



Review

Treatment of early episode in patients with schizophrenia: the role of long acting antipsychotics

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ABSTRACT

The use of long-acting injectable antipsychotics (LAIs) in schizophrenia is usually restricted to patients in long-term treatment, who prefer them to oral antipsychotics, and to patients with multiple relapses who have a history of non-adherence. However, preliminary evidence from patients in the early phases of the disease suggest that second generation LAIs may be superior to second generation oral medications with regard to the control of negative symptoms and psychosocial functioning. Moreover, several studies have found that psychiatrists are generally reluctant to prescribe LAI antipsychotics and under-estimate their acceptability by patients. Key elements to take into account when offering a LAI in the early course of schizophrenia should include their potential superiority in allowing early detection of non-adherence and in reducing the number of rehospitalisations and relapses.

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1. Background

Schizophrenia has a chronic course in most cases characterised by recurrent episodes of acute psychosis alternating with periods of full or partial remission [1]. Patients require ongoing care for symptomatic control, relapse prevention and psychosocial rehabilitation [2].

Antipsychotic agents are the mainstay treatment of schizophrenia, as they have been shown in clinical trials and routine practice to decrease symptoms in the acute phase and also to prevent symptom recurrence and relapse in the longer term [3]. Long-acting injectable antipsychotics (LAIs) were developed

several decades ago as a strategy to address partial or covert non-adherence and to simplify complex medication schedules [4–6]. More recently, second generation antipsychotics (SGAs), have also become available as LAIs thus widening the therapeutic options [7–10]. In clinical practice, LAIs are prescribed to a low proportion of patients overall, and to an even lower proportion of first-episode patients [11–13]. In this review we describe the benefits and challenges associated with the use of antipsychotic LAI in patients in the early phase of the disease based on available evidence from the current literature.

2. Rationale for continuity of care in schizophrenia

The early phase of schizophrenia, comprising the first 2 to 5 years after the first acute episode are considered to be crucial in determining long-term prognosis [14]. For instance, a minimum of 3 months sustained remission of both positive and negative

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symptoms over the first 2 years of treatment is predictive of good functional recovery in first-episode patients [15]. Although most patients show a good initial response to antipsychotic treatment and achieve symptomatic remission after their first episode, recovery rates from both a clinical and a social perspective are generally low (13.5%) [16], and around 15% of patients have a chronic course of illness after relapse despite long-term treatment [17]. The incidence of acute episodes is particularly high in the first 5 years after the initial episode with a cumulative first relapse rate of 81.9%; of those 78% will have a second relapse, and a further 86.2% of those will go on to have a third relapse [1]. Relapse risk is the same in remitted and non-remitted patients, and even with detailed assessment clinicians are not able to predict who will suffer a relapse [18]. Subsequent episodes are associated with a progressively longer time to achieve remission [19], worse treatment response, increased risk of symptom chronicity [20], and a gradual psychosocial deterioration [21].

The risk of relapse is mitigated by antipsychotic medication. The risk increases immediately after stopping medication and remains high over time [1], while maintaining antipsychotic treatment is associated with reduced risk of relapse, fewer hospitalizations, and better quality of life compared with placebo or no treatment [18]. Stopping antipsychotic medication after an acute episode or using medication intermittently during maintenance treatment is associated with increased risk of symptom worsening or relapse [22]. In patients who have remitted from a first episode, the mean one-year risk of psychotic symptom recurrence after medication discontinuation is 77% compared to 3% under maintenance treatment [23]. Moreover, after stopping medication, recurrence of psychotic symptoms usually occurs within a short period of time (16 days on average), even in patients with optimal outcome, and does not depend on the time to achieve remission or the length of remission [17,24,25].

The consequences of relapse faced by patients include the risk of harming themselves or others, impoverishment in personal relationships, discontinuation of education or work, and stigmatization, all leading to loss of self-esteem and reduced quality of life [26,27]. Relapses often have a negative emotional and financial impact on families and caregivers, and are associated with risk of rehospitalisation and high costs due to increased healthcare resource utilization [28–32].

