RAP

Review article

May second generation long-acting injectable antipsychotics be prescribed as a first-line treatment of first episode in patients with schizophrenia? An overview

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Abstract

Schizophrenia is a chronic and disabling disorder, characterized by positive, negative, cognitive and affective symptoms. The first episode of schizophrenia (FES) usually occurs after a variable period of prodromic symptoms and the importance of early detection and treatment of FES has been raised in psychiatric literature from long time. In fact, it has been suggested that the first years of the schizophrenic disorder may be a critical period for long-term prognosis, as the relationship between the poor medication adherence and poorer outcome is well demonstrated. Long-acting injectable formulations of second-generation antipsychotics (SGAs-LAIs) provide constant medication delivery and the potential for improved adherence. Currently, four SGAs-LAIs are available for the treatment of schizophrenia, risperidone long-acting injectable, olanzapine pamoate, paliperidone palmitate and aripiprazole. Several studies have also demonstrated efficacy and safety of such drugs in patients with schizophrenia. In the present paper the literature on SGAs-LAIs atypical antipsychotics in the treatment of FES will be reviewed and practical advice will be given concerning the use of this drug in the everyday clinical practice.

KEY WORDS: first-episode of schizophrenia, long-

acting, second-generation antipsychotics, risperidone long-acting, olanzapine pamoate, paliperidone palmitate, schizophrenia, adherence, efficacy, tolerability.

Introduction

Schizophrenia is a chronic and disabling disorder, characterized by positive, negative, cognitive, and affective symptoms (1-3). The course of schizophrenia may be complicated by the potential occurrence of suicidal and/or violent behaviors, substance abuse and medical comorbidity, with sustained morbidity and disability that may severely impair quality of life of patient and shorten their lives (4-6). The first episode of schizophrenia (FES) usually occurs after a variable period of prodromic symptoms and the importance of early detection and treatment of first-episode schizophrenia has been raised in psychiatric literature from long time (7). In fact, it has been suggested that the first years of the schizophrenic disorder may be a critical period for long-term prognosis, as the relationship between the delay in treatment of FES and poorer outcome is well demonstrated (8).

Long-acting injectable antipsychotics (LAIs) have been commonly considered as an adherence intervention for patients who are 'non-compliant' with the oral medication they have been prescribed (9). In particular, there are some concern of their use as a first-line treatment in FES, and this may be particularly true for first generation LAIs, that are burdened by several adverse effects (such as extrapyramidal side effects, tadive diskynesia and QT prolongation) (10). However, the availability of the second-generation long-acting injectable antipsychotics (SGAs-LAIs) represents an advance in the long-term management of schizophrenia, particularly regarding subjective tolerability (11). In fact, SGAs-LAIs have been shown to have at least equal or even superior efficacy and to be associated with less propensity to induce parkinsonism and tardive diskynesia compared with first generation LAIs, although some SGAs-LAIs may be associated with an increased incidence of metabolic side effects (12).

Interestingly, another point in favour of SGAs-LAIs could be their potential efficacy in problematic patients with schizophrenia such as those in comorbidity with alcohol and substance use disorder. This aspect has been recently reported in some studies. Risperidone long-acting injection (RLAI) was more effective than zuclopenthixol-depot in improving substance abuse and schizophrenia symptoms in subjects with dual diagnosis (13). This observation was confirmed also by Meredith et al. (14).

Currently, in Italy, there are four available SGAs-LAIs (Tab. 1): RLAI, paliperidone palmitate (PLAI), olanzapine pamoate (OLAI) and aripiprazole. In the present review the literature on SGAs-LAIs in the treatment of FES will be reviewed and practical advice will be given concerning the use of these drugs in the everyday "real world" clinical practice.

Schizophrenia is associated with poor medication adherence: is this mostly true for first episode?

