TOLERABILITY OF LAIS: MANAGEMENT ISSUES IN CLINICAL PRACTICE

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Summary
Antipsychotics are the mainstay of treatment in schizophrenia and are used to treat acute psychotic symptoms as well as protect against relapse. Nonadherence to treatment is common, and reinforces cycles of recidivism. Long-acting injectable antipsychotic therapy may facilitate continuity of treatment and support better outcomes, particularly in patients with chronic illnesses, whose management is frequently complicated by factors such as comorbid substance abuse. Therefore, these formulations can both decrease the chance of a patient's illness relapsing and improve their recovery. Additionally, some patients prefer to choose this type of formulation over having to take tablets on a daily basis. The choice of LAI must be individualized for each patient, taking into account both the efficacy and the specific tolerability of the patient, but also considering the patient's preference, cost and treatment adherence and potential risk of incorrect drug assumption.

Key words: long-acting antipsychotics, safety, tolerability, side effects

Introduction

The chronic development of schizophrenia and its ability to generate high disability [1] needs an adequate pharmacological treatment during the acute phases to be continued in the medium and long term. Unfortunately, adherence to psycho-pharmacological treatments has always been one of the main psychiatric barriers in managing complex disorders such as schizophrenia. Regarding to oral therapy with antipsychotics, the literature reported discontinuation rates of 74% at 18 months of treatment [2] and 42% at one year, regardless of Second generation Antipsychotics (SGAs) or First Generation Antipsychotics (FGAs) treatment [3]. The consequences of this condition are devastating both in clinical, relational and functional terms. Although long acting formulations were introduced at the end of the 1960s, they were considered therapeutic options to be used only when all the previous ones had failed. Despite the obvious benefits on side effects and the role of preventing the relapse, long acting antipsychotics continue to be an underutilized option with employment rates ranging between 10% and 25% [4 5]. One of the reasons for their poor use may be our concern for the possible onset and the management of side effects during long acting therapy. These effects must be considered and adequately monitored and managed, but they can not be an obstacle to their use.

Rationale

Tolerability and effectiveness of antipsychotics are important to increase treatment compliance in people with schizophrenia. Symptoms of schizophrenia can be treated effectively with antipsychotic medication;

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however, poor adherence to prescribed treatment is one of the biggest challenges of managing the symptoms of schizophrenia and delaying time to relapse [6]. Discontinuation of antipsychotic treatment for schizophrenia can interrupt improvement and exacerbate the illness. In general, oral FGAs are associated with a different side effects profile than SGAs with a higher risk of movement disorders, for example, extrapyramidal symptoms (EPS) and tardive dyskinesia, although SGAs have been more linked to weight gain and metabolic risk.

Long-acting injectable antipsychotics (LAIAs) were introduced to improve treatment adherence and tolerability of oral formulations. Long-acting injectable antipsychotics deliver therapeutic concentrations over several weeks, eliminating the need for daily dosing and providing clinicians with certain knowledge of adherence or nonadherence. These agents increase the likelihood of continuous and effective treatment and may reduce patients' risk for relapse. This, in turn, could decrease the likelihood of institutionalization in hospitals and incarceration [7]. The difference of pharmacokinetics of LAIs compared with oral antipsychotics, such as the long elimination half-life, can delay both the onset and the remission of adverse effects.

Objectives

The aims of the presented research are to generate estimates of relative tolerability, and safety for second-generation LAI antipsychotic treatments using available evidence althought only a few direct comparisons between one LAI and another have been conducted.

After risperidone was introduced as the first long-acting injectable second-generation antipsychotic, during the last five years olanzapine pamoate, once-monthly paliperidone palmitate and once-monthly aripiprazole has also been marketed [8].