3. Challenges of continuity of therapy for early episode patients

Despite general agreement on the need for continued, long-term treatment for relapse prevention, non-adherence to oral medication is a well-known problem that occurs regardless of the type of antipsychotic prescribed, first or second generation [33–35]. Partial and complete non-adherence are recognised as strong predictors of relapse in patients treated after their first-episode [1,36,37]. The discontinuation rates of oral antipsychotics in chronic schizophrenia have been estimated to be as high as 74% after 18 months of therapy [38]. In first-episode about 46% continued their initial treatment for 30 days or longer [13], and 42% discontinued treatment within 1 year [39]. Risk factors for non-adherence may be patient-related (e.g. impaired insight or substance abuse); environment-related (e.g. stigmatization or poor social and familial support); physician-related (e.g. poor relationship or contact with the therapist); and treatment-related (e.g. lack of efficacy or complex medication schedule) [40]. A recent systematic review on medication adherence in schizophrenia found that lack of insight, mistrust of the effectiveness of medication and substance abuse were the key drivers, and greater risk of relapse, hospitalization and suicide were the key consequences [41]. Finally, subjective ratings by psychiatrists, chart reviews, and

self-reports by patients or relatives, show that adherence to oral medication is overestimated and that non-adherence is often not accurately identified [40].

Strategies to improve adherence include psychosocial interventions (e.g. psychoeducation, compliance therapy, and cognitive adaptation therapy), programmatic strategies (e.g. directly observed therapy [DOT] programs based on the direct observation of patients taking their medications), and interventions related to pharmacotherapy (e.g. close monitoring for medication side effects such as weight gain, sedation or extrapyramidal symptoms), simplification of medication regimens (e.g. considering agents with longer plasma half-lives or using medications with once-daily dosing), and switching to LAI antipsychotics [42]. Different approaches may be necessary to improve adherence depending on the patient, since non-adherence can be non-intentional (when the patient deviates from dosage or timing), related to cognitive impairment, or intentional (leading to overt or covert full or partial non-adherence), related to poor insight [43–45].

4. Place of LAI antipsychotics in early stages of schizophrenia

LAI antipsychotics are recommended by most evidence-based clinical guidelines for patients who need maintenance treatment and explicitly prefer them over oral antipsychotics, and in patients with multiple relapses who have a history of non-adherence [22,46,47]. However, the Texas Medication Algorithm Project (TMAP) for antipsychotics in schizophrenia [48], and the recent Canadian guidelines recommend the use of LAI antipsychotics in all phases of the disease, including the first 2 to 5 years [49]. Moreover, the recently published consensus-based guidelines for the use and management of LAI antipsychotics in clinical practice by the French Association for Biological Psychiatry and Neuropsychopharmacology (AFPBN) is the first to recommend systematic offering of LAI antipsychotics as first line treatment to schizophrenic patients who need maintenance treatment [50].

There is general reluctance in using LAI antipsychotics in routine clinical practice in first-episode patients. This reluctance may be present even when patients are considered poorly adherent [51]. More than 50% of patients are not offered the option of LAI antipsychotics [11,52]; and less than 30% of patients are prescribed LAIs in preference to oral antipsychotics [12,53–55]. A recent study conducted in Germany found that clinicians were reluctant to prescribe LAI antipsychotics even when, by their own assessment, they suspected or anticipated non-adherence [56]. In the case of first-episode patients, a survey conducted in the UK reported that although half of the psychiatrists considered LAI antipsychotics as an option, less than 15% went on to prescribe LAIs [11–13]. Results from surveys of clinician attitudes conducted in 2007 and 2011 show that psychiatrists believe that patients with first-episode schizophrenia will probably reject LAI antipsychotics [11,12]. However, 73% of first-episode patients participating in a prospective trial accepted the recommendation to receive risperidone LAI (RLAI) [57]. Psychiatrists are also of the opinion that patients are difficult to convince because they have not yet experienced further relapses and that the availability of SGAs in LAI formulations is limited [12]. This latter concern has been addressed as several SGAs are now available as LAIs and data are accumulating on their efficacy and tolerability in first-episode patients [8,9,58].

