipsychotic medication is a clinical priority” within the treatment plan. Kane and Garcia-Ribera [50] also mentioned that LAI can be indicated to “any schizophrenia” patients requiring long-term treatment, nonadherent, or having risk of relapse. They further suggested that even if patients refuse this option, it would be better to help them understand the potential advantages. On the other hand, recent guidelines from the British Association for Psychopharmacology [51] described that the place of antipsychotic depot/long-acting injections for first-episode schizophrenia remains uncertain on account of the absence of long-term data comparing LAI with oral antipsychotics after first-episode schizophrenia.

It is still true that LAI has a conservative position in treating first-episode schizophrenia according to the majority of the current guidelines. Nevertheless, considering the results from LAI studies in first-episode psychosis previously, future guidelines might be needed to update a treatment option to recommend LAI antipsychotics for any patients with schizophrenia who showed poor adherence attitude and behavior including first-episode schizophrenia.

5. Conclusions

With the availability of the different second-generation LAI antipsychotics, there are improved treatment options for schizophrenia in terms of duration of action and side effects. Psychiatrists, however, seem to conservatively use depot formulations and mostly introduce them after several episodes. The acceptability of prescribing LAI antipsychotics to patients with first-episode psychosis is currently under debate. Many clinical and technical issues should be addressed to encourage increased acceptability of LAI antipsychotics for the treatment of patients with first-episode schizophrenia. Nevertheless, given that low compliance is a frequent cause of relapse in the early course of schizophrenia, more active consideration of LAI drugs should be encouraged, and patients should be informed about the different types of medication that are available during the early stages of the illness. Further studies, especially randomized controlled trials, are urgently needed to clarify the advantages of second-generation LAI antipsychotics in patients with first-episode schizophrenia.

Disclosure

The English in this document has been checked by at least two professional editors, both are native speakers of

English. For a certificate, please see <http://www.textcheck.com/certificate/Wh824O>.

Conflict of Interests

The authors declare that they have no conflict of interests with any commercial or other associations in connection with this paper.

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Clinical Study

Hospitalisation Utilisation and Costs in Schizophrenia Patients in Finland before and after Initiation of Risperidone Long-Acting Injection

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Objectives. Quantify changes in hospital resource use in Finland following initiation of risperidone long-acting injection (RLAI). **Materials and Methods.** A retrospective multi-center chart review (naturalistic setting) was used to compare annual hospital bed-days and hospital episodes for 177 schizophrenia patients (mean age 47.1 years, 52% female, 72% hospitalized) before and after initiation of RLAI (between January 2004 and June 2005) using the within-patient “mirror-image” study design. The base case analytical approach allocated hospital episodes overlapping the start date entirely to the preinitiation period. In order to investigate the impact of inpatient care ongoing at baseline, the change in bed-days was also estimated using an alternative analytical approach related to economic modelling. **Results.** In the conventional analysis, the mean annual hospitalisation costs declined by €11,900 and the number of bed-days was reduced by 40%, corresponding to 0.19 fewer hospital episodes per year. The reductions in bed-days per patient-year were similar for patients switched to RLAI as inpatients and as outpatients. In the modelling-based analysis, an 8% reduction in bed-days per year was observed. **Conclusion.** Despite uncertainty in the choice of analytic approach for allocating inpatient episodes that overlapping this initiation, consistent reductions in resource use are associated with the initiation of RLAI in Finland.

1. Introduction

Schizophrenia is a serious mental illness causing significant social or occupational dysfunction. With an annual global incidence of 8 to 40 individuals per 100,000 per year [1], the total costs of treating schizophrenia are high [2] and may be as much as 3% of all health expenditures [3]. Most of the direct costs of schizophrenia (79%) result from hospitalisation or other residential care [3], thus a principal aim of treatment in schizophrenia patients is to prevent relapse, reduce the requirements for in-hospital treatment, and enable patients to lead near-normal lives.

Pharmacological treatments for schizophrenia have been available since the mid-1950s. The first class of medication,

“typical antipsychotics,” is effective at treating psychotic symptoms but, while still used widely, is associated with problematic extrapyramidal side effects. The second generation of drugs, “atypical antipsychotics,” became available in the 1990s and may cause fewer extrapyramidal side effects, though medication noncompliance continues to be common in schizophrenia patients in part because of serious metabolic concerns. Long-acting depot formulations of some first-generation antipsychotic agents have been developed to improve medication compliance by shifting responsibility from unpredictable patients to their health care providers [2], and the extent to which long-acting injectable medication can reduce rates of relapse and rehospitalisation is a topic of active research [4].

Risperidone long-acting injection (RLAI, available in many countries as RISPERDAL CONSTA) is the first long-acting depot formulation of an atypical antipsychotic and was introduced in Finland in February 2003. Administered once every two weeks by intramuscular injection, RLAI provides steadier plasma levels than oral formulations and hence a more consistent relief of symptoms and lower rates of side effects [3].

While the unit cost of RLAI is higher than the unit costs of alternative antipsychotics at comparable doses, RLAI may provide a number of potentially offsetting economic benefits (in particular, reduced healthcare costs related to relapse and hospitalisation [3]). Indeed, a number of studies have identified reductions in hospital admission rates following initiation of risperidone in a host of countries. For example, Eriksson and colleagues [5, 6] found a 65% reduction in annual inpatient bed-days in Sweden; Chue and colleagues [7] found that the number of patients requiring hospitalization decreased continuously from 38% in the 3 months prior to RLAI to 12% after 1 year of treatment in an international study; Fuller and colleagues [8] found reductions of 37% in psychiatric-related hospitalizations and 56% in psychiatric-related hospital bed-days in the USA; Niaz and Haddad [9] found roughly 50% reductions in both number of admission and hospital days per patient-year in the UK though Taylor et al. [10] found little difference; Su and colleagues [11] found reductions in hospital admissions of 55% and inpatient bed-days of 48% in Taiwan; Willis and colleagues [12] found reductions of 27% in hospitalization rate and 45% in hospital bed-day; Carswell and colleagues [13] found that patients in New Zealand had fewer hospital admissions but longer lengths of stay. Health care is setting specific, however, and the economic efficiency of interventions in one country is seldom generalizable to another. We are not aware of data for Finland.

2. Aims of the Study

This study aim is to estimate the change in resource usage, hospitalisation rates, and costs seen in actual practice in Finland for schizophrenia patients before and after initiation of treatment with RLAI.

3. Patients and Methods

3.1. Study Design. We collected data using a retrospective, observational review of patient charts for patients suffering from schizophrenia or schizoaffective disorders and treated with RLAI in Finland. To estimate the changes in resource use associated with RLAI treatment, data for the periods before and after initiation are compared on a patient-by-patient within-subject basis (sometimes labelled “mirror-image” analysis [14]).

3.2. Endpoints. Outcome measures include the differences in the mean number of inpatient hospital bed-days per year, the mean rate of hospitalisation per year, and the mean annual

costs of inpatient hospital care related to schizophrenia (reported in 2007 €).

3.3. Ethics Approval. Ethics approval was sought from the ethics review board at the Joint Municipal Authority for Medical and Social Services in North Karelia and granted. Informed consent was not required.

3.4. Patient Selection. Based on participation in previous studies or because they were known to use RLAI, 10 Finnish psychiatry sites were selected to participate: Pohjois-Karjala central hospital (Paihola), Harjavalta psychiatric hospital (Harjavalta), Pori mental health care centre (Pori), Turku city psychiatry department (Turku), Kaivanto psychiatric hospital (Kangasala), TaUCH Pitkänieniemi hospital (Pitkänieniemi), Helsinki and Uusimaa hospital district area Kellokoski psychiatric hospital (Kellokoski) and Tammiharju psychiatric hospital (Tammisaari), Kitee mental health care centre (Kitee), and Helsinki city psychiatric department (Helsinki).

Patients who participated in any RLAI clinical trial were excluded from this study. The inclusion criteria were at least 18 years old, diagnosed with schizophrenia or schizoaffective disorder, first initiation of RLAI treatment between 1 January 2004 and 30 June 2005, and medical chart record covering at least two years prior to RLAI treatment and at least until 31 July 2006. At each study site, investigators aimed to enlist all eligible subjects up to a maximum of 40 (to prevent overrepresentation of some sites).

3.5. Data Analytic Procedures. Single hospital episodes were recorded in the data collection forms using dates of admission and discharge. Hospitalisations that involved changes in level of care (psychiatric, psychiatric intensive, and forensic) were recorded in the hospital charts as a sequence of separate “episodes” with individual dates of admission and discharge. We merged these into a single episode except when calculating hospital costs.

When attributing observed resource use to RLAI or the prior treatment, hospitalisation episodes that overlapped the index initiation RLAI must be allocated to the periods before and after the index initiation. Given the seriousness of schizophrenia, withdrawal effects associated with the previous drugs [15], and time to adequate blood serum levels for most depot formulations (RLAI reaches satisfactory blood serum levels first after 3 weeks, until which time additional antipsychotic treatment is required to maintain adequate control [16]), an improvement sufficient for discharge to occur instantaneously after RLAI initiation cannot be expected. An intent-to-treat definition based strictly on the day of initiation, thus, would artificially penalise the RLAI by attributing the consequences of the failure of previous medications (and consequent poor health requiring hospitalization) to the postinitiation treatment.

We adopt the simple allocation rule used by Fuller and colleagues [8], Niaz and Haddad [9], and others, who assigned the entire episode of hospitalisations ongoing at the time of initiation to the treatment ongoing at admission

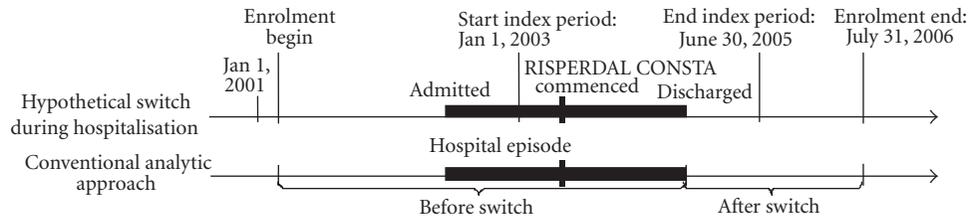


FIGURE 1: Illustration of the conventional allocation rule for hospitalisation episodes ongoing at the time of initiation. The start of the post-initiation period is adjusted so the entirety of hospitalisations episode overlapping the initiation date are included in the pre-switch period.

TABLE 1: Patient characteristics at time of initiation of RLAI.

Variable	N	Mean
Age (years)	177	47.1 (SD 13.6) Range 22–84
Female (%)	177	92 (52.0%)
Disease duration		
Years	137*	15.3 (SD 12.5)
% less than 4 years	137*	31 (17.5%)
% 4 to 10 years	137*	44 (24.8%)
% more than 10 years	137*	102 (57.7%)
GAF (raw score)	21*	22.5 (SD 13.9) Range 5–60
GAS (raw score)	49*	35.2 (SD 9.6) Range 19–58
CGI-S (%)		
Normal	177	0
Borderline or mildly Ill	177	1 (0.6%)
Moderately Ill	177	2 (1.1%)
Markedly Ill	177	16 (9.0%)
Severely or among most extensively Ill	177	8 (4.5%)
Unknown	177	150 (84.7%)
Occupational status (%)		
Full time	177	2 (1.1%)
Part time	177	0
Sheltered work	177	1 (0.6%)
Unemployed	177	13 (7.3%)
Retired	177	121 (68.4%)
Long-term sick leave	177	33 (18.7%)
Other	177	7 (4.0%)
Unknown	177	0
Accommodation status (%)		
Psychiatric nursing home	177	15 (8.5%)
Sheltered living	177	5 (2.8%)
With parents or relatives	177	20 (11.3%)
Own apartment	177	125 (70.6%)
Other	177	12 (6.8%)
Unknown	177	0

* Missing information resulted in reduced sample sizes.

(“conventional analytic approach,” Figure 1). This approach seems reasonable because hospital resource use is more likely attributable to the treatment that was ongoing and failing at admission (possibly due to insufficient efficacy, sideeffects, or

low adherence) than to a treatment that was begun after admission to hospital. The start of the exposure period to RLAI in a patient hospitalised when initiating RLAI is then adjusted to the date of hospitalisation episode discharge. Conservatively, patients who were initiated on RLAI as outpatients are assumed to start the post-initiation period at the actual time of initiation. The end of the exposure period is at death or study completion (31 July 2006), whether or not the patient was still taking RLAI. The control period runs from 2 years prior to treatment initiation with RLAI to the start of the treatment exposure period.

By allocating to the prior treatment the entirety of the hospitalisation episodes that overlap the initiation, the conventional analytic approach may bias the results in favour of RLAI. This bias is stronger in proportion to the prevalence and length of overlapping hospitalisation episodes and ameliorated by longer study follow-up durations. Because this allocation affects only measures of resource use on-going at the time of initiation (bed-days and hospital costs), whereas a hospitalisation event is clearly before or after initiation, this source of bias does not apply to the endpoint of hospitalisation rates.