It is generally recognized that treatment non-adherence is a remarkable problem in the management of patient with schizophrenic disorder, with reported discontinuation rates more than 50% in several studies (15-17). It has been demonstrated that adherence with oral conventional and/or atypical antipsychotics is poor in both short and long term (18) and is associated with relapse, even if it is unclear whether non-adherence precedes the relapse or is a consequence of it (19-21). In the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) trial (22) the 74% of patients discontinued the treatment prematurely. Moreover, in the European First Episode Schizophrenia Trial (EUFEST) about 40% of patients discontinued their treatment within one year after the onset of the disorder (23).

In FES, there are a couple of variables that may cooperate in causing nonadherence (24, 25). The most common are the lack of insight, the sensation of a subjective distress as a result of side effects, the fear of potential side effects and the poor medication efficacy with symptoms' persistence (26-28). However, above all, one of the main factor associated with non adherence may be the wrong belief that treatment is no longer needed after few weeks or months, especially (and paradoxically) in presence of a perceived improvement (29). Furthermore, the comorbidity with substance abuse, the lack of a familiar and social effective support, the failure of therapeutic alliance, the complexity of some treatment regimens and, last but not least, the perceived stigma that is still associated with psychiatric disorders and antipsychotic treatment, may further contribute to non-adherence (30-34).

It has been demonstrated that neurocognitive dysfunctions are important predictors for non-adherence in patient with schizophrenia (35). The importance of cognitive deficits in schizophrenia is highlighted by reports indicating that the severity of cognitive deficits is predictive of treatment compliance, adherence, and risk of relapse among FES individuals (36-38). Moreover, social cognition appears to be compromised in all FES patients compared to healthy controls and this may be also a predictor of non adherence (39).

Even in case of successfully treatment of FES, the eventual non-adherence may be associated not only with relapse, but also with an increased mortality (40, 41). In fact, treatment nonadherence after the FES may be associated with increased suicide rates and death for consequences of medical illnessess such as diabetes, cardiovascular disorders, cancer and stroke (42-44). As stated by Kane (45) "…clinicians should educate patients about adherence and consider treatment options that will improve adherence. Recovery is attained when patients experience symptom remission, vocational role fulfillment, independent living, and social relationships for at least 2 years". Moreover, it has been demonstrated that SGAs-LAIs

Table 1 - SGA-LAIs currently available in Italy.

SGA	Brand name in Italy	Dosages	Initial Dosage	Maximum dosage	Type of injection	Dosage schedule	Cost Range (Euro)	Refrige-ration	Evidences for use in FES	Other
Risperidone	Risperdal IM ®	25 mg, 37.5 mg and 50 mg	25 mg	50 mg every two weeks	Intramuscular gluteal	Two weeks	157.41-253.88	Yes	Yes	It must be supplemented with oral formulation for 21 days from the first injection
Paliperidone	Xeplion™	50 mg, 75 mg, 100 mg, 150 mg	150 mg intradeltoidal and 100 mg intradeltoidal after one week	150 mg every month	Initial two injections intradeltoid, the others intradeltoid or gluteal	Four weeks	337.30-680.04	No	No	No oral supplementation required
Olanzapine	Zypadhera ™	210 mg, 300 mg, 405 mg	210-300 mg every two weeks	300 mg every two weeks	Intramuscular gluteal	Two or four weeks	244.28-488.55	No	No	Patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours
Aripiprazole	Abilify Maintena™	400 mg	400 mg	400 mg every month	Intramuscular gluteal	Four weeks	418.40	No	No	It must be supplemented with oral formulation for 14 days from the first injection

treatment may reduce the suicide risk in patient with schizophrenia, simply improving adherence. Ascher-Svanum et al. (46) demonstrated that OLAI was associated with a significantly lower incidence of psychiatric hospitalization due to suicide threats. However, most studies investigating incidence and predictors of suicide and mortality in patients with FES have relatively short follow-up intervals and, to date, no data have been published concerning the reduction of suicide risk with SGAs-LAIs treatment.
Therefore, the availability of SGAs-LAIs may be a favourable treatment option and should be considered since the first episode and not only at the last stages of schizophrenia (47). As argued by Stephen Stahl (48), "shall the last be first?".