Method

A review of all english-language published literature during the last five years (from 2012 to the present) was conducted with the electronic searches by using PubMed for current data regarding the topic of LAIs and the role of tolerability. Keywords used for the search were "long-acting injectable antipsychotics" and "second-generation antipsychotics" in association with one of the following: "Tolerability,"and "side effects." References to key articles were further explored for relevancy to this proposal. In addition to long-acting injection (depot) antipsychotics and second-generation (atypical) antipsychotics, a separate search was performed for each available drug: aripiprazole LAI, olanzapine pamoate, paliperidone palmitate, and risperidone LAI. Articles were excluded if they were single case reports, case series studies, small naturalistic studies and studies providing no safety data. The safety and tolerability outcomes included incidence of clinically relevant weight gain and incidence of EPS during the treatment or clinically relevant adverse events (AEs) in term of treatment discontinuation.

Peculiarities of long acting formulations

The drug release mechanism in long acting formulations allows a reduction in first-pass absorption and metabolism variability (Table I). Advantage results in greater reliability in achieving more stable plasma concentrations over time [9]. Compared to oral formulations, the long acting ones create a better correlation between the administered dose and the plasma levels of the drug. Once steady-state is reached, the plasma level of the molecule remains relatively stable, avoiding fluctuations related to daily administration [10]. Table I shows the differences existing between the different molecules (risperidone, olanzapine, paliperidone, aripiprazole) in relation to their mechanism of drug release. The release mechanism influences the fluctuations of the drug once the steady-state is reached. In the case of olanzapine pamoate, the 4-week formulation compared to the 2-week formulation or the same oral formulation, determinate a significant variation [11]. While, in the case of paliperidone palmitate, compared to the oral formulation, which already had a controlled release, the variation is minimal. Furthermore, it should be considered the pharmacodynamic properties of the individual molecules, and in particular their affinity to the dopaminergic, serotoninergic, istaminergic and muscarinic receptors for the specificity of the side effects (Table II). Some authors report that the benefits described may conflict with the concern of clinicians for the use of a high dose at the time of administration and therefore the inability to obtain a rapid reduction in the dose of the drug as well as its interruption at the time of occurrence of a side effect [10].

Result

LAI Risperidone Tolerability

Risperidone long-acting injection (RLAI) was the first second-generation antipsychotic available as a

Table I. Pharmacokinetic Characteristics and Release Mechanism of Long-acting Second Generation Antipsychotics.

	Olanzapina pamoato	Risperidone microspheres	Paliperidone palmitate	Aripiprazole
Formulation	Suspension of microcrystals in water suspension	Microspheres in water suspension	Water suspension using crystals of the molecule	Powder in water suspension
Release mechanism	Salts: dissociation in olanzapine and pamoic acid	Microspheres erosion and diffusion	Prodrugs: hydrolysis by esterase	Powder of particles with low solubility
Frequency of administration	Every 2-4 weeks	Every 2 weeks	Every 4 weeks	Every 4 weeks
Conservation	Ambient temperature (15-30 ° C)	2-8 °C	Ambient temperature (15-30°C)	After reconstitution but can be stored at temperatures below 25 ° C for up to 2 hours in the syringe
Tmax (days)	4	21	13	5-7
Elimination half life (days)	30	28-42	25-49 (range dose 25-150 mg)	46,5 for 400 mg 29,9 for 300 mg

long-acting injection. It was developed in 2002. It has been shown good tolerability and almost no interruption due to adverse effects or to relevant biological parameters alterations. Also, weight gain was not significant. Fernández-Miranda et al (2015) [12] indicate Clinical Global Impression Severity ($p < 0.01$) and Camberwell Assessment of Need ($p < 0.01$) decreased and also Disability Assessment Schedule in the 4 areas ($p < 0.01$). Regarding Medication Adherence Rating Scale the score increased from 3.6 to 8.9 ($p < 0.001$). Morover, it has been seen significantly few hospital admissions than during the previous 36 months (1.9 *vs* 0.31, $p < 0.001$).

Other authors demonstrated that In patients with recently diagnosed schizophrenia, the tolerability and efficacy of Paliperidone Palmitate (PLAI) and RLAI is generally similar over 13 weeks. The overall adverse events rates at week 13 for PLAI and RLAI were 54.7 and 50.3%, respectively, for any AE; 11.2 and 8.1% for extrapyramidal symptom-related adverse events (AEs); and 2.5 and 2.3% for prolactin-related AEs. No significant differences in the mean weight change,

Table II. Pharmacodynamic characteristics of second-generation antipsychotics available in long acting formulations.