To investigate the sensitivity of study results to this allocation rule, we conducted two additional analyses. First, the primary endpoints are presented separately for patients who were hospitalised and were not hospitalised at the time of initiation. Results for the subgroup who started RLAI as outpatients are unaffected by this bias. Second, we present an alternative approach in which we model the change based on the fact that the number of bed-days per year is the product of annual hospitalisation rate and average length of inpatient stay per episode. Specifically, we multiply the empirical estimates of hospitalisation rates before and after the initiation of RLAI by the average lengths of stay per hospitalisation episode *strictly before* and *strictly after* initiation. This modelling-based estimate of resource use eliminates the effect of hospitalisation episodes ongoing at the time of initiation.

In analyses of inpatient bed-days, number of episodes, and hospitalisation costs, the unit of analysis is the patient. Results are presented as mean, standard error, and two-sided 95% confidence intervals. A difference was interpreted as statistically significant if the confidence interval for the estimated mean difference did not contain 0. To estimate the costs of hospital resource use, the recorded durations of episodes were multiplied by unit costs for bed-days in the different levels of inpatient service [17, 18]. Adjusted to 2007 € prices using Finnish price indices, the costs per bed-day are

TABLE 2: Length of follow-up and of hospitalisation episodes.

Variable	N	Mean	Standard deviation	Min	Max
Follow-up prior to initiation of RLAI (years)	177	2.00	—	—	—
Follow-up following initiation of RLAI (years)	177	1.80	0.45	0.43	2.56
Proportion of patients hospitalised at initiation of RLAI	177	127 (72%)	—	—	—
Hospital length of stay (days per episode)					
All Episodes	576	65.0	95.4	0*	816
Episodes strictly before RLAI initiation	227	45.6	53.2	1	405
Episodes overlapping RLAI initiation	128	120.1	145.0	9	816
Episodes strictly after RLAI initiation	221	53.0	80.3	0*	638

* Inpatient hospitalisation episodes that recorded discharge on the day of admissions were assigned a duration of zero days.

€280.46 for standard psychiatric care, €542.48 for psychiatric intensive care, and €510.00 for forensic care.

Additional subgroup analyses were carried out with regard to type of previous antipsychotic treatment based on recorded treatments on the day of initiation of RLAI or the previous day. Patients are classified into the following five mutually exclusive categories: typical oral only, typical depot only, atypical oral only, combination of any of these, or untreated (which does not necessarily imply drug-naïve).

4. Results

4.1. Descriptive Results. Data were collected for 199 patients. Twenty-two subjects were excluded from analysis because they were hospitalised before the start of RLAI and not discharged before the end of follow-up (2 patients), the start date of RLAI could not be established ($n = 6$), their RLAI prescription record was incomplete or inconsistent ($n = 5$), they started RLAI before 1 January 2004 ($n = 2$), or the number and duration of hospitalisation episodes could not be clearly established ($n = 9$). Multiple exclusion criteria applied to 2 patients. The analysis sample, thus, consists of 177 patients.

Descriptive statistics for the patient population at the time of initiation to RLAI are presented in Table 1. Mean age at initiation of RLAI therapy was 47.1 years, 52% of the sample was female, and mean disease duration was 15.3 years. Patient functioning was poorly documented in hospital charts. Indeed, only 21 had a recorded Global Assessment of Functioning (GAF) score, only 49 had a recorded Global Assessment Scale (GAS) score, and only 27 had a recorded Clinical Global Impressions Scale (CGIS) score, and 92 patients had neither.

The lengths of the coverage periods and hospitalisations are presented in Table 2. By definition, two years of data on each patient are available prior to the initiation. Postinitiation data coverage ranges from 0.43 years (five patients died during study follow-up) to 2.56 years, with a mean of 1.80 years. 576 hospitalisation episodes were recorded during the study, of which 227 were entirely before the initiation of RLAI and 221 were entirely after the initiation. 128 patients (72%) were hospitalised when initiated on RLAI therapy. The mean duration of hospitalisations overlapping the index initiation was 120 days, considerably longer than the mean duration of

hospital episodes observed strictly before (46 days) or strictly after initiation (53 days).

Statistics on the use of RLAI are detailed in Table 3. The most frequently cited reasons for initiating therapy with RLAI were noncompliance on other medications (63%), lack of efficacy on other medications (34%), and relapse (27%). The average duration of RLAI treatment observed during the study period was 1.33 years, ranging from 0 days (i.e., first and last dose occurring on the same day) to 2.56 years. For 66 patients, RLAI therapy was discontinued during the study follow-up, primarily for the following reasons: lack of efficacy (35%), non-compliance (35%), and patient choice (33%). Table 4 shows the distribution of RLAI dosing over time. Seventy-six percent of patients started at 25 mg, doses above 50 mg were rarely observed.

4.2. Main Analysis. The results of the conventional analytic approach are shown in Table 5. The mean number of bed-days per patient per year was reduced by 24.89 bed-days (40%), from 62.89 to 38.00 per patient-year, a statistically significant difference. The mean number of hospitalisations per year was reduced by 0.19 episodes (20%), a statistically significant reduction from 0.93 episodes per year before initiation of RLAI to 0.74 episodes after. Statistically significant reductions in total hospitalisation costs are also associated with the initiation of RLAI therapy. Mean hospital costs per patient-year decreased by €11,948 (43%), from €28,046 per year before initiation of RLAI to €16,098 after initiation.

Table 6 presents results for the subgroups of patients who were initiated on RLAI during a hospitalization ($n = 128$) or on an outpatient basis ($n = 49$). Statistically significant reductions of 21.81 (36%) and 32.93 (48%) in the mean number of bed-days per year were observed in the inpatient and outpatient cohorts, respectively. A statistically significant reduction of 0.24 episodes (24%) in the mean number of hospitalisations per patient-year was observed in the inpatient subgroup; a reduction of 0.06 episodes (8%) in the outpatient subgroup did not reach statistical significance due to small sample size. For the modelling-based approach, the estimates of episodes per year in the two periods (0.93 and 0.74 episodes per patient-year, resp.) are multiplied with the average lengths of stay associated with hospitalisation in the two periods, excluding any hospitalisation episodes ongoing at the time of initiation (45.6 and 53.0 days, resp.). This complementary approach estimates a reduction in the mean

TABLE 3: Use of RLAI.

Variable	N	Mean
Reasons for initiation to RLAI* (%)		
Adverse event: weight gain	177	3 (1.7%)
Adverse event: extrapyramidal symptoms	177	14 (7.9%)
Adverse event: other	177	11 (6.2%)
Lack of efficacy	177	61 (34.5%)
Relapse	177	47 (26.6%)
Patient choice	177	26 (14.7%)
Noncompliance	177	112 (63.3%)
Unknown	177	0
Duration of RLAI use (days)	177	485.5 (SD 287.4)range 0–936
RLAI persistence (proportion of patients known to continue therapy during)		
at least 6 months	175 [†]	134 (76.6%)
at least 12 months	172 [†]	122 (70.9%)
at least 18 months	128 [†]	87 (68.0%)
at least 24 months	68 [†]	45 (66.2%)
Reasons for stopping RLAI* (%)		
Adverse event: weight gain	66	2 (3.0%)
Adverse event: extrapyramidal	66	3 (4.5%)
Adverse event: other	66	10 (15.2%)
Lack of efficacy	66	23 (34.8%)
Relapse	66	2 (3.0%)
Patient choice	66	22 (33.3%)
Noncompliance	66	23 (34.8%)
Unknown	66	0

* Multiple answers were allowed. [†] Reduced sample size reflects follow-up durations.

TABLE 4: RLAI dose distributions in patients beginning with RLAI, and every 6 months onwards. For each patient, the last known observation on dose was carried forward to the time point. Two patients were excluded from the analysis of dose changes at later time points because of missing information.

	At treatment beginning	6 months later	12 months later	18 months later	24 months later
N (patients)	177 (100%)	132 (100%)	121 (100%)	87 (100%)	45 (100%)
25 mg	134 (76%)	41 (31%)	33 (27%)	24 (28%)	17 (38%)
37.5 mg	24 (14%)	40 (30%)	35 (29%)	26 (30%)	13 (29%)
50 mg	19 (11%)	48 (36%)	49 (40%)	34 (39%)	14 (31%)
62.5 mg	0	1 (1%)	1 (1%)	0	0
75 mg	0	2 (2%)	3 (2%)	3 (3%)	1 (2%)
100 mg	0	0	0	0	0

number of bed-days per patient per year by 3.2 (i.e., 8%), from 42.4 to 39.2 bed-days per patient-year.

Results by previous treatment are presented in Table 7. The results are suppressed for patients treated exclusively with typical antipsychotic agents just prior to the initiation as sample sizes were small. The combination therapy subgroup is made up predominantly of patients who receive atypical and typical oral agents in combination.

In the large subgroups of patients with previous atypical oral agent (alone or in combination), results are generally similar to the overall results, for example a reduction of 0.22 episodes in the single atypical oral subgroup, from 0.90 episodes per year before initiation to 0.69 episodes per year after the initiation of RLAI. For the small subgroup of patients

untreated at the time of initiation ($n = 9$), the annual number of hospitalisation episodes before the initiation is estimated to be higher (1.18 per year) than the overall average, and a larger reduction by 0.77 is seen with the initiation to a postinitiation mean annual number of 0.41 hospitalisations. Resource use as measured by bed-days per year is, however, below average for this subgroup, with mean 50 days per year prior to the initiation and 18 days after initiation.

5. Discussion

Results suggest that RLAI is associated with sizeable and statistically significant reductions in resource use. The mean number of hospitalisations per year decreased by 20%. This

TABLE 5: Results of the main analysis. Hospitalisation episodes overlapping the date of RLAI initiation are allocated to the period before initiation. Sample unit (N) is the patient.

Endpoints	Before initiation		After initiation		Difference	
	Mean (SE)	95% CI	Mean (SE)	95% CI	Mean (SE)	95% CI
Inpatient bed-days per patient-year ($N = 177$)	62.89 (4.16)	(54.74; 71.04)	38 (5.19)	(27.83; 48.17)	-24.89 (5.93)	(-36.51; 13.26)
No. hospitalizations per patient-year ($N = 177$)	0.93 (0.05)	(0.83; 1.03)	0.74 (0.09)	(0.57; 0.91)	-0.19 (0.09)	(-0.36; -0.01)
Hospital costs per patient-year, € ($N = 177$)	28,046 (1,782)	(24,554; 31,539)	16,098 (2,117)	(11,949; 20,248)	-11,948 (2,555)	(-16,995; -6,941)
Cost of other antipsychotic agents, € per patient-year ($N = 177$)	907 (148)	(617; 1,197)	1,130 (174)	(788; 1,471)	233 (135)	(-43; 488)
Cost of RLAI per patient-year, € ($N = 177$)	—	—	4,193 (196)	(3,809; 4,576)	—	—

TABLE 6: Results of the subgroup analysis for the endpoints: inpatient bed-days per patient and year, and number of hospitalisations per patient and year. Results are presented for subgroups of patients who are in- or outpatients at the time of initiating RLAI.

Endpoints	Before initiation		After initiation		Difference	
	Mean (SE)	95% CI	Mean (SE)	95% CI	Mean (SE)	95% CI
Inpatient bed-days per patient-year						
Inpatient ($N = 128$)	60.88 (4.03)	(52.97; 68.79)	39.07 (6.13)	(27.06; 51.09)	-21.81 (7.21)	(-35.94; -7.68)
Outpatient ($N = 49$)	68.13 (10.76)	(47.05; 89.22)	35.2 (9.82)	(15.96; 54.44)	-32.93 (10.23)	(-52.98; -12.98)
No. hospitalizations per patient-year						
Inpatient ($N = 128$)	0.99 (0.06)	(0.87; 1.11)	0.76 (0.11)	(0.54; 0.97)	-0.24 (0.11)	(-0.45; -0.02)
Outpatient ($N = 49$)	0.77 (0.09)	(0.59; 0.95)	0.71 (0.14)	(0.43; 0.98)	-0.06 (0.14)	(-0.34; 0.21)

translated into reduced inpatient bed-days and corresponding costs, but the magnitude is sensitive to the method of allocating hospitalisation episodes on-going at the time of initiation. The conventional approach resulted in a reduction in bed-days per patient-year by 40% and a corresponding cost-saving of over €16,000 per patient-year, while the alternative modelling-based approach found a reduction in inpatient days of 8%. The subgroup of patients who were initiated on RLAI on an outpatient basis (and which does not suffer from uncertainty about the appropriate allocation of hospital episodes overlapping the initiation) experienced a 48% reduction of bed-days per patient-year (similar to the conventional approach). Despite variation in the magnitude of this reduction between the three approaches, all analyses point to a consistent and considerable reduction in resource use associated with the initiation to RLAI.

5.1. Study Strengths and Weaknesses. This study has some important strengths. First, the use of a noninterventive design allowed us to answer questions about “real-world” resource use in a timely manner. Through the use of chart review, re-

source use in schizophrenia patients could be observed as it occurred in actual practice rather than in the context of controlled clinical trials with corresponding protocol bias [11]. Moreover, the study endpoints are highly likely to be captured in patient charts, resulting in data integrity on hospitalisation episodes and costs.