Current guidelines on LAIs use in first-episode Schizophrenia

In 1998, the first published guidelines recommended that conventional LAIs should be considered for any patients with schizophrenia when a long-term treatment was necessary (49).
More recently, the American Psychiatric Association (50) recommended LAIs for patients with recurrent relapses related to partial or full nonadherence, but not explicitally as a first-line treatment in FES. In line with APA guidelines, also the Canadian Psychiatric Association Clinical Practice Guidelines (51) recommended LAIs to lower nonadherence in patients with recurrent and multiple episodes and/or with persistent positive symptoms. Also the International Psychopharmacology Algorithm Projects (IPAPs) schizophrenia algorithm (http://www.ipap.org/schiz/) proposed the utilization of LAIs in patients with partial or complete noncompliance: again, there is no explicit recommendation on their use as a first-line treatment in FES, but one can argue that, implicitally, in case of non adherence, they may be accordingly used. On the other hand, the National Clinical Excellence (NICE) guidelines (52) recommend that LAIs (especially SGAs-LAIs) may be given after an acute episode of schizophrenia if the patient prefers and to avoid covert nonadherence to oral medication. This was also the advice of the World Federation of Societies of Biological Psychiatry (53). Also the PORT Recommendations (54) proposed that "long-acting injection antipsychotic medication maintenance treatment should be available and considered for persons who have a history of frequent relapse on oral medication, or a history of problems with adherence on oral medication, or who prefer the long-acting injection depot regimen".
In general, the current guidelines on schizophrenia treatment consider LAIs as drugs of choice for long-term therapy in patients who are nonadherent with antipsychotic medication and the use of such medications, especially SGAs-LAIs, may represent a promising strategy that should be employed in such patients to achieve symptoms' remission, prevent relapse and reduce all-causes mortality (55). Thus, even not formally declared, it can be argued that, implicitally, in all cases of non adherence in FES, the LAIs (preferably SGAs-LAIs) may be consequently used.

Psychiatrists' attitude toward LAIs use in the first episode of schizophrenia

Despite the effectiveness of LAIs in the treatment of schizophrenia, sometimes psychiatrists' attitude toward these agents is negative, especially in the treatment of FES (56, 57). In fact, concerning FES, some of the common reasons against early usage of LAIs are the long-established association of depot treatment as a coercive and stigmatizing therapy, the recommendation of guidelines to use first oral antipsychotics, the belief that a good therapeutic relationship may be a pro-adherence factor, the relative lack of long-term studies and the tolerability profile of LAIs (58). Although LAIs were recognized to be adherence-enhancing and strongly preventive of relapse, a great number of psychiatrists seemed to avoid prescribing depot antipsychotics especially for patients with FES (59). Psychiatrists frequently imagine that patients with FES would not accept depot antipsychotics and that depots are generally eligible for chronic patients (60). However, it should be argued that these belief are often not supported by scientific evidences that, instead, point out the need of ensuring adherence after FES even with the use of LAIs (61).
Moreover, lack of knowledge, misperceptions and stigma related to LAIs and other treatment options should be addressed by providing patients with accurate information (62). Psychiatrist should avoid making assumptions about patients' attitudes to LAIs as even if these attitudes vary, some FES patients not prescribed LAIs are favorable to considering this treatment (63). However, depot antipsychotics prescribing should always result from a shared decision-making process in which clinicians and patients explicitly discuss the pros and cons of different formulations and drugs (57).
Llorca et al. (64) selected 53 French psychiatrists working in the "real world" clinical practice and considered to be experts in the use of LAIs and submitted to them a questionnaire consisting of 32 questions that covered 539 therapeutic options grouped into 3 areas that were judged as essential: 1) Target-population: Description of the different indications of the LAI antipsychotics and of the most appropriate period of the illness to introduce the treatment. 2) Prescription and use: Choice of the molecule, methods of introduction, specific strategies depending on the psychiatric disorder or co-morbidities, and treatment monitoring. 3) Specific population: Use of LAI antipsychotics in pregnant women, elderly patients, subjects in a precarious situation, and subjects having to be treated in a prison establishment. Results showed that, in an evidence-based clinical approach, psychiatrists, through shared decision-making, should