5. Evidence for the use of LAI antipsychotics in first-episode schizophrenia

The evidence on the use of LAIs in first-episode or recent onset schizophrenia is far from conclusive as available studies have methodological limitations, particularly single-arm designs not

comparing oral antipsychotics with LAIs, the lack of differentiation between first and second generation LAIs, and confounding factors such as patient selection bias. For this review we only included studies comparing oral with first and second generation LAI antipsychotics, and only considered prospective naturalistic studies or randomised controlled trials. The search yielded a total of six studies that are summarised below; exhaustive information on all available studies can be found in other recent reviews [8–10].

Kim and colleagues compared relapse rates in patients diagnosed with first-episode schizophrenia and treated in an open label design either with RLAI ($n = 22$) or oral risperidone ($n = 28$) [59]. At 1 and 2 years of follow-up, patients on RLAI had significantly lower relapse rates associated with longer periods of adherence and higher rates of adherence than patients on oral risperidone (68% vs. 32%). Additional benefits in the RLAI treated patients included greater reduction in the total Positive and Negative Syndrome Scale (PANSS) (10% vs. 2%; $p = 0.001$), and in the Clinical Global Impression-Severity (CGI-S) scale (10% vs. 2.5%; $p = 0.001$) and greater functional improvement as measured by the General Assessment of Functioning (GAF) scale, with patients on RLAI showing an increase of 26% while patients on oral risperidone experienced a 0.5% improvement ($p = 0.001$).

A prospective randomised controlled study specifically compared medication adherence during continuation treatment in first-episode patients (with ≤ 16 weeks of lifetime total antipsychotic medication exposure) following stabilization with oral risperidone [57]. Eleven patients received continuation treatment with oral risperidone while twenty-six were treated with RLAI. Almost three-quarters of patients (73%) accepted the recommendation to take RLAI. At 12 weeks, patients on RLAI were more likely to remain adherent than patients who remained on oral risperidone (89% vs. 59%; $p = 0.035$). There was no effect of RLAI on attitudes such as stigma, distress from side effects or problems with medication route. A subsequent follow-up of the same patients when they entered maintenance treatment [60] did not find any significant difference between RLAI and oral risperidone in time to initial non-adherence at 104 weeks and in attitudes to medication.

Another recent randomised controlled trial enrolled subjects in the early phase of the disease (schizophrenia diagnosis < 3 years before study entry) who were either medication naïve or had been taking SGA (oral risperidone, olanzapine or quetiapine), and started maintenance treatment after stabilisation [61]. There were no differences in the CGI-S scores, PANSS total and positive symptoms subscale scores between patients randomised to RLAI ($n = 42$) or continuing on oral SGA ($n = 35$). However, the post-hoc analysis on the change in PANSS negative symptom subscale scores showed differences between groups over time. Negative symptom scores decreased between baseline and study endpoint for both groups. During the stabilization phase, this decrease was greater and only significant in the RLAI- but not in the oral treatment group ($p = 0.0007$). However, from stabilisation to study end only the oral group showed a significant decrease in negative symptom scores ($p = 0.005$). There were no statistically significant differences between groups regarding time to stabilization, defined as at least 4 weeks of improved or stable values (< 4) on the CGI-S scale, or time to relapse according to Csernansky et al. criteria [62].