Second, the retrospective study design was chosen to ensure recruitment of a reasonably-sized patient sample within the time constraints imposed by demands of the Finnish Pharmaceuticals Pricing Board (Lääkkeiden Hintalautakunta), which would have been impossible to achieve in a prospective study. With a relatively long patient follow-up of, on average, 1.8 years after initiation of RLAI, this study may also be more likely to capture the effects of treatment persistence and compliance, which a shorter study is likely to underestimate [4]. The “mirror-image” design, moreover, provides a within-group comparison that controls for time-invariant individual patient covariates.

Third, informed consent was not required. This may have avoided the selection bias related to willingness to participate in clinical studies [19] and facilitated the recruitment of a

TABLE 7: Results of the subgroup analysis for the endpoints: inpatient bed-days per patient and year, number of hospitalisations per patient and year, and hospital costs per patient and year. Results are presented for previous therapy subgroups containing more than 5 patients.

Endpoints	Before initiation		After initiation		Difference	
	Mean (SE)	95% CI	Mean (SE)	95% CI	Mean (SE)	95% CI
Inpatient bed-days per patient-year						
Atypical oral only (<i>N</i> = 129)	61.63 (4.30)	(53.20; 70.05)	37.69 (6.03)	(25.87; 49.51)	-23.94 (7.21)	(-38.07; -9.81)
Atypical oral combination (<i>N</i> = 32)	70.76 (12.80)	(45.67; 95.86)	38.95 (13.27)	(12.95; 64.95)	-31.81 (14.35)	(-59.93; -3.98)
Untreated (<i>N</i> = 9)	50.06 (15.94)	(18.82; 81.30)	17.8 (6.65)	(4.77; 30.84)	-32.26 (16.19)	(-63.99; -0.54)
No. hospitalizations per patient-year						
Atypical oral only (<i>N</i> = 129)	0.9 (0.06)	(0.80; 1.01)	0.69 (0.09)	(0.51; 0.86)	-0.22 (0.09)	(-0.40; -0.03)
Atypical oral combination (<i>N</i> = 32)	0.96 (0.14)	(0.69; 1.24)	0.78 (0.23)	(0.32; 1.24)	-0.18 (0.17)	(-0.51; 0.15)
Untreated (<i>N</i> = 9)	1.18 (0.30)	(0.59; 1.78)	0.41 (0.14)	(0.13; 0.68)	-0.77 (0.29)	(-1.34; -0.21)
Hospital costs per patient-year, €						
Atypical oral only (<i>N</i> = 129)	27,560 (1,934)	(23,770; 31,351)	16,177 (2,546)	(11,187; 21,167)	-11,383 (3,007)	(-17,276; -5,491)
Atypical oral combination (<i>N</i> = 32)	32,415 (5,439)	(21,755; 43,075)	15,666 (5,027)	(5,812; 25,519)	-16,749 (6,782)	(-30,041; -3,457)
Untreated (<i>N</i> = 9)	20,561 (6,633)	(7,561; 33,562)	8,435 (3,379)	(1,812; 15,059)	-12,126 (7,735)	(-27,28; 3,035)

relatively large sample. Moreover, because the data before the initiation of RLAI are compared with data from the same patients after initiation, the study design controls for biases due to time-invariant individual covariates, irrespective of whether these are recorded in the study.

There are also several important study limitations. First, “mirror-image” studies are subject to inherent biases [14]. Because the treatment under investigation (RLAI) is typically initiated during an acute episode when patient health was sufficiently poor to necessitate a treatment initiation, gravitation to the mean [20] may have contributed to optimistic estimates in this study. The asymmetrical definition of treatment periods may have introduced a conservative bias because the dose titration period is included in the estimation of the RLAI treatment effect. The strict temporal sequence of periods before and after the initiation of RLAI may have caused biases relating to disease progression or changes in the health-care system (period bias), such as the conservative bias associated with the worsening severity status in schizophrenia patients over time. While the lack of a concurrent control group precludes assessment of these biases, leading some authors to consider results from “mirror-image” studies inconclusive [21], this design is nonetheless often used in studies of health resource use [14].

Second, this study may not represent schizophrenia patients generally because it appears to have recruited, on average, quite severely ill schizophrenia patients. Indeed, a “first-wave” effect, in which severely ill patients are more likely than others to receive a novel drug, may have occurred because the recruitment index period began soon after the launch of RLAI in Finland. Seventy-two percent were initiated on RLAI while hospitalised, which indicates above-average severity in the sampled schizophrenia patients.

Treatment success may be less likely in these difficult-to-treat patients, so the resource use reductions reported here for the subgroup of patients initiating RLAI as outpatients may be more representative of the broader population of schizophrenia patients than the overall results reported here.

Third, controversy exists regarding the appropriate definition of treatment periods. Gianfrancesco et al. [14] argue that a pure intent-to-treat principle cannot and should not be applied to “mirror-image” studies because the before-treatment period is not defined according to intent-to-treat. This is a clear deficit inherent in the “mirror-image” study design. Health-economic studies, however, aim to compare the patient outcomes resulting from the decision to start different therapies, rather than during a treatment-specific period in which treatment is considered “successful.” It is therefore appropriate to follow the pragmatic, intent-to-treat principle when analysing health-economic datasets in general [22] and in schizophrenia [23]. The conventional analytic approach adjusts the initiation date in some patients and its results are thus, strictly speaking, not associated with the start of RLAI therapy. The subgroup results presented for patients initiating RLAI as outpatients are consistent with the intent-to-treat principle in the postinitiation period.

Fourth, there is no comparison with relevant treatment alternatives. Choosing a relevant comparator is difficult because typical depots differ from atypical depots in their sideeffects profile, atypical oral preparations differ in patient compliance with the treatment [24], and RLAI is the first-to-market atypical depot.

Fifth, there is methodological uncertainty about how to analyse hospitalisation episodes that are ongoing at initiation. Specifically, the entirety of these hospitalizations that overlapped the index initiation of RLAI could be

allocated to the preinitiation treatment as in the conventional analytic approach in this study as well as elsewhere [5, 6, 8]. Other studies have excluded patients who initiated on an inpatient basis [10, 12] or carried out sensitivity analyses in which they were excluded ([5, 8] and here). The magnitude of treatment effect appears sensitive to analysis methods, which is significant here because nearly 75% of the sample falls into this category and because these hospital stays were longer (mean 120 days) than other stays on average (around 50 days).

Many of the above design weaknesses are due to a lack of consensus on the correct method for analysing resource use episodes that overlap the initiation date. Ideally, these limitations would be overcome in future studies by comparing data on the initiation of RLAI with data on the initiation of another therapy, suitably chosen to avoid introducing patient selection biases. The biases introduced by choice of method would then affect both arms equally so that the conclusions should be more robust to the chosen methods of analysis and allocation. Additionally, studies with longer follow-up durations would reduce the impact of the methodological uncertainty associated with attribution of the episode ongoing at initiation because its contribution to overall resource use will be smaller. Health-economic analysis would benefit from both innovations because long-term comparative results on the different consequences of relevant treatment options are of more use to decision makers than studies of single-treatment options.

5.2. Interpretation of Study Results. Several other studies have collected data on resource use in patients diagnosed with schizophrenia or schizoaffective disorder and treated with RLAI. The results of the conventional analytic approach in the present study appear generally consistent with other studies (accounting for some differences in the design and recruitment) [6, 8, 10–13]. The similarities with an identically designed study in neighbouring Sweden is striking, 40% fewer bed-days in the current study and 45% in Willis et al. [12].

While the present study was not designed to investigate the reasons for reduced resource use in patients being treated with RLAI, the large proportion of patients who were initiated on RLAI because of noncompliance with the previous treatment (63%) suggests that doctors choose RLAI to improve medication compliance, a likely benefit of RLAI compared to oral medication [3].

6. Conclusion

This study found consistent evidence that sizable reductions in resource usage are associated with the initiation of RLAI in Finland. The choice of analytic approach for allocating inpatient episodes that are ongoing at the initiation of therapy affects estimates of the magnitude, however, and future work to evaluate a novel approach based on economic modelling is desired.

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Review Article

Role of Long-Acting Injectable Second-Generation Antipsychotics in the Treatment of First-Episode Schizophrenia: A Clinical Perspective

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Approximately 80% of patients with the first-episode schizophrenia reach symptomatic remission after antipsychotic therapy. However, within two years most of them relapse, mainly due to low levels of insight into the illness and nonadherence to their oral medication. Therefore, although the formal data available is limited, many experts recommend prescribing long-acting injectable second-generation antipsychotics (mostly risperidone or alternatively paliperidone) in the early stages of schizophrenia, particularly in patients who have benefited from the original oral molecule in the past and agree to receive long-term injectable treatment. Early application of long-acting injectable second-generation antipsychotics can significantly reduce the risk of relapse in the future and thus improve not only the social and working potential of patients with schizophrenia but also their quality of life.

1. Depot Antipsychotics for the Treatment of Schizophrenia

First-generation long-acting injectable (depot) antipsychotics (AP1G) emerged in clinical practice in the 1960s. For the treatment of schizophrenia, their use resulted in a significant decrease in the number of patients relapses, including length and frequency of hospitalizations [1]. However, when oral second-generation antipsychotics (AP2G) were introduced thirty years later, the position (in clinical practice) of depot AP1G dramatically changed. Despite the benefits of AP1G, psychiatrists prescribed them for long-term therapy of schizophrenia much less often and started to switch to oral AP2G as they were seen as more efficient and better tolerated [2]. This trend persisted for many years, despite evidence to suggest from meta-analyses and naturalistic studies that depot AP1G were more effective in reducing

schizophrenic relapses than oral AP2G [3]. The same finding was later logically replicated also for long-acting injectable (LAI) AP2G [4–7]. Although patients with schizophrenia are often willing to use depot or LAI antipsychotics, these preparations are today prescribed only for approximately 20% of them [8–10]. In a survey [11] psychiatrists answered that they only offer long-acting injectable antipsychotics to one in every three patients with schizophrenia.

2. Specifics for First-Episode Schizophrenia Therapy

Therapy for the first episode of schizophrenia has certain specific features. Patients respond to low doses of antipsychotics relatively well; yet they are more sensitive to the adverse effects, particularly extrapyramidal ones [12, 13]. Patients

with first-episode schizophrenia, however, typically show low willingness to use antipsychotics in the long-term treatment, likely due to their high unawareness of the disease severity. Recommended duration of antipsychotic administration after the first episode of schizophrenia usually ranges from 1 to 2 years [12–14]. A five-year observation study of first-episode patients showed that the risk of relapse is five times higher after discontinuation of therapy compared to continuous medication [15]. Despite the recommendations from their psychiatrists, patients with schizophrenia discontinue their therapy often. Results of the clinical antipsychotic trials of intervention effectiveness (CATIE) study indicate that up to 74% of patients with schizophrenia discontinued their therapy after 18 months; the European First Episode Schizophrenia Trial (EUFEST) shows that up to 42% of patients terminated their treatment within one year after the disease onset [16, 17]. When considering the length of subsequent prophylactic treatment after the first episode of schizophrenia; not only its efficacy but also the profile or severity of adverse events of the given antipsychotic must be taken into account. Moreover, it should be taken into consideration that approximately 20% of first-episode patients will never experience a subsequent exacerbation of schizophrenia, irrespective of whether they receive or the type of therapy they receive [14, 18].

3. Problems Associated with Nonadherence to Pharmacological Treatment of Schizophrenia

Schizophrenia is a chronic mental disease characterized among other things by a high degree of nonadherence to prescribed medication [19]. It has been reported that patients take on average only 58% of their prescribed drugs, 41.2% of patients do not use their medication according to prescription, and one- to two-thirds of patients take their pills irregularly [20–22]. These are the results of questionnaire surveys, and therefore they reflect only the situation of patients that agreed to take part in the research; in reality, therefore the rates of nonadherence may be much higher. In general, the current guidelines on schizophrenia treatment consider depot or long-acting injectable antipsychotics as drugs of choice for long-term therapy in patients who are nonadherent with antipsychotic medication [12–14]. Systematic surveys of specific studies indicate that patients treated with depot antipsychotics show only a 24% non-adherence rate while they are sufficiently covered by medication for 91% of the total therapy time [23–25].

4. Long-Acting Injectable versus Oral Antipsychotics in the Treatment of Schizophrenia

Since available studies differ in methodology and primary observation goals [26], it is difficult to generalize on the effects of oral or long-acting injectable administration of

antipsychotics on the course of schizophrenia. In a meta-analysis, Adams et al. [27] did not prove dominance of depot AP1G over oral antipsychotics in terms of reduction of the number of relapses. Nevertheless, overall improvement was seen more often in patients treated with depot antipsychotics [27]. On the other hand, a recent meta-analysis [7] found lower levels of relapse in patients with schizophrenia treated with depot AP1G or LAI AP2G, compared with those treated with oral antipsychotics. Still, the two therapeutic strategies did not differ in the number of rehospitalizations, terminations of therapy, or cases of non-adherence. Inconsistency of results might be explained by the nature of double-blind randomized studies that, of course, do not typically enroll non-adherent patients who are likely to benefit most from the depot/LAI formulation of antipsychotic therapy. Conditions of real clinical practice are therefore better simulated by observation studies where depot and oral antipsychotics are often compared with a mirror design. These studies describe almost consistently lower number of days of hospitalization during depot or LAI antipsychotic therapy, as compared with the same period of oral medication [1, 28]. The main methodological problem of these studies lies in the fact that, when the initial oral antipsychotic medication fails, a new oral treatment is prescribed, whilst the injectable medication remains the same. This can significantly affect the comparison of the therapy efficacy in identical time periods [26].

5. Long-Acting Injectable Antipsychotics in First-Episode Schizophrenia

Depot AP1Gs, let alone LAI AP2G, are rarely prescribed for patients with first-episode schizophrenia, although their levels of non-adherence and hence the risk of subsequent relapse are in reality very high [29, 30]. Importantly, adverse course of early schizophrenia has a profound negative influence on psychosocial integration of patients, not to mention a patients ability to remain in education and/or employment. Economic consequences of schizophrenia therefore represent a burden not only for health system but also for the social system of public health insurance. Psychiatrists usually explain the low prescription rate of LAI antipsychotics in the initial/early stage of schizophrenia treatment as an unwillingness of patient to receive injections on an outpatient basis or generally by negative attitudes to depot/LAI antipsychotics [31, 32].

6. Long-Acting Injectable Antipsychotics in First-Episode Schizophrenia: Attitudes of Psychiatrists

Heres et al. [33] used a questionnaire to ask almost 200 German psychiatrists at the national congress in 2008 about their attitudes towards the use of LAI antipsychotics in patients with first-episode schizophrenia. They found that long-term injectable therapy was only offered to 26.7% of patients with first-episode schizophrenia; it was actually prescribed to 13.3% of those offered (i.e., one of every

two). Respondents also reported that up to 60.4% patients taking antipsychotics irregularly will relapse within one year after the first episode [33]. The main outcome of this questionnaire was that it identified the three principal reasons for *not* using LAI antipsychotics in patients with first-episode schizophrenia. German psychiatrists stated that they find it difficult to present the benefits of a long-term injectable antipsychotic therapy to patients who do not have any personal experience with schizophrenia relapse, as they are still at the very beginning of their illness. Poor availability of LAI AP2G was identified as another reason, particularly when AP2G are strongly preferred over AP1G, especially in patients with first-episode schizophrenia. The last reason was mainly personal reservations of the psychiatrists associated with difficult control of adverse effects of depot antipsychotics, negative impact on patient-psychiatrist relationship, or higher amount of psychiatrist's time needed to manage depot medication administration [33]. The survey indicates that the only barrier to more frequent use of LAI AP2G in patients with first-episode schizophrenia, which is not influenced by perceptions of patients and psychiatrists, is the issue with market availability, price, and method of reimbursement. At present, only LAI risperidone, olanzapine pamoate, and paliperidone palmitate are available in most countries. For many reasons, limited availability of these drugs is today considered as the main barrier of their more common use in the therapy of schizophrenia [2, 11, 32]. This is problem mainly in first-episode patients in whom AP2G are strongly preferred as drugs of first choice [13, 34, 35]. Hopefully, better availability of LAI AP2G, simpler prescription rules, and better reimbursement from public health insurance will result in more common use of these products in clinical practice. However, this logical sequence of thoughts is in conflict with the real situation in the UK where better availability of LAI risperidone did not increase the use of LAI antipsychotics for treatment of schizophrenia despite previous belief of British psychiatrists that availability of these products was highly desirable and would significantly change their prescription habits in favor of LAI antipsychotics [2, 32]. Keeping this in mind, the latter assumption that better availability of LAI AP2G would make psychiatrists prescribe LAI preparations more often sounds ironic [32]. Other reasons for not prescribing LAIs reflect subjective attitudes of psychiatrists and patients towards injectable therapy in general. The questionnaire by Heres et al. clearly highlighted that only one in four patients with first-episode schizophrenia was offered the possibility of treatment with LAI AP2G and half of those that were, agreed. That means that three out of four patients were not offered this type of therapy from their psychiatrist. Actually, the fact that psychiatrists, driven by their own personal negative attitudes/perceptions, offer LAI AP2G less frequently is a true barrier to using these products more commonly in patients with first-episode schizophrenia. Psychiatrists often say that first-episode patients reject LAI AP2G because they have not yet experienced a schizophrenic relapse. In this sense, higher efficacy of a LAI AP2G in prevention of relapses may not be a feasible argument [1, 5, 36]. Alternatively, low prescription rates can be explained by the fact that psychiatrists suppose

beforehand (without discussing the issue with patients) that first-episode patients will not be interested in LAI AP2G therapy for the above-mentioned reasons. Interestingly, high self-confidence of psychiatrists to foreknow attitudes of their patients is considered to be one of the key factors of less frequent use of LAI AP2G in clinical practice [2, 32].

7. Long-Acting Injectable Antipsychotics in First-Episode Schizophrenia: Current Knowledge

Recent studies show that long-term injectable AP2G therapy is effective and also acceptable for first-episode patients, which is in opposition to the above-mentioned "conservative" attitudes [30, 37]. Unfortunately, studies comparing long-term injection or depot therapy with oral antipsychotic treatment after the first episode of schizophrenia are rare [38]. From this perspective, unique data can be drawn from a nation wide cohort study aimed at identification of the risk of rehospitalization and therapy discontinuation in more than 2,500 patients first hospitalized for schizophrenia between 2000 and 2007 in Finland [26]. The results show that in Finland, where antipsychotics are fully reimbursed from general health insurance systems, only 45.7% patients pick up prescribed drugs within one month and continue their therapy. Data are highly representative, since the study used the national registry and incorporated every single patient in Finland who was hospitalized for schizophrenia for the first time. Although information about medication during hospitalization was not available, almost all patients were recommended to start subsequent antipsychotic therapy. As compared with studies such as CATIE [16] or EUFEST [17], the Finnish study indicated higher rate of therapy discontinuation. This could be explained by the nature of the study which made it possible to capture real everyday behavior of patients, irrespective of their motivations or willingness to cooperate. As Finland, just as the majority of other countries, has not established any compulsory outpatient psychiatric screening, comparison of efficiency of individual antipsychotics can be generalized only for persons who were willing to visit their psychiatrist on an outpatient basis. It turned out that administration of depot AP1G and LAI risperidone resulted in reduction of the risk of rehospitalization by 50% or 65%, respectively, compared with oral formulations of the same antipsychotics. Depot AP1G or LAI risperidone were the first-choice drug in 8% of patients, and, in total, they comprised 10% of treated patient-years [26]. This is relatively low, especially when compared with patients with chronic schizophrenia. So far, these antipsychotic formulations have been earmarked mainly for patients with low insight into the illness and poor adherence to the therapy. However, if the target population for LAI AP2G would be extended to include also patients with better insight and apparent adherence, rehospitalization rate should decrease. Of course, this would apply only to patients who are willing to use these products on an outpatient basis.

TABLE 1: Survey of studies on LAI risperidone in first-episode schizophrenia patients.

Author, year	Study design	Duration of schizophrenia	N	Comparator	Result
Parellada et al., 2005 [39]	Six-month open study	Median one year, no more than 3 years	382	0	73% patients completed the study, statistically significant decrease of PANSS; 40% patients achieved at least 20% reduction of total PANSS score.
Malla et al., 2006 [44]	Two-year open study	Up to 3 years	15	Oral AP2G	More significant reduction of total PANSS score versus oral risperidone.
Emsley et al. 2009 [30]	Two-year open study	First episode	50	0	72% patients completed the study; 78% of them reached at least 50% reduction of symptoms; remission persisted for two years in 62% patients [42].

8. Long-Acting Injectable Second-Generation Antipsychotics in First-Episode Schizophrenia

As far as LAI AP2G products are concerned, researchers have clinical experience with LAI risperidone, olanzapine pamoate, and paliperidone palmitate. Although many studies in schizophrenia with these products have been performed, relatively limited data on their use specifically in first-episode patients is available. Only LAI risperidone has been specifically studied for the use in early stage of schizophrenia (see Table 1) in addition specific post-hoc analyses have been performed in patients classified as having recent onset schizophrenia. Parellada et al. [39] designed a six-month open-label study with LAI risperidone to analyze a subgroup of 382 patients with recent schizophrenia or schizoaffective disorder (diagnosed ≤ 3 years ago) [40]. Schizophrenia was diagnosed in 84% of patients, with median of one year after the diagnosis was established. Previous medication included mainly AP2G (70%) and depot AP1G (24%). Non-adherence (42%) and poor efficacy (31%) of previous medication were the main reasons for changing the therapy. The study was completed by 73% patients who showed significant decrease of severity of schizophrenic symptomatology, reflected by statistically significant reduction of not only total PANSS score (positive and negative syndrom scale) [41] but also all PANSS subscales. In 40% of patients, total PANSS score decreased by at least 20%. At the same time, patients showed an improvement of overall functioning, quality of life, and satisfaction [39]. In other study, Emsley et al. [30] administered LAI risperidone monotherapy to fifty patients with the first episode of schizophrenia: this two-year observation study was completed by 36 patients (72%), 39 patients (78%) showed reduction of symptoms by at least 50%; 4 of them relapsed, 32 patients (64%) reached remission according to the proposed criteria for the remission in schizophrenia [42], and 31 patients (62%) reached remission that persisted throughout the two years of the study [30]. After two years, 33 patients decided to terminate the therapy. Seventy-nine percent (79%) of those then subsequently relapsed (median to relapse: 163 days). Based on these results, Emsley et al. [43] assert that first-episode patients who reached remission are prone to relapse after discontinuation of continuous

long-acting injectable risperidone therapy. Antipsychotic treatment in such patients should therefore be continuous and maintained for at least two years [43]. Malla et al. [44] published data from their two-year prospective open multicentric study that was performed with young patients (aged 18 to 30 years) suffering from schizophreniform disorder, schizophrenia, or schizoaffective disorder (for no longer than 3 years). Patients were randomized to treatment with oral AP2G or LAI risperidone. Although it is difficult to generalize the results due to low number of subjects enrolled in the study ($n = 15$), patients treated with LAI risperidone showed more significant reduction of total PANSS score (by 16.1), as compared with oral AP2G (by 5.0) [44]. Weiden et al. [37] published preliminary data about early adherence from their randomized controlled study that compared LAI risperidone with oral AP2G in first-episode patients [37]. Nineteen (19, 73%) of 26 patients who were asked to participate in the study agreed to be treated with LAI risperidone; the other group consisted of 11 patients. Adherence rate in the twelfth week of observation was comparable in both groups. However, adherence questionnaires indicated that patients accepting LAI risperidone therapy showed higher probability of adherence, as compared with patients treated with oral antipsychotics [37]. Bartzokis et al. [45] examined the impact of antipsychotic formulation on the myelination trajectory during a randomized six-month trial of LAI risperidone versus oral risperidone in first-episode schizophrenia subjects. Two groups (11 patients treated with LAI risperidone and 13 patients treated with oral risperidone) that were matched in prerandomization oral medication exposure and 14 healthy controls were prospectively examined. Frontal lobe white matter volume was estimated using inversion recovery MRI (magnetic resonance imaging) images. A brief neuropsychological battery that focused on reaction times was performed at the end of the study. White matter volume remained stable in the LAI risperidone group and decreased significantly in the oral risperidone group resulting in a significant differential treatment effect, while the healthy controls had a white matter change intermediate and not significantly different from the two schizophrenia groups. White matter increase was associated with faster reaction times in tests involving frontal lobe function. The results suggest that LAI risperidone may improve the trajectory of myelination in first-episode patients and has a beneficial

impact on cognitive performance. Better adherence provided by LAI AP2G may underlie the modified trajectory of myelin development [45].

9. Benefits of Long-Acting Injectable Antipsychotics in First-Episode Patients with Schizophrenia: Clinical Perspective and Summary

LAI AP2G have been used in clinical practice for several years. Nowadays, LAI AP2G are reserved mainly for patients with long-term course of schizophrenia who show low adherence to oral medication. The studies performed especially with LAI risperidone in patients with first episode or early stage of schizophrenia clearly indicated that this form of therapy could be effective and well tolerated also in this subgroup of patients with schizophrenia. Thanks to the familiar mother molecule (paliperidone is 9-OH risperidone, which is the active metabolite of risperidone) data concerning efficacy and tolerability of LAI risperidone in first-episode schizophrenia, patients could be applicable for paliperidone palmitate as well. Combined benefits of AP2G characteristics with an assured route of administration raise a question whether LAI AP2G should be recommended also in first-episode patients [46, 47]. Instead of foreknowing/guessing whether patients will accept LAI therapy or not, psychiatrists should offer this form of treatment as a routine choice to all appropriate patients with schizophrenia, including first-episode subjects. Selection between long-term injectable therapy and oral medication should be based on educational and therapeutic dialogue of the psychiatrist and the patient who can then in turn discuss the potential benefits and disadvantages of the proposed therapeutic strategy [48, 49].

Approximately 80% of patients with a first episode of schizophrenia reach symptomatic remission after antipsychotic therapy. However, within two years most of them relapse mainly due to low insight into the illness and non-adherence to oral medication. Therefore, although the formal data available are limited many experts recommend prescribing long-acting second-generation antipsychotics (especially LAI risperidone or alternatively paliperidone palmitate) in the early stages of schizophrenia, particularly in patients who benefited from the original oral molecule in the past and agree to receive long-term injection treatment. Early application of long-acting injectable second-generation antipsychotics can significantly reduce the risk of relapses in future and thus improve not only social and working potential of patients with schizophrenia but also their quality of life.

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Clinical Study

Treatment Adherence with Early Prescription of Long-Acting Injectable Antipsychotics in Recent-Onset Schizophrenia

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Although response to treatment for the first episode of schizophrenia is generally favourable, nonadherence with the treatment is the first cause of relapse and rehospitalisation within the next few years. Long-acting injectable antipsychotics (LAIs) combine the advantages of the newer antipsychotics and the long-acting formulation. The evaluation concerns 25 schizophrenic patients hospitalised for the first time, treated with risperidone long-acting injectable (RLAI) associated with reintegration methods, and followed up for at least 18 months. Clinical observation was completed using Clinical Global Impression (CGI) scale and Global Assessment of Functioning (GAF). Clinical improvement was coupled with a good reintegration rate, very few relapse, or rehospitalisation. Bimonthly injection combined with psychosocial methods improved interactive followup, and therefore patients' compliance with the treatment. Treating with LAIA as early as possible, from the first episode if possible, can reduce relapse, number and duration of rehospitalisation, and cognitive symptoms and improve the quality of life and prognosis.

1. Introduction

Schizophrenia remains a chronic disease concerning about 1% of the general population in the world; although response to treatment in the early phases of evolution is generally favourable, it is estimated that rates of adherence to treatment 1 year after discharge from hospital are only about 50%, and 75% in the first two years of treatment [1, 2].

The causes are multifactorial: denial of disease, side effects of medication, cognitive impairment, comorbidity especially substance abuse [3] and also doctor-patient relationship [4].

Relapses and rehospitalisations worsen the prognosis of patients with schizophrenia, impact both patients and families' insertion and quality of life, and increase direct and indirect health costs [5, 6]. Treatment with LAIAs, which encourage adherence (fewer side-effects, stabilization of drug levels), can prevent the risk of interruption of treatment which is the main cause of relapse and rehospitalisation. This type of treatment, used as early as possible, since first-episode schizophrenia, may improve the long-term prognosis [7], particularly when associated with reintegration methods [8]

and interactive followup using interest of monthly or bi-monthly injection.

The aim of our study is to present the followup in "real life" of 25 patients, hospitalised for the first time, treated with RLAI associated with reintegration methods and multidisciplinary followup, for at least 18 months, in order to evaluate the impact: 1/on relapse and rehospitalisation rate; 2/on treatment adherence.

2. Materials and Methods

2.1. Study Design. The data presented here derive from a naturalistic prospective study of 120 patients treated with Risperidone Long Acting Injectable (RLAI) which was currently the only atypical long-acting injectable antipsychotic available at that time in France, associated with rehabilitation methods, and followed up for at least 18 months [9]: among them, 25 patients were hospitalised for the first time, and therefore younger in age and illness duration.

It was an epidemiological, observational, noninterventional study in usual-care settings, in which patients were

treated with flexible dose of RLAI, without randomization nor controlled trial. All patients were aware of the aim of the study and had given oral informed consent.

The aim of our study was to investigate the outcome of the illness according to a better compliance with RLAI integrated in a psychosocial treatment programme, notably the number and duration of hospitalisations, and also the possibility of familial and socioprofessional reintegration.

2.2. Inclusion and Exclusion Criteria. All patients were men or women of minimally 18 years of age, recruited consecutively in the same catchment urban area corresponding to their district of psychiatric healthcare in Paris (all of them were residents of the 14th district of Paris). All of them were psychotics according to DSM IVR criteria for schizophrenia [10].

Exclusion criteria were serious medical condition, history of malignant syndrome, pregnant or breast-feeding female, history of clozapine treatment, known allergies, hypersensitivity or intolerance to risperidone, and patients who had not given informed consent.

2.3. Assessments. Patients were assessed at baseline and after 6, 12, and 18 months for adherence, efficacy, RLAI dosage, number and duration of hospitalisation, social functionality, and reintegration (work, studies, apartment).

Clinical observation was completed using Clinical Global Impression scale (CGI) [11] representative of clinical improvement, and Global Assessment of Functioning (GAF) [12] representative of functional improvement, whose results are statistically significant.

2.4. Treatment. All patients were treated with risperidone per os, with doses ranging from 4 mg to 8 mg before changing to RLAI. The first injection was given prior to discharge, and the oral treatment was continued for 3 or 4 weeks.

The following injections were given at the out-patient center, or in the hospital depending on where each patient was consulted, and on their need to maintain a more controlled therapeutic regimen. The nurses supervised administration of the treatment and could call them when they missed time of injection. The starting dose was calculated according to the patient's acute state and comorbidity, especially substance abuse (alcohol, cannabis). The initially prescribed dosage changed over time, according to the evolution, and to the physician.

2.5. Reintegration Measures. Day hospital, part-time therapy center, sheltered housing, protected employment center, and also dietetic education, physical exercise were used; each patient was cared for by two nurses and a social worker; these measures were adapted to each patient's needs, using bimonthly injection to consult their physician and/or a nurse.

2.6. Statistical Analyses. Descriptive statistics (mean standard deviation) were generated for quantitative data for all patients. For statistical analysis of the CGI and GAF data, subgroups were created with those patients who

completed the survey after 18 months. Statistical analysis of hospitalisation data was performed for the subgroup of patients who had received treatment during the preceding 18 months, who completed the 18-month followup, and who had at least one hospitalisation during these two time periods. Quantitative data was first tested for normality using the Kolmogorov-Smirnov test, followed by analysis for statistical significance using either the Wilcoxon signed rank test or the paired Student's *t*-test, as applicable. Qualitative data was subjected to McNemar's test. Bowker's test for symmetry was used to analyse dosage change over time.

3. Results

3.1. Sociodemographic Data and Clinical Characteristics. The patient population comprised 14 men and 11 women, the mean age was $30,08 \pm 7,54$ years, the mean duration of illness $6,84 \pm 5,45$ years; all of them were hospitalised for the first time, in acute or very acute state (positive symptoms: 20 patients, negative symptoms: 5 patients); the most common diagnosis was paranoid schizophrenia (13 patients), followed by schizoaffective disorder (5 patients), disorganised schizophrenia (3 patients), undifferentiated schizophrenia (2 patients), and acute psychotic disorder (2 patients).

3.2. Previous Treatment. 17 of 25 patients (64%) were not taking any treatment before being hospitalized; only 3 of them were naïve of all treatments. 8 of 25 were treated with Olanzapine (4 patients), Haloperidol (3 patients), Pipotiazine (1 patient).

None of them had previously received Risperidone.

Reasons for prescription were lack of efficacy or compliance (16 patients), lack of tolerability (2 patients), prescriber's choice (4 patients), and comorbidity such as substance abuse.

3.3. Dosage, Tolerability, Discontinuation Rate. RLAI dosage changed over time: 24 received a starting dosage of 50 mg, according to their very acute state and coexisting alcohol dependence and substance abuse (especially cannabis use), and also our normal clinical practice; 1 received a starting dose of 37,5 mg. The dosage has been decreased during the course of the survey. Most patients (16 patients) went on 50 mg, some of them went on 37,5 mg or 25 mg, 5 of them were treated with 25 mg at M18, end of our study.

Five patients interrupted their treatment (including 3 quickly after initiation) because of illness denial, weight gain, or partial efficacy.

3.4. Socioprofessional Evolution. After RLAI instauration, 19 patients could live in their own apartment, 1 in sheltered housing; 11 could restart work or find a job (100%: 5 patients, 50%: 4 patients, professional training: 2 patients), 3 patients could restart studies. Other patients had activities in day hospital or part-time therapy center, some of them needing some more time to attend a protected employment center. All of them improved their quality of life over time,

with more possibilities to meet friends and family, to live a more stable and independent life, outside the psychiatric hospital.

3.5. Clinical Efficacy CGI. Evolution of the CGI score is representative of clinical improvement: the level of severity of the illness (CGI-S) decreased from 5.44 (range 4–6, SD \pm 0.58) on day 0 to 3.14 (range 1–5, SD \pm 1.21) at M18. This result is statistically significant ($P < 0.0001$). CGI-I score showed that at M18, 3 patients were very greatly improved, 3 greatly improved, and 1 slightly improved.

3.6. Functional Improvement GAF. Evolution on the GAF scale is representative of functional improvement: the score increased from 36.16 (range 11–70, SD \pm 13.55) on day 0 to 75.71 (range 65–85, SD \pm 7.32) at M18. This result is statistically significant ($P < 0.0001$). The largest improvement was observed during the first 6 months of treatment, during which the mean GAF score increased by 20 and then more slowly until M18.

3.7. Hospitalisation Rate and Duration. Only 4 patients relapsed (16%), and only once: 3 patients between D0 and M6 (mean duration of hospitalisation: 21 days), and 1 during M6 and M12 (mean duration of hospitalisation: 7 days); no patient relapsed between M12 and M18. These results, when compared with the whole cohort's results, show that fewer patients were hospitalised after RLAI therapy, with a short duration of hospitalisation. We cannot compare with their own rate of hospitalisation, because it is their first hospitalisation, but we can notice that their rate of hospitalisation is better when compared with those who had already been treated and hospitalised in the whole cohort (37% for the whole cohort versus 16% for the 25 recent onset patients).

4. Discussion

These results compared with those of the whole cohort (120 patients) are very consistent and very close to them: marked improvements in CGI and GAF scores, reduced rates and durations of hospitalisation. They are globally better, and we think that is due to the recent onset in this population (patients younger in age and duration of illness) and they convince us to begin RLAI treatment as soon as possible (CGI improvement from 5,6 to 3,6 for the whole cohort versus 5,4 to 3,1 for 25 recent onset patients; GAF improvement from 34,1 to 67,5 for the whole cohort versus 36,1 to 75,7 for the 25 recent onset patients).

We currently used starting dosage of 50 mg, according to the very acute state and comorbidity (especially alcohol and cannabis use) of our patients, but also to our normal clinical practice in front of this “very difficult-to-treat-population,” considering underdosing can contribute discontinuation when patients are severely ill [13, 14], and also lower plasma levels of Risperidone and 9OH risperidone at the beginning of the treatment [15, 16]

Clinical benefits may be linked with psychosocial programme associated with RLAI treatment from the beginning of the treatment, and multidisciplinary long-term followup

(18 months in our study) in order to improve adherence with the medication.

Treatment plan including early warning signs developed for each patient, based on psychoeducation programme, family involvement in order to acquire and improve insight are regularly emphasized [1, 17–19].

Interest in functional outcome is based on subjective satisfaction with life, occupational and social functioning [18, 20], less and shorter inpatient stays, less long-term institutionalization, solitary living, and dependence on disability pension; greater frequency of outpatient visits, better information, improved access to supported employment, and rehabilitation should help the patients to agree with LAIA formulation [21, 22].

The importance of early intervention in schizophrenia treatment [23, 24] is based on acute clinical symptomatology (often positive symptoms), high risk of non- and partial adherence, risk of accruing morbidity and persistent deficits [25], and also high sensitivity to antipsychotics.

Treating as early as possible, from the first episode if possible, can reduce relapse, number and duration of hospitalisation, and also cognitive symptoms, illness worsening and suicide attempts [26], and thus improving the prognosis, and also direct and indirect cost [27–30].

Long-acting injectable antipsychotics combine the advantages of both the newer antipsychotics (efficacy, fewer extrapyramidal symptoms) and the long-acting formulation [31, 32]; they can reduce relapse through the increased medication adherence in patients with schizophrenia [33] and lower fluctuations in plasma concentrations.

Although response to treatment for the initial psychotic episode is generally favourable, most patients are unable to maintain this improvement [25, 34, 35]; poor adherence may be particularly common after a first episode of schizophrenia and may occur very early [22]: according to Coldham et al., 39% are not adherent and 20% inadequately adherent in the first year of treatment; non-adherence with medication is the first cause of relapse, it could be one of the most preventable, but it stays one of the most difficult to solve [1].

According to the neurodegenerative theory, relapse and recurrences make brain structures more neurotoxic: ventricular enlargement, cortical atrophy in brain, longer duration of illness, less effectiveness of the medication, deficient cognitive function, and prominent negative symptoms [23, 36].

Relapse predictors include medication discontinuation as a high risk [34]; relapse prevention is a major objective, and long-term treatment is indicated [37]. In recent publications concerning patients in the early phase of schizophrenia, two potentially risk factors for rehospitalisation are confirmed: short duration of first hospitalisation (shorter than two weeks) and early nonadherence to medication [38], even though periods of nonadherence are brief [35].

Long-acting injectable antipsychotics should not be considered by psychiatrists as a last resort in persistently ill patients; some recent studies show that patients, especially young patients, with a good insight, and sometimes a high study level, when informed on long-acting formulation, agree with them and prefer to receive their medication via a long-acting formulation rather than in tablet form [39, 40].

Psychiatrists' attitude towards LAIA should evolve [4, 41]. They should be recommended as a part of an integrated treatment plan, including multidisciplinary followup and treatment teams administering and supervising the medication [21], using interest of monthly or bimonthly injection in order not to forget treatment, and also to improving more frequent and regular contact between patients and healthcare professionals, interactive followup with nurse, psychiatrist, and also peers [14, 42].

A number of studies and pharmacoeconomic models have demonstrated that long-acting risperidone decreases direct healthcare costs largely by reducing the rates of relapse and hospitalisation [5, 43].