be systematically offering to most patients that require long-term antipsychotic treatment an LAI antipsychotic as a first-line treatment. In particular, SGA-LAIs were recommended as maintenance treatment after the first episode of schizophrenia whereas first-generation LAIs were not recommended in the early course of schizophrenia.
However, it should be specified that, in some patients, a decision not to consider LAIs may be more suitable. As pointed out by Kane and Garcia-Ribera (65), this may be particularly true in: 1) patients who has consistently demonstrated his or her ability to take oral medication and chooses to continue doing so, 2) patients who regardless of adequate discussion of potential benefits and risks, and sufficient psychoeducation regarding the nature of the illness, obstinately refuses even to try a LAI and 3) patient unable to tolerate or unresponsive to the drugs available in LAI formulations.

SGAs-LAIs in the treatment of first episode in patients with schizophrenia

The successful treatment of FES is essential to improve long-term outcomes, as it has been demonstrated that the majority of clinical and psychosocial deterioration with cognitive impairment and increasing structural changes in brain volume take place within the first five years from the disorder' onset (66). In FES, pharmacological intervention favourably affect symptomatic control and functional outcomes and, therefore, the primary objective of treatment during this phase is to prevent relapses, possibly restoring the socio-occupational functioning to the premorbid level (67).
However, as above described, poor medication adherence is particularly common in FES and the most important goal should be the improvement of medication adherence. In a Finnish cohort study (68) conducted on 2588 FES patients, it was demonstrated that fewer than 50% of patients in the Finnish healthcare system continued treatment for the first two months after their first hospitalization. Grippingly, the type of administration affected relapse and LAIs had a 64% lower relapse rate than the equivalent oral treatment. Regarding which LAI may be more appropriate for FES, there is, to date, a relative lacking of long-term RCTs comparing LAIs with oral medication regarding effectiveness, tolerability, relapse prevention and overall outcomes (69, 70). Research supporting the usefulness of SGA-LAIs in FES has been mainly performed using RLAI since RLAI was the first marketed SGA-LAI and, therefore, the most evidence in the treatment of FES concerns it (Tab. 2).

Risperidone long-acting injection (RLAI)
RLAI represents the first long acting formulation of second-generation antipsychotic drugs, launched in North America in 2004, available for the treatment of schizophrenia and closely related psychiatric conditions (71). Several studies demostrated that RLAI administered once every 2 weeks, has notably efficacy and well tolerated in both schizophrenia and schizoaffective disorder patients (72-77). Due to its tolerability, RLAI is an important antipsychotic treatment available for use in vulnerable groups of patients, as elderly patients with psychosis (78). Compared to oral atypical and conventional long-acting agents, RLAI reduced the numbers of relapses in schizophrenia patients (79-82). In addiction, concomitant medications as anticholinergics, anxiolytics, hypnotics, sedatives, antipsychotics used in combination, antidepressants and mood stabilizers were reported to be reduced in use (38, 83). For its favourable profile, it may be a rational choice for patients with FES or in the early phases of schizophrenia as demonstrated by Parellada et al. (84), Lasser et al. (85), Napryeyenko et al. (86) and Malla et al. (87).
Specifically concerning FES, Kim et al. (88) conducted a prospective, naturalistic, controlled, and open-label study over two years in 50 patients with FES. 22 patients with schizophrenia were assigned to the RLAI group and 28 patients with schizophrenia to the oral risperidone group as control. RLAI group showed significantly lower relapse rate and higher medication adherence than the control group. On the other hand, Emsley et al. (89, 90) evaluated the efficacy of RLAI (25-50 mg per every two weeks) among 50 patients with FES and 36 of these (72%) completed the trial, suggesting a relatively low discontinuation rate. A reduction of at least 50% on the PANSS total score was obtained by 42 of the 50 FES patients (84%) and 32 patients (64%) met the Remission in Schizophrenia Working Group (RSWG) remission criteria. 31 patients (97%) among that 32, maintained this remission status for two years until the completion of the study. Weiden et al. (91) conducted a prospective randomized controlled trial to compare acceptance and adherence between RLAI and continued oral antipsychotics (such as haloperidol, olanzapine, quetiapine and risperidone) in FES. Patients who were treated with RLAI were significantly more adherent than patients who were taking oral antipsychotics.
More recently, Bartzokis et al. (92) evaluated the treatment effects of RLAI on frontal lobe white matter volume in FES patients in a randomized 6-month trial. Researchers, using inversion recovery magnetic resonance imaging, showed that the frontal lobe white matter volume was stable in the RLAI group whereas it significantly decreased in the oral risperidone group. This finding suggests that RLAI can improve the trajectory of myelination in FES patients and may be related with positive effects on cognitive functions and processes. Moreover, Tiihonen et al. (65) conducted a nationwide cohort study in Finland between 2000 and 2007 and evaluated 2588 patients with schizophrenia hospitalized for the first time. They found the RLAI or depot formulations were associated with a 50-65% reduced rehospitalisation rate compared to the identical medication in oral form. On the other hand, Weiden et al. (93) have also demonstrat-