	Olanzapine	Risperidone	Paliperidone	Aripiprazole
D2	20	3.77	2.8	0.66
5HT1A	610	190	480	5.5
5HT2A	1.5	0.15	1.2	8.7
5HT2C	4.1	32	48	22
α1	44	2.7	10	26
α2	280	8	80	74
H1	0.08	5.2	3.4	30
M1	2.5	> 10,000	> 10,000	6,780
M2	622	> 10,000	> 10,000	3,510
M3	126	> 10,000	> 10,000	4,680
M4	350	> 10,000	> 10,000	1,520
Main side effects	Sedation, weight gain, dyslipidemia	EPS, Akathisia, Hyperprolactinemia	EPS, Akathisia	Akatisia

Table III. Procedures for subjects with AP LAI [26].

General Clinical evaluation	Personal and family medical history (diabetes, dyslipidaemia, cardiovascular disease)
	Healthy lifestyle (eating habits, physical activity, substance use, smoking, alcol)
	Weight, Body Mass Index calculation, waist circumference
	Blood pressure, Cardiac frequency, Body temperature
1st line clinical exams	Complete blood count, blood electrolyte (K, Na, Ca, Mg),urea, creatinine and fasting glucose
	Liver function tests
	Lipid profile
	Beta hCG
	Electrocardiogram and QTc evaluation
2nd line exams (depending on the clinical state of patient)	Thyroid function test
	Prolactinaemia
	Electroencephalogram

most metabolic parameters, or mean efficacy measures were observed at end point [13].

LAI Olanzapine Tolerability

Postinjection delirium/sedation syndrome (PDSS) is a potentially serious adverse event that has been shown to be associated with one currently available LAI antipsychotic, olanzapine pamoate [14]. In a routine clinical practice study over a 5 year period a total of 388 post injection delirium/sedation syndrome were indetified with 91% within 1 hour of injection and 52% occurred within 15 minutes [15]. Other symptoms of PDSS include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypotension or possible convulsion. In most cases (80%) initial symptoms appeared within one hour of injection with complete recovery within 24-72h after injection. Due to the possible emergence of this framework in the olanzapine pamoate technique, it is necessary to monitor for 3 hours after injection.

In recent years, this aspect has also been investigated for long acting risperidone and paliperidone formulations.

In the course of studies on risperidone (RP), 15 trials with 3,164 subjects (approximately 115,000 injections) and post marketing studies, no PDSS cases were found. With paliperidone palmitate, only one episode of PDSS was highlighted in 10 trials [7]. Although there are reported cases of sedation/drowsiness with the use of both molecules, the incidence of these events was not different from placebo. In fact, some authors point out that PDSS syndrome, described for olanzapine, can not be generalized to all long acting second-generation antipsychotics [7].

LAI Paliperidone Tolerability

Paliperidone (9-hydroxyrisperidone) is the active metabolite of risperidone. The long-acting Paliperidone (PLAI) has been developed as a suspension of paliperidone palmitate nanocrystals in an aqueous formulation, administered monthly by intramuscular injection.

Has been shown that PLAI is effective in controlling the acute symptoms of schizophrenia as well as delaying time to relapse. PLAI and RLAI have similar safety and tolerability profile. Several studies have demonstrated that schizophrenia patients treated with PP show higher rates of improvement of psychotic symptoms compared to placebo and similar efficacy and tolerability outcomes when comparing PP to RLAI or oral paliperidone extended release [16]. Thus, PLAI may represent the rational development of RLAI with greater ease of use [17].

The Paliperidone Palmitate efficacy, tolerability, and patient acceptability has been demonstrated in relevant number of short and long term studies, both RCTs and open label studies a also in patients switched to once- monthly long-acting paliperidone palmitate (PLAI) following previously unsuccessful treatment with oral or other depot APs.