Relapse and hospitalisations are costly: direct medical costs in healthcare, indirect costs on the basis of productive activity (for the patient and family) [6, 29]. Even though adherence interventions in psychotic disorders have produced mixed results, possible cost benefits for the society and prevention of hospitalisation are necessary for patients [44] and a challenge for public health.

Limitations. No randomization, nor comparative group, the small number of patients are limitations to our study. However, results are encouraging when compared with those of the whole cohort, and the recent publications of the literature. They will need further investigations.

5. Conclusion

The treatment of schizophrenia is an ongoing challenge in psychiatry. The literature on long-acting injectable antipsychotics for early-phase schizophrenia, first episode, or recent onset, is limited, there are very few long-term data and guidelines are not yet available [38, 45, 46].

Using injectable long-acting antipsychotics as initial therapeutic treatment can reduce relapse rate and improve the prognosis and should be maintained in the long-term treatment of schizophrenia, using interactive, interdisciplinary followup, corresponding with psychosocial biological continuum, in order to progress from compliance to adherence: working with family and caregivers, information about the illness and its treatment, psychoeducation, bimonthly injection combined with nurse and psychiatrist assessment, telephone call and home visit when patient is late, and reintegration programme (housing, work, studies) may improve adherence and outcomes in these patients. An additional pertinent function is motivational enhancement fostering compliance and active participation in schizophrenia treatment plans for patients, relatives, and psychiatrists.

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Review Article

Oral versus Long-Acting Injectable Antipsychotics in the Treatment of Schizophrenia and Special Populations at Risk for Treatment Nonadherence: A Systematic Review

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Long-acting injectable antipsychotics (LAIs) should offer better efficacy and tolerability, compared to oral antipsychotics due to improved adherence and more stable pharmacokinetics. However, data on LAIs has been mixed, with some studies finding that they are more effective and tolerable than oral antipsychotics, and others finding the contrary. One possibility for the disparate results may be that some studies administered different antipsychotics in the oral and injectable form. The present systematic review examined the efficacy and tolerability of LAIs versus their oral equivalents in randomized and naturalistic studies. In addition, it examined the impact of LAIs on special populations such as patients with first-episode psychosis, substance use disorders, and a history of violence or on involuntary outpatient commitment. Randomized studies suggest that not all LAIs are the same; for example, long-acting risperidone may be associated with equal or less side effects than oral risperidone, whereas fluphenazine decanoate and enanthate may be associated with equal or more side effects than oral fluphenazine. They also suggest that LAIs reduce risk of relapse versus oral antipsychotics in schizophrenia outpatients when combined with quality psychosocial interventions. For their part, naturalistic studies point to a larger magnitude of benefit for LAIs, relative to their oral equivalents particularly among first-episode patients.

1. Introduction

Schizophrenia is a severely disabling psychiatric disorder that often includes hallucinations, delusions, cognitive deficits, poor insight, and comorbid substance use disorder (SUD) [1–3]. The first decade of illness in schizophrenia patients is often characterized by repeated episodes of psychosis with varying levels of remission between episodes and increased disability following each episode [3–5]. Moreover, the bulk of functional deterioration tends to occur in the first five years after onset of schizophrenia, after which the illness typically progresses into a stable phase, wherein positive symptoms are decreased and negative, and cognitive symptoms become predominant [3].

Antipsychotics—drugs that block dopamine D_2 receptors—attenuate positive symptoms in schizophrenia and help improve outcomes, especially in the early stages of

illness [4, 6–8]. For example, a pivotal study by May [8] revealed that treatment with antipsychotics or electroconvulsive therapy increased the rate of release from the hospital, reduced the length of hospital stay, and decreased the need for sedatives and hydrotherapy in newly admitted first-episode psychosis (FEP) patients, relative to psychotherapy or milieu therapy. Another study by Crow et al. [6] showed that 46% of 120 FEP patients maintained on antipsychotics relapsed within two years, compared to 62% of patients on placebo. Importantly, the chance of subsequent relapse was significantly increased in patients with a longer duration of untreated psychosis. Overall, multiple reviews found that that early antipsychotic treatment is crucial for improving outcomes in FEP patients and may prevent some functional deterioration and development of a chronic course [4, 5].

Despite the benefits of compliance with antipsychotic therapy during the early stage of illness, data from 2,588 FEP

TABLE 1: Characteristics of some older and newer LAIs [12, 17, 19].

	Vehicle	Preparation	Dosing interval	Injection site pain/reactions	Comments
Flupenthixol	Ester (decanoate)	Viscoleo	2–4 w	+++ [20, 21]	—
Fluphenazine	Ester (decanoate)	Sesame seed oil	2–5 w	+++ [20, 21]	—
Haloperidol	Ester (decanoate)	Sesame seed oil	4 w	+++ [20–22]	—
Zuclopenthixol	Ester (decanoate)	Viscoleo	2–4 w	++++ [20, 21]	—
Paliperidone	Ester (palmitate)	Water (nanosuspension)	4 w	++ [23]	Metabolite of risperidone
Olanzapine	Salt (pamoate)	Water (microcrystalline suspension)	2–4 w	++ [24, 25]	Monitoring required for at least three hours due to small risk of IAIV
Risperidone	Microspheres	Water	2 w	+ [23, 26, 27]	Refrigeration required

IAIV: inadvertent intravascular injection; +: minimal; ++: low; +++: moderate; ++++: high.

patients revealed that only 58% collected their prescription during the first 30 days of hospital discharge, and only 46% continued their initial treatment for 30 days or longer [9]. Indeed, studies have consistently shown that more than 40% of patients with FEP are nonadherent and discontinue medication during the first nine months of treatment, at which point the chances of relapse increase dramatically [10, 11]. The high rate of noncompliance can be explained by poor insight into illness, cognitive deficits, and elevated substance abuse associated with schizophrenia and by side effects associated with antipsychotics such as anhedonia and extrapyramidal symptoms (EPS) [3]. Clearly, the goal of treatment of FEP patients should be to increase compliance with antipsychotic therapy, thereby decreasing the negative effects of untreated psychosis and—at the same time—to minimize the amount of antipsychotic-induced side effects. This goal may, in part, be achieved by the use of long-acting or depot antipsychotics (LAIs) [12–14].

LAIs have a number of advantages over oral antipsychotics. First, they should decrease noncompliance due to forgetfulness and loss of insight (e.g., due to psychotic relapse or substance abuse) because patients are followed up if they miss an appointment for their injection [15]. Moreover, LAIs should maximize pharmacokinetic coverage and minimize antipsychotic withdrawal symptoms resulting from partial compliance [16]. In addition, LAIs are not influenced by first-pass metabolism, decreasing the potential for drug-drug interactions. Finally, some have argued that because the slow rate of absorption associated with LAIs leads to reductions in differences between C_{max} (peak) and C_{min} (trough) plasma levels [17], they should induce less side effects (an important predictor of poor treatment compliance), relative to oral antipsychotics [18].

Older (typical) LAIs were made by forming an ester with a fatty acid such as decanoic acid and injecting it in an oily solution such as sesame seed oil or low viscosity vegetable oil, thereby maximizing its lipophilicity and affinity for fatty tissue [19]. Moreover, the resulting highly lipophilic compounds possess more complicated, multicompartiment tissue binding [28]. Oil-based formulations must be injected slowly and are commonly associated with acute injection site pain, and skin reactions that can last for up to three months

[20, 22]. They may induce “breakthrough EPS” on the day of the injection, which is caused by a small amount of free drug released immediately into the patient’s system [29–33]. They may also be detectable in plasma for as long as six months following an injection, increasing the possibility of interaction with other drugs [34–36]. By contrast, some of these phenomena should be minimized with the atypical, water-based LAIs, including risperidone microspheres, and olanzapine pamoate (Table 1) [24, 31, 37, 38].

Interestingly, studies on efficacy of LAIs versus oral antipsychotics have produced conflicting results. For example, a 2-year study by Rosenheck et al. [39] revealed that risperidone LAI did not significantly decrease relapse over mixed oral antipsychotics, but it produced more EPS in unstable schizophrenia patients. Our own 2-year, randomized trial among FEP in/outpatients did not find any efficacy or tolerability differences between risperidone LAI and mixed oral atypical antipsychotics; however, the former medication was associated with a reduction in noncompliance [40]. Altogether, a meta-analysis by Adams et al. [41] did not find major efficacy differences between LAIs and oral antipsychotics in randomized studies of schizophrenia inpatients and outpatients. However, in these studies, the combination of inpatients with outpatients may have biased results towards oral antipsychotics, since medication compliance should be more strictly controlled in an inpatient setting [42]). More recently, Leucht et al. [43] showed LAIs to be superior to oral antipsychotics for preventing relapse among schizophrenia outpatients only.

Although the limitation of including both inpatients and outpatients was addressed by Leucht et al. [43], there is still the confound of comparing different molecules in the oral and injectable forms—an effect that may have confounded results due to the fact that not all antipsychotics possess an equal efficacy and tolerability profile [44–46]. The present systematic review will examine the efficacy and tolerability of oral and injectable forms of the same antipsychotic in randomized studies. However, since noncompliant patients are unlikely to participate in randomized studies, we will also include naturalistic studies administering LAIs to a general population of schizophrenia patients and to special populations at risk for treatment nonadherence such as

patients with FEP, SUDs, and those with a history of violence or on involuntary outpatient commitment.

2. Methods

A systematic search was carried out in the electronic databases, PubMed and EMBASE, using the keywords “antipsychotic” and “depot” or “injectable” and “randomized” or “naturalistic” or “first-episode” or “noncompliance” or “substance abuse” or “substance use disorder,” or “alcohol” or “drug” or “cannabis,” or “cocaine” or “heroin” or “amphetamine” or “violence” or “involuntary outpatient commitment” or “community treatment order.” This search looked for studies published between 1 January 1960 and 1 July 2011. In addition, studies and published abstracts were identified by cross-referencing of review articles. Unpublished studies were identified using clinicaltrials.gov.

For our analyses of randomized (open-label and double-blind) and naturalistic studies in the general population of schizophrenia patients, we included only trials comparing an LAI with its oral equivalent. However, due to a lack of studies, we included any comparative pharmacological trial in our examination of LAI-treatment of individuals with FEP, SUDs, and those on involuntary outpatient commitment. Mirror-image studies were excluded. Due to the fact that there were no studies investigating paliperidone LAI versus oral paliperidone, it was not included in the analyses.

3. LAIs Versus Oral Equivalent—Randomized Studies

Studies comparing an LAI with its oral equivalent in hospitalized patients are conducted to show the “non-inferior” efficacy and/or to study differences in tolerability and pharmacokinetics of the formulations. Hospitalized patients are useful for these purposes because compliance with oral antipsychotics should be maximized in an inpatient setting, limiting the potential confounding effect of noncompliance. By contrast, studies of LAIs versus oral antipsychotics conducted in outpatients are designed to mimic the “real world” setting where compliance is a problem.

3.1. Haloperidol Decanoate. One four-month study among schizophrenia inpatients revealed that haloperidol decanoate was associated with marginally better efficacy and more EPS, relative to oral haloperidol (Table 2) [47].

3.2. Fluphenazine Enanthate and Decanoate. Four short-term studies compared the efficacy and tolerability of fluphenazine enanthate versus oral fluphenazine among inpatients. All of the studies found that fluphenazine enanthate was equivalent to oral fluphenazine for schizophrenia symptoms [48–51]; however, two of the studies also showed that the former produced more EPS than the latter [50, 51]. Interestingly, in the Van Praag et al. [51] study, a marked increase in EPS was witnessed on the week of each injection, and it decreased somewhat the following week, which may be evidence of “breakthrough EPS.” Pharmacokinetic studies have shown that fluphenazine plasma levels spike after

administration of the decanoate and enanthate formulations [29, 30]. However, plasma levels of the latter decline much more slowly than that of the former, which may be another reason why two of the aforementioned studies found that fluphenazine enanthate was associated with more EPS overall.

Four pivotal, long-term studies compared fluphenazine enanthate and decanoate with their oral equivalent in stabilized outpatients [52–55]. A 21-month study by Del Giudice et al. [52] showed that fluphenazine enanthate was superior to the oral fluphenazine in reducing relapse among 82 schizophrenia outpatients. Analysis of tolerability outcomes revealed that 6 patients on fluphenazine enanthate experienced EPS, whereas none experienced EPS on oral fluphenazine. The design of this study was unique because a nurse was available to administer injections on home visits, which may have increased compliance with injections and reduced relapse. On the other hand, the short length of her visits may have led to underreporting of side effects, since fluphenazine levels may take days to peak following administration of the enanthate [29, 30, 52]. Accordingly, comparisons between the two esters showed that the decanoate produces the majority of EPS up to nine hours after the injection, whereas the enanthate produces it 12–48 hours after the injection [62].

Fluphenazine decanoate was compared to its oral equivalent in a study by Rifkin et al. [53]. The authors found that both treatments were equally superior to placebo in decreasing 1 year relapse rates among 73 outpatients. However, there were significantly more terminations due to toxicity in the fluphenazine decanoate compared with the oral group, and this was attributed to the fact that 35% of patients receiving the former treatment developed severe akinesia. Akinesia was measured by the BPRS and included such items as emotional withdrawal, depressed mood, blunted affect as well as motor retardation [63]. Importantly, the authors noted that patients on oral fluphenazine were relatively reliable pill takers (as defined by pill counting and urine tests)—a fact that renders the efficacy results fairly meaningless.