Table 2 - Summary of studies that evaluated SGA-LAIs in the treatment of early schizophrenia and FES.

Authors	Year	SGAs-LAIs	Study design	Patients	Duration	Measures	Remarks
Parellada et al.	2005	RLAI	Non-randomised,single-arm, multicentre, follow up study	382 patients who needed a treatment change	6 months	PANSS, global assessment of functioning, quality of life, patient satisfaction and movement disorders; spontaneously reported AEs, ESRS, body weight	RLAI was effective and well tolerated in patients in the early phases of schizophrenia and schizoaffective disorders
Lasser et al.	2007	RLAI	Follow-up of an open-label trial	66	50 weeks	Clinical response guided by PANSS scores; ESRS and injection site pain ratings	RLAI was associated with clinical benefits in stable young adults with early schizophrenia or schizoaffective illness
Emsley et al.	2008	RLAI	Open-label, follow-up study	50	12 months	Clinical response guided by the PANSS total, general psychopathology subscales, CGI-S, SOFAS, short-form 12 (SF-12) mental component; remission, EPRS, prolactin levels, weight gain	Low discontinuation rates and sustained remission with RLAI
Kim et al.	2008	RLAI	Prospective, naturalistic, controlled, open label trial	50	24 months	Adherence, time to nonadherence and relapse rate; PANSS, GAF, CGI, ESRS	RLAI was effective in maintaining medication adherence and preventing relapse
Weiden et al.	2009	RLAI	Prospective, randomized controlled trial	37	12 weeks	Acceptance and initial adherence outcomes	Medication adherence was significantly better in the group receiving RLAI
Napryeyenko et al.	2010	RLAI	Open-label	307	6 months	SF-36 health-related quality of life measure completed by patient; PANSS, CGI-S, global assessment of functioning scores, ESRS, CGI-C, AEs	RLAI was effective in in recent-onset schizophrenia
Tiihonen et al.	2011	RLAI (and other FGA-LAIs)	Nationwide cohort study in Finland Between 2000 and 2007	2588 patients hospitalised for the first time	7 years	All-cause discontinuation of the initial antipsychotic medication, rehospitalisation due to schizophrenia and death from any cause	Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds.