Besides studies focused on clinical outcomes, there may be evidence that improved medication adherence with LAI in early treatment of schizophrenia (less than 2 years from onset) may influence frontal lobe intracortical myelin and white matter volume [63,64]. Structural magnetic imaging data were acquired at baseline and at 6 months from patients randomized to RLAI ($n = 9$ –11) or oral risperidone ($n = 13$) and healthy individuals ($n = 12$ –14). Brain scans were analysed by a rater who was blinded

to clinical and demographic characteristics of subjects. Frontal white matter volume remained stable over the 6-month study period in patients on RLAI but declined significantly in the oral risperidone group ($p < 0.05$). Of note, stability in frontal lobe white matter volume was associated with a faster reaction time in executive tasks of working memory ($p = 0.045$) and mental flexibility ($p = 0.029$). A further analysis focused on intracortical myelination (ICM) volume, which is known to decline with illness chronicity in schizophrenia [64]. Compared to baseline, patients treated with RLAI had increased ICM volume compared with controls ($p = 0.005$), while ICM volume the group treated with oral risperidone was comparable with controls. This preliminary evidence indicates that improved adherence associated with LAIs might mitigate disruption in myelination that has been hypothesised to contribute to the aetiology of schizophrenia.

6. Discussion

Effective treatment in schizophrenia is crucial in order to avoid the high risk of relapse after the first psychotic episode. Subsequent episodes have a negative impact in the patients' quality of life and psychosocial functioning, are associated with negative long-term prognosis and gradual clinical deterioration and increase the health and economic burden to families and society. Although antipsychotic treatment helps to prevent relapse, regular medication adherence remains a major challenge, since about half of patients treated for their first-episode will discontinue initial treatment within a short time period.

LAIs have several advantages over oral antipsychotics: they are administered by a mental health professional which has the potential of increasing therapeutic contacts; allow for the easy and quick detection of non-adherence which facilitates immediate intervention; decrease the risk of accidental or deliberate overdose; the parenteral route avoids first-pass metabolism, which reduces the risk of drug-drug interactions; and last but not least, injections offer stable plasma concentrations that avoid high fluctuations and reduce risk of drug levels below or above the desired range. Compared with oral antipsychotics, meta-analyses based on randomised clinical trials (RCTs) [65–67] regarding the effectiveness of LAIs in patients at any stage of the disease suggest that LAIs reduce hospitalizations and may also reduce the rate of relapse. A meta-analysis of mirroring studies, which seem closer to a real-life clinical setting than RCTs, found substantial superiority of LAIs compared with oral antipsychotics in preventing hospitalization [67]. A significant advantage for LAIs versus oral antipsychotics was also observed in prospective and retrospective observational studies, which reflect real-life treatment settings in terms of discontinuation, relapse and rehospitalisation rates [68,69].

It is arguable whether RCTs are the most appropriate study design in comparing LAIs with oral antipsychotics in particular regarding adherence [70,71] since patients enrolled in such studies are likely to be more compliant with treatment advice in general. This is why alternative “effectiveness trials” closer to real-world conditions have been proposed. Ideally, they should be prospective, conducted at multiple sites, use broad inclusion criteria, require minimal data, focus on patients in a relatively early phase of illness, and follow patients for at least 2 years, with the primary outcome measures being relapse and/or hospitalisation [70].

Although we excluded several studies because of their methodological limitations they also support the role of LAIs in prevention of relapse and hospitalization [13,72,73]. The studies we included all compared risperidone LAIs with its oral formulation because data on more recently introduced SGA-LAIs such as olanzapine pamoate, paliperidone palmitate, and

aripiprazole depot are still lacking in first-episode or recent onset schizophrenia.

A noteworthy observation emerging from existing studies is that psychiatrists are reluctant to offer LAIs in patients at the early stages of their illness and tend to over-estimate potential objections by patients. Given that LAIs are likely to reduce hospitalisation and relapse they should be given due consideration in the treatment of early schizophrenia. Other potential beneficial effects on negative symptoms, cognitive deficits and brain plasticity should also be taken into account.

7. Conclusion

Newer, second generation antipsychotics (SGAs), including some LAIs, are an important and valuable treatment option for patients with first-episode or recent onset schizophrenia.

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