Hogarty et al. [54] conducted an important two-year study in 105 schizophrenia outpatients. The authors demonstrated that fluphenazine decanoate decreased relapse, but only when combined with intensive individual and family social therapy. In fact, no patient relapsed in the group treated with fluphenazine decanoate and social therapy after month eight, until the end of the study. Interestingly, there was no impact of social therapy in patients treated with oral fluphenazine. Moreover, analyses revealed that fluphenazine decanoate was associated with significantly more symptoms of depression and anxiety, whereas fluphenazine hydrochloride was associated with more positive symptoms [54]. A larger study by Schooler et al. [55] among 214 schizophrenia outpatients did not find a difference in relapse or side effects between fluphenazine decanoate and oral fluphenazine in schizophrenia outpatients over a period of 1 year. However, the oral equivalent mean dose was higher (25 mg/d), and the decanoate dose was lower (34 mg/3 w) than in some previous studies, which makes interpretation difficult [55]. Taken together, the aforementioned studies suggest that

TABLE 2: Randomized and naturalistic studies comparing LAIs with their oral equivalents.

Study	N	Duration	In/out, patient	Design	Antipsychotic dose	Dropouts <i>Relapse</i>	Dropouts <i>Side effects</i>	Comments
Zuardi et al. [47]	22	16 weeks	In	RDM DB	HAL DEC 20 mg IM/4 w: 1 mg/d PO*	ND	ND	LAI = marginally better efficacy and more EPS
Kinross-Wright and Charalampous [48]	40	6 weeks	In	RDM DB	FLZ ETH# 25 mg IM/2 w versus 2.5–7.5 mg PO	ND	ND	—
Ravaris et al. [49]	39	24 weeks	In	RDM DB	FLZ ETH 12–25 mg IM/2 w versus 2.5–10 mg PO	5% (LAI) 0% (PO)	5% (LAI) 6% (PO)	—
Haider [50]	43	6 weeks	In	RDM DB	FLZ ETH 25 mg IM/2–3 w versus 2.5–10 mg/d PO	ND	ND	LAI = more EPS
van Praag et al. [51]	50	4 weeks	In	RDM DB	FLZ ETH# 25 mg IM/3 w versus 7 mg/d PO	ND	ND	LAI = more EPS
Del Giudice et al. [52]	88	15 months	Out	RDM SB ^p	FLZ ETH# 25 mg IM/2 w versus 22 mg/d PO	ND	ND	LAI = longer time to relapse and more EPS
Rifkin et al. [53]	73	12 months	Out	RDM DB	FLZ DEC 12.5 mg IM/2 w: 5 mg/d PO ⁺	4% (LAI) 7% (PO)	22% (LAI) 4% (PO)	LAI = more EPS
Hogarty et al. [54]	105	24 months	Out	RDM DB	FLZ DEC 34–43 mg IM/2 w versus 10–12 mg/d PO	23% (LAI ^{+ST}) 50% (LAI) 55% (PO) 66% (PO ^{+ST})	9% (LAI) 0% (PO)	LAI = more anxiety/depression, but less positive symptoms
Schooler et al. [55]	214	12 months	Out	RDM DB	FLZ DEC# 34 mg IM/3 w versus 25 mg/d PO	24% (LAI) 33% (PO)	5% (LAI) 4% (PO)	—
Arango et al. [56]	46	12 months	Out	RDM OL	ZUC DEC# 233 mg IM/2 w versus 35 mg/d PO	4% (LAI) 5% (PO)	ND	LAI = less violence
Chue et al. [26]	541	3 months	Both	RDM DB	RIS MIC 25–75 mg IM/2 w versus 2–6 mg/d PO	4% (LAI) 3% (PO)	6% (LAI) 5% (PO)	LAI = less prolactin elevation
Bai et al. [57]	50	12 months	In	RDM SB ^l	RIS MIC 25–50 mg IM/2 w versus 4–6 mg/d PO	8% (LAI) 0% (PO)	4% (LAI) 0% (PO)	LAI = lower UKU score, lower EPS and prolactin levels

TABLE 2: Continued.

Study	N	Duration	In/out, patient	Design	Antipsychotic dose	Dropouts <i>Relapse</i>	Dropouts <i>Side effects</i>	Comments
Eli Lilly [58]	524	24 months	Out	RDM OL	OLZ PAM 150–405 mg IM/4 w versus 5–20 mg/d PO	16% (LAI) 10% (PO)	10% (LAI) 10% (PO)	LAI = less rehospitalisations
Kane et al. [25]	1065	6 months	Out	RDM DB	OLZ PAM 45 mg IM/4 w versus 150 mg IM/2 w versus 405 mg IM/4 w versus 300 mg IM/2 w versus 10, 15, 20 mg/d PO	6% (LAI ^{HI}) 13% (LAI ^{MD}) 19% (LAI ^{LO}) 8% (PO)	3% (LAI ^{HI}) 3% (LAI ^{MD}) 5% (LAI ^{LO}) 3% (PO)	—
Kim et al. [60]	50	24 months	Out	NAT (FEP)	RIS MIC [#] 29 mg/2 w versus 3 mg/d PO	23% (LAI) 75% (PO)	ND	LAI = lower relapse rate
Zhu et al. [59]	299	12 months	Out	NAT	HAL DEC [#] 100 mg/4 w versus 11 mg/d PO FLZ DEC [#] 25 mg/2 w versus 12 mg/d PO	ND	ND	LAI = longer time to discontinuation
Tiihonen et al. [61]	2230	3.6 years [#]	Out	NAT (FEP)	PER DEC versus oral equivalent	ND	ND	LAI = lower risk of rehospitalization
Tiihonen et al. [9]	2588	24 months	Out	NAT (FEP)	RIS MIC, HAL DEC, PER DEC, ZUC DEC versus oral equivalent	ND	ND	LAI = lower risk of rehospitalization

In = inpatients; Out = outpatients; # = mean; * = ratio; +ST = fluphenazine decanoate + social therapy; : = ratio; FEP = first-episode psychosis; UKU = Udvalg for Kliniske Undersøgelser Side Effect Rating Scale; LAI = long-acting injectable antipsychotic; PO = oral equivalent; NAT = naturalistic design; RDM = randomized; DB = double blind; SB^I = investigator blind; SB^P = patient blind; OL = open label; ND = no usable data; FLZ DEC = fluphenazine decanoate; FLZ ETH = fluphenazine enanthate; ZUC DEC = zuclopenthixol decanoate; HAL DEC = haloperidol decanoate; PER DEC = perphenazine decanoate; RIS MIC = risperidone microspheres; OLZ PAM = olanzapine pamoate; HI = high dose; MD = medium dose; LO = low dose; + = the typical patient was treated with 10–20 mg oral fluphenazine.

fluphenazine decanoate and enanthate may be associated with similar or more side effects than oral fluphenazine. This finding could be explained by the initial spikes in plasma levels as well as decreased conversion of fluphenazine to its clinically inactive sulfoxide metabolite [30, 64]. Additionally, the results may be explained by the fact that more patients are assumed to be noncompliant in the oral fluphenazine group, and thus to experience less side effects (but see [53]). Concerning efficacy, the studies suggest that there is a benefit of injectable fluphenazine preparations in reducing time to relapse among schizophrenia outpatients when combined with additional interventions such as intensive social therapy and/or a nurse available for home visits.

3.3. Zuclopenthixol Decanoate. The only study involving zuclopenthixol was a 1-year study in 46 schizophrenia outpatients with previous violence [56]. The study demonstrated

that schizophrenia patients on zuclopenthixol decanoate reduced the number of violent episodes per month of the study and increased the number of months of adherence to medication. Moreover, the authors found that PANSS positive scores were nonsignificantly lower in decanoate-treated patients. However, it is possible that the lack of difference in symptoms may be a type-II error since these patients also had significantly higher PANSS-positive scores at baseline, relative to patients treated with the oral formulation (despite randomization) [56].

3.4. Risperidone Microspheres. Long-acting risperidone was compared with its oral equivalent in two randomized trials. A 12-week study among 541 inpatients and outpatients found no efficacy difference, but risperidone LAI (25 mg, 50 mg or 75 mg/2 w) produced significantly less prolactin elevation than oral risperidone (2 mg, 4 mg, or 6 mg/d)

[26]. Similarly, a 48-week study by Bai et al. [57] in 50 inpatients revealed no significant differences in overall efficacy; however, long-acting risperidone (25 mg, 37.5 mg, or 50 mg/2 w) produced significantly less EPS and prolactin elevation and lower serum concentrations of 9-hydroxy-risperidone (9-OH risperidone, paliperidone), relative to oral risperidone (4 mg, 5-6 mg, or 7+ mg/d) [57]. However, subanalyses revealed that patients who received the two lowest doses showed increased PANSS scores and an increased tendency to relapse. Taken together, these data reveal that risperidone LAI may produce equal or less side effects, compared to oral risperidone. The data may be explained by the fact that treatment with long-acting risperidone leads to significantly lower serum concentrations of risperidone and 9-OH risperidone [65, 66]—the latter which also displays high affinity for D₂ receptors [67]. They may also be explained by the lack of “breakthrough EPS” and depressive symptoms associated with long-acting risperidone, in contrast to fluphenazine LAIs. Finally, the differences may be explained by the difficulty in finding equivalent doses between LAIs and oral antipsychotics. Interestingly, Bai et al. [57] found that 25 mg and 37.5 mg/2 w provided insufficient efficacy when switching from 4 mg and 5-6 mg/d oral risperidone, respectively. Based on their results, the authors recommended that the threshold for switching should be reduced to oral risperidone 3 mg/d for risperidone LAI 37.5 mg/2 w, and oral risperidone 5 mg/d for risperidone LAI 50 mg/2 w.

3.5. Olanzapine Pamoate. An unpublished, open-label, 2-year study among 524 outpatients evidenced that those treated with olanzapine pamoate required significantly fewer hospitalizations; however, there were no other major differences in efficacy or side effects [58]. Moreover, a recent 24-week study has found similar efficacy between a high and a medium of olanzapine pamoate (300 mg/2 w; 405 mg/4 w) and oral olanzapine (10, 15, and 20 mg/d) in 1065 schizophrenia outpatients [25]. Patients treated with a low dosing regimen (150 mg/2 w) evidenced significantly more psychotic exacerbation, compared to those treated with the high dose. Olanzapine plasma levels in patients treated with the 405 mg/4 w dose were lower than that of patients maintained on the oral equivalent of 15 mg/d, and they evidenced (nonsignificantly) less weight gain (15%; criteria $\geq 7\%$ of baseline) than patients treated with 300 mg/2 w (21%) and patients on 15 mg/d oral olanzapine (21%) [25], suggesting that this may be the optimal dosing to maintain high efficacy, without compromising tolerability, especially given the risk of inadvertent intravascular injections [24].

It is important to note that in most of the aforementioned randomized studies patients were selected on the basis of having been stabilized on (and likely adherent to) the oral equivalent prior to the study, resulting in a potential bias in favor of oral formulations [25]. This interpretation is consistent with results of Rifkin et al. [53], which found that patients on oral fluphenazine were, in fact, reliable pilltakers.

4. LAIs versus Oral Equivalent—Naturalistic Studies in Schizophrenia and FEP Patients

Naturalistic studies are an important indicator of the value of LAIs because they include patients for whom these agents are typically prescribed. Four naturalistic studies all found that LAIs were superior to their oral equivalents. Among the general population of schizophrenia patients, there is evidence that patients treated with haloperidol or fluphenazine LAI had a significantly longer mean time to all-cause medication discontinuation and were twice as likely to stay on medication, compared to patients treated with oral haloperidol or fluphenazine [59]. Among FEP patients, a 2-year study showed that risperidone LAI significantly reduced relapse and improved compliance, relative to oral risperidone [60]. Similarly, a cohort study of 2,234-consecutive FEP patients showed that perphenazine depot was associated with the lowest relative risk of rehospitalization, compared to oral perphenazine and other typical and atypical antipsychotics [61]. A more recent study by the same authors examined the risk of rehospitalization and drug discontinuation in 2,588 FEP patients [9]. The authors found that the risk of rehospitalization for FEP patients receiving LAIs was two thirds lower than for patients receiving the oral equivalent. These data support the notion that randomized studies in outpatients may underestimate the efficacy benefits of LAI therapy because they underrepresent noncompliant schizophrenia patients.

5. LAIs for SUDs

The lifetime prevalence of comorbid SUDs in schizophrenia patients is estimated to be nearly 50% [68]. Among FEP patients, a recent 2-year followup study found that 24% of individuals abused either alcohol or drugs at baseline and 72% of substance abusers, and 31% of nonabusers had experienced at least one occasion of involuntary hospitalization [69]. In general, studies suggest that compared to nonabusing patients, dual diagnosis schizophrenia patients have more psychiatric symptoms and EPS [70], they are more frequently hospitalized, suicidal, impulsive and violent, homeless, and unemployed, and they have more legal and health problems [71, 72]. Moreover, substance use is commonly associated with poor adherence to antipsychotic treatment, and, naturally, LAIs are commonly recommended as for improving adherence in psychosis patients with comorbid SUDs [14, 31, 73]. In order to better elucidate the potential implications of prescribing LAIs to SUD patients, we examined the literature for comparative studies in dual diagnosis patients. Due to the lack of LAI trials in this group, we also included randomized studies administering LAIs in nonpsychosis substance abusers.