to be continued

Table 2 - Continue

Bartzokis et al.	2012	RLAI	Randomized	24	6 months	White matter volume change scores	The frontal lobe white matter volume was stable in the RLAI group whereas it significantly decreased in the oral risperidone group
Weiden et al.	2012	RLAI	Prospective, open-label, randomized controlled trial	37	104 weeks	Medication attitudes assessed with the Rating of Medication Influences scale	Nonadherence was more easily detected among first-episode patients treated with LAI therapy than it was with oral antipsychotics
Malla et al.	2013	RLAI	Randomized controlled trial	85	104 weeks	PANSS, CGI-S	RLAI and oral SGAs are equally effective, but RLAI is likely to be effective and safe for those who may have problems with adherence
Fu et al.	2014	RLAI, PLAI	Post-hoc, subgroup analysis of a 13-week, double-blind, double-dummy, multicenter study	161 with PLAI, 173 with RLAI	23 weeks	Adverse effect profile and onset of efficacy	The tolerability and efficacy of PLAI and RLAI were generally similar

ed that acceptance of RLAI was associated with an initial adherence benefit that was not sustained over time. However, they also observed that. Even if nonadherence was almost universal in first-episode cohort, nonadherence was more easily detected among FES patients treated with RLAI therapy than it was with oral antipsychotics.

Other SGAs-LAIs

Fu et al. (94), in a post-hoc, subgroup analysis of a 13-week, double-blind, double-dummy, multicenter study, evaluated patients recently diagnosed with schizophrenia (≤ 5 years) who were administered PLAI or RLAI. They found that the tolerability and efficacy of PLAI and RLAI were generally similar over 13 weeks.

To date, no studies were present concerning OLAI and aripiprazole long-acting in the treatment of early schizophrenia or FES.

Conclusions

All SGA-LAIs have been approved for long-term treatment of patients with schizophrenia (95). Potential advantages and disvantages of SGA-LAIs in the treatment of FES in everyday clinical practice are summarized in Table 3. On the basis of existing literature, it can be argued that the usage of SGA-LAIs in first-episode schizophrenia may have beneficial impacts on treatment outcomes, but, to date, evidences are limited to RLAI. Due to its efficacy and tolerability, RLAI is an important antipsychotic treatment available for use in at-risk group of patients, such as FES patients. Especially in terms of adherence and relapse prevention, prescribing other SGA-LAIs might be another treatment option even in FES, when RLAI is not indicated, but no evidences still exist. In fact, there is limited research data (focused only on RLAI) for clinical trials in FES. More well-designed, randomized controlled clinical trials for the use of SGA-LAIs in FES are undoubtely needed.

Table 3 - Summary of potential pros and cons of SGA-LAIs in FES as compared to oral antipsychotics.

Pros	Cons
Improved adherence after FES	Less flexibility of dose regulation in case of problems or adverse effects
Less risk of relapse after FES	Slow dose titration and longer time to attain steady state levels
If a relapse happens, it is due to other reasons than noncompliance	Side effects, when present, may be distressing as may take a longer time to disappear
Less number of hospitalizations after FES	No available data on PLAI, OLAI and aripiprazole long-acting in the treatment of FES
May prevent progressive cognitive impairment after FES	Elevated costs of all SGA-LAIs (relatively less for RLAI)
No need for daily administration	Pain at the injection site can occur (relatively more with PLAI)
Minimal gastrointestinal absorption problems, circumventing first-pass metabolism with more consistent bioavailability	Concerning OLAI, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours to observe the onset of a post-injection syndrome (rare but unpredictable)
Good relationship between SGA-LAIs dosage and plasma levels	Long-term side effects such as weight gain (OLAI > RLAI, PLAI > Aripiprazole), QT prolongation (RLAI, PLAI > OLAI > Aripiprazole) and increase in prolactin levels (RLAI, PLAI > OLAI > Aripiprazole) may be considered when choosing a SGA-LAI
Reduced risk of unintentional or intentional overdose	Perception of stigma may be distressing for the patients
RLAI is the most studied SGA-LAI in FES	RLAI needs refrigeration with appropriate storage
Less loss of frontal lobe white matter volume observed with RLAI after FES	
Patients with a lower functioning may prefere a SGA-LAI	
Relatively good safety profile and tolerability	
May guarantee a regular contact between the patient and the psychiatrist after FES	
Allows healthcare professionals to be alerted and to intervene properly if patients fail to take their medication after FES	

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