Journal of Neuropsychopharmacology & Mental Health

De Berardis, J Neuropsychopharmacol Mental
DOI: 10.4172/2472-095X.1000e106

Editorial Open Access

Second Generation Long-acting Injectable Antipsychotics as a First-line Treatment of First Episode Schizophrenia: "Lights" and "Shadows"

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Received date: April 25, 2016; **Accepted date:** April 27, 2016; **Published date:** April 29, 2016

Editorial

Schizophrenia is a chronic and disabling disorder, characterized by positive, negative, cognitive, and affective symptoms [1,2]. 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 [3,4]. 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 [5].

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 [6]. In FES, there are several factors that may cooperate in causing nonadherence [7,8]. 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 [9]. 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 [10]. 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 [11]. As specified by Kane [12] "…clinicians should educate patients about adherence and consider treatment options that will improve adherence. Recovery is attained when patients experience symptom remission, vocational role fulfilment, independent living, and social relationships for at least 2 years".

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 [13]. 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 dyskinesia and QT prolongation) [14]. 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 [15]. 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 tadive dyskinesia compared with first generation LAIs, although some SGAs-LAIs may be associated with an increased incidence of metabolic side effects [16]. Currently, in Italy, there are four available SGAs-LAIs: Risperidone Long-Acting Injection (RLAI), paliperidone palmitate (PLAI), olanzapine pamoate (OLAI) and aripiprazole long-acting (ALI).

Therefore, the availability of SGAs-LAIs may be a favourable treatment option and should be considered since the FES and not only at the last stages of schizophrenia [17]. As argued by Professor Stephen Stahl [18], "shall the last be first?"

In general, the current guidelines on schizophrenia treatment (NICE, APA et al.) consider LAIs as drugs of choice for long-term therapy in patients who are no adherent 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 symptom' remission, prevent relapse and reduce all-causes mortality [19]. Thus, even not formally declared, it can be argued that, implicitly, in all cases of non-adherence in FES, the LAIs (preferably SGAs-LAIs) may be consequently used.

However, despite the effectiveness of LAIs in the treatment of schizophrenia, psychiatrists' attitude toward these agents is sometimes negative [20,21]. In fact, although LAIs are widely 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 [22]. 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 [23]. Psychiatrists frequently imagine that patients with FES would not accept depot antipsychotics and that depots are generally eligible for chronic patients [24]. However, it should be argued that these beliefs are often not supported by scientific evidences that, instead, point out the need of ensuring adherence after FES even with the use of LAIs [25].

However, it should be specified that, in some patients, a decision not to consider LAIs may be more suitable [13]. As pointed out by Kane and Garcia-Ribera [13], 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 psych education 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.

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.

Specifically concerning FES, Kim et al. [26] 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. [27,28] 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. [29] 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. [30] 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. 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. [31] have also demonstrated that acceptance of RLAI was associated with an initial adherence benefit that was not sustained over time. However, they also observed that. Even if non-adherence was almost universal in first-episode cohort, non-adherence was more easily detected among FES patients treated with RLAI therapy than it was with oral antipsychotics.

Concerning other SGAs-LAIs than RLAI, Fu et al. [32] in a post-hoc, subgroup analysis of a 13-week, double-blind, double-dummy, multicentre 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 FES.

In conclusion, potential advantages ("lights") and disvantages ("shadows") of SGA-LAIs in the treatment of FES in everyday clinical practice are summarizeded in Table 1.

"Lights"	**"Shadows"**
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	

Table 1: Lights and shadows in prescribing SGA-LAIs in FES with regards to oral antipsychotics.

However, 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. 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 undoubtedly needed.

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