Only one published study exists, which randomized dual diagnosis patients to treatment with an LAI. It was a 6-month, open-label trial that compared long-acting risperidone with zuclopenthixol decanoate in outpatients with mixed SUDs [74]. The authors found that schizophrenia patients treated with risperidone LAI evidenced significantly diminished substance use (measured by urine screens), less

PANSS-negative symptoms, less EPS, and better compliance with a substance abuse treatment program. Unfortunately, however, all patients relapsed in both treatment groups [74]. In addition, a retrospective study compared the effectiveness of oral olanzapine, risperidone, ziprasidone, and typical LAIs in tobacco-dependant inpatients with mixed SUDs, undergoing a 90-day substance abuse treatment program [75]. Results revealed that significantly fewer patients treated with olanzapine and typical LAIs completed the program, relative to those treated with risperidone. Moreover, patients treated with oral olanzapine and typical LAIs stayed for a shorter time in treatment, and all claimed that they planned to smoke immediately after discharge, compared to only 56% for risperidone and 50% for ziprasidone [75]. Knowing that cigarette smoke induces the enzyme (CYP1A2) responsible for the metabolism of olanzapine and most typicals [76, 77], and that patients were forbidden to smoke during the program, it was hypothesized that individuals on olanzapine and typicals were noncompliant with treatment because they were experiencing more side effects due to rising plasma levels of the antipsychotics. Indeed, the authors noted subtle effects such as mild sedation that affected cognitive ability or motivation and led the patients to be recorded as being “sleepy” or “inattentive” [75].

Four studies randomized nonpsychosis SUD patients to treatment with an LAI, relative to placebo. A large 6-month trial in nonpsychosis alcoholics found that flupenthixol decanoate (10 mg) aggravated relapse to alcohol use, relative to placebo, possibly due to increased craving for alcohol [78]. Another study reported that long-acting risperidone had no effect on cocaine use or craving but significantly aggravated depressive symptoms, compared to placebo [79]. Two other studies evidenced high rates of EPS following the administration of flupenthixol decanoate in cocaine abusers [80–82]. Specifically, a pilot trial found that a large portion of individuals treated with flupenthixol decanoate (12 mg) experienced severely disturbing akathisia, dysarthria, myalgia, and dystonia that required medical intervention after they smoked crack cocaine [80, 81]. More recently, an experimental study by Evans et al. [82] has showed that flupenthixol decanoate (10 and 20 mg) dose dependently increased the desire for cocaine, drug liking, drug potency and good drug effects in cocaine abusers given intravenous injections of cocaine. The study was terminated by the sponsor after the second of seven subjects experienced a dystonic reaction in the high-dose flupenthixol group. Intriguingly, the latter two studies provide clinical evidence for the existence of dopaminergic supersensitivity to psychostimulant challenge—a consequence of repeated antipsychotic treatment in preclinical models [83].

Altogether, the preliminary studies on LAIs in psychosis and nonpsychosis substance abusers show the potential for these agents to aggravate of substance abuse, possibly through increased incidence of adverse events (anhedonia, EPS, sedation) and drug liking/craving. In comparison to typical LAIs, long-acting risperidone seems to produce better outcomes and may be helpful, especially when relapse and rehospitalization due to noncompliance is a concern. In addition, oil-based vehicle should be avoided for SUD

patients because they are cleared from the system more slowly. Oil-based vehicles such as sesame seed oil and viscoleo may extend the half-life of antipsychotics by accumulating in tissue and prolonging absorption [84]. For example, there is evidence that six months after discontinuation of treatment with low-dose haloperidol decanoate (30–50 mg/4 weeks), D₂ receptor occupancy reached 24%, 32% and 34% in three of four patients [85]. Likewise, other studies have reported persistently elevated plasma fluphenazine and prolactin levels for up to six months following administration of the decanoate ester [33–35]. The aforementioned findings suggest that risperidone LAI should be preferred to typical LAIs when the goal is to minimize side effects, whilst combating relapse due to that noncompliance, in psychosis patients with comorbid SUDs. Further research is required to make conclusions about other atypical LAIs for schizophrenia patients with SUDs.

6. LAIs for Involuntary Outpatient Commitment

Despite the potential benefits, prescription of LAIs is not a guarantee of compliance. For example, a study by Olfson et al. [86] in California MEDICAID patients prescribed an LAI for poor compliance found that less than 10% of patients continued treatment after the six-month follow-up. This suggests that a legal framing in the form of involuntary outpatient commitment—in conjunction with the help of an interdisciplinary team—can be necessary to ensure the observance of LAIs. In Québec, the order for involuntary outpatient commitment is obtained within via the Supreme Court of Québec for the patients whose capacity to take care of themselves is deteriorated by lack of awareness of illness and difficulty of evaluating the advantages/disadvantages of agreement or refusal of treatment. The purpose of it is to help the patients to control their disease and possibly, to regain control of their life. Even if it appears paradoxical, this coercive step aims at as well as possible guaranteeing the autonomy of the person, especially because lack of insight is an integral symptom of the disease [3]. Moreover, despite obvious concerns that outpatient commitment may negatively affect the therapeutic alliance, our data among 39 schizophrenia patients who explicitly refused treatment revealed that the therapeutic alliance remained unchanged, even after the legal procedure [87]. Recently, an expert consensus panel from the *association des médecins psychiatres du Québec* (AMPQ) has recommended more widespread prescription of LAIs and involuntary outpatient commitment—with the goal of increasing treatment compliance among FEP patients (Figure 1) [12]. In the countries where the regulation of LAIs is more frequent, it is generally less difficult enforce outpatient commitment than in Québec. In Australia, for example, a one-page report of health signed by only one psychiatrist, the “community treatment order”, is enough to obtain authorization to treat a patient without his consent, with the aim of avoiding future deterioration and preventing it when it occurs [88, 89].

In this context, three studies compared oral to depot antipsychotics for schizophrenia patients on involuntary

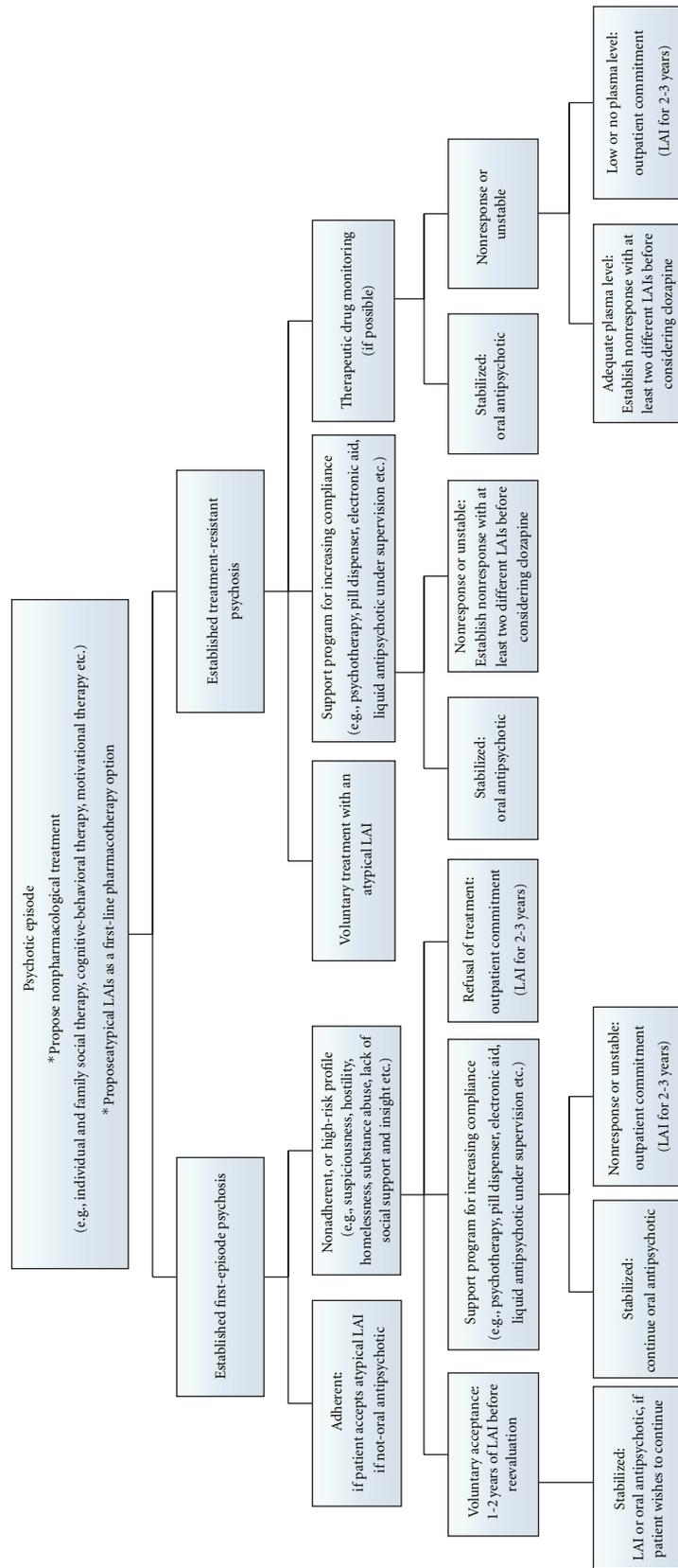


FIGURE 1

Expert consensus guidelines for LAI use in schizophrenia (adapted from Stip et al. [12]).

outpatient commitment/community treatment orders [88–90]. One retrospective study found significantly less medication adherence and more rehospitalization among 123 patients on community treatment orders who were receiving oral antipsychotics, compared to those receiving LAIs [88]. Another retrospective study among 94 community treatment orders patients revealed that LAIs were associated with fewer crisis team referrals and other episodes of relapse [89]. In addition, a prospective study found that patients undergoing sustained periods of involuntary outpatient commitment (six months or more) were more likely to remain compliant with medication and other treatment, relative to those who underwent only brief outpatient commitment or none [90]. In that study, administration of depot antipsychotics significantly improved treatment adherence independently of the effect of sustained outpatient commitment. As a whole, these preliminary case-control trials reveal that LAIs may be an important tool to improve outcomes in patients on involuntary outpatient commitment and they highlight the need for better controlled trials to confirm the superior efficacy of LAIs in this population.

7. Conclusion

The present systematic review compared LAIs with their oral equivalents in order to avoid bias associated with comparing different molecules in the oral and injectable forms. Randomized studies suggest that not all LAIs are the same; for example, long-acting risperidone may be associated with equal or less side effects than oral risperidone, whereas fluphenazine enanthate and decanoate may be associated with equal or more side effects than oral fluphenazine. These differences may be the result of more predictable drug delivery via the use of microspheres [17, 31]. However, these conclusions are limited because of the difficulty in finding appropriate equivalent doses from oral antipsychotics to LAIs and the wide ranges of equivalent doses noted in different studies [91–93]. In addition, randomized studies suggest that LAIs reduce risk of relapse when combined with additional interventions such as individual and family social therapy and/or a nurse available for home visits. On the other hand, randomized studies may have underestimated the benefits of LAIs because of underrepresentation of the nonadherent patient population. Indeed, large-scale naturalistic studies show major benefits of LAIs versus oral antipsychotics, especially among FEP patients [9, 61]. Among SUD patients, preliminary studies indicate that risperidone LAI may be the preferred compound, possibly due to a lower rate of side effects and interactions with drugs of abuse. Nonetheless, clinicians must be aware of the potential for antipsychotics to interact with psychostimulants, resulting in increased EPS and, in some cases, enhanced drug liking/craving and drug relapse, especially at high doses [75–77]. Preliminary studies also suggest that LAIs may reduce violence in patients with a history of violence and decrease relapse and rehospitalization in schizophrenia patients on involuntary outpatient commitment, relative to oral antipsychotics [56, 88–90].

Despite the potential advantages of LAIs, their use in the United States, Canada, and Germany remains the lowest among developed countries [94]. We feel that the evidence in favor of more widespread use of LAIs in schizophrenia (especially among FEP patients) is mounting, having been boosted by the advent of newer molecules and better methods of delivery. Nevertheless, we acknowledge that the efficacy benefits of LAIs may be constrained by the limitations of antipsychotics themselves. For example, at the end of the Del Giudice et al. [52] study, the chance of experiencing a relapse in patients treated with fluphenazine enanthate returned to the level of those treated with oral fluphenazine. These data indicate that LAIs do not prevent a patient from relapsing, but they may increase the time between relapses by improving adherence. Indeed, it is crucial that the only patients that evidenced sustained improvement on LAIs for over two years was the group who received intensive individual and family social therapy [54]. This finding is a testament to the importance of psychotherapy and quality followup services to maintain the benefits of LAIs [95, 96]. Further research is required to elucidate which special populations may benefit most from LAI therapy and which psychosocial interventions work best when paired with LAIs.

Disclosure

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