As mentioned above, it has been shown that the tolerability (including rates of EPMS and prolactin-related TEAEs) and efficacy of PLAI and RLAT were generally similar and the higher incidences of weight gain and depression were reported in recently diagnosed compared with more chronic patients [13]. The greater incidence of weight gain in recently diagnosed patients is in line with another study of early schizophrenia in which most weight gain occurred within the first 3 to

6 months of treatment as well as data showing that patients with a higher baseline BMI gain less weight than those with a lower BMI [18]. The data suggest that PLAI is also generally well tolerated in a patient population more representative of routine clinical practice with higher rates of comorbidities, comedications, and substance abuse. However, among the most frequently occurring treatment-emergent adverse events was somnolence/sedation (5-7% paliperidone palmitate group *vs* 3% placebo). Hargarter et al. (2016) [19] demonstrate that recently diagnosed patients treated with PLAI had a significantly higher treatment response and better functioning, as assessed by the Personal and Social Performance scale (PSP), compared with more chronic patients. These data support current discussions that earlier continuous and effective AP treatment may be associated with better outcomes in patients with schizophrenia.

LAI Aripiprazole Tolerability

LAI Aripiprazole appears cost-effective *versus* other SGA-LAIs, with improved health-related quality of life and functioning in a head-to-head study with paliperidone LAI. A 6 month (pre and post), mirror-image switch study demonstrated a reduction in hospitalization and associated costs compared with previous antipsychotic treatment [20]. Safety and tolerability are comparable to oral aripiprazole with no new safety signals [17]. The overall tolerability profiles of both products are consistent with what is known about oral aripiprazole. Due to its specific pharmacological and tolerability profile, Aripiprazole long acting once-monthly (AOM) represents a suitable alternative for patients with schizophrenia requiring a switch to a new LAI treatment because of lack of efficacy or persistent side effects from other LAI [21].

The tolerability profile of a therapeutic agent is important in guiding long-term treatment decisions. AOM 400 was generally safe and well tolerated by patients with BP-I during long-term treatment with few discontinuations because of treatment-emergent AE (TEAEs).

The overall discontinuation rate during the 26-week randomized withdrawal phase in a study evaluating oral aripiprazole for to the 51.9% of patients on AOM 400 who discontinued during the longer 52-week randomized withdrawal phase of the present study. The majority of patients (> 80% at each injection visit) received the recommended dose of 400 mg. No new safety signals were noted, and observed TEAEs were mostly mild to moderate. Mean weight gain was low in the randomized phase and was similar between treatment groups. There were no clinically meaningful changes in extrapyramidal symptom scales, metabolic parameters, or vital signs. Prolactin elevation and the associated sexual dysfunction are troublesome consequences of antipsychotic treatment. Among the atypical antipsychotics, aripiprazole is known to be prolactin-sparing, whereas others, including risperidone, study didreveal any clinically meaningful alterations in prolactin levels with AOM 400 *versus* placebo, and there were few TEAEs related to prolactin or sexual dysfunction [22].

LAI Paliperidone 3 Month Tolerability

Compared with placebo, PP3M showed a longer time to relapse and good safety and tolerability profiles. In a recent randomized clinical trial the most frequently reported TEAEs (≥2%) in the group receiving 3-month paliperidone palmitate during the maintenance phase were anxiety (6%), insomnia (5%), weight increased (4%), and head- ache (3%) [23]. In general the 3-month formulation was generally tolerable and has a safety profile consistent with other marketed paliperidone formulations [24]. In view of its efficacy, tolerability, and safety, together with the longer timespan between injections, PP-3M may contribute towards addressing the issue of poor adherence, even in early psychosis [25].

Procedures for monitoring

The monitoring procedures for LAI antipsychotics are the same as for oral antipsychotics. However in a specific survey on LAI, based on a literature review, performer by 42 national experts in France some procedures are recommended in particolar in subjects treating with LAI [26]. These procedures are generally indicated for all patients during antipsychotic treatment but it are more important for those receving LAI (Table III). The frequency will depend on the risk factors found in the patient and on the clinical signs or medical condition that appear during the treatment.

Discussion

Although first-generation depot antipsychotics that use oil-based formulations are associated with pain on injection, aqueous-based formulations of LAI antipsychotics generally have good injection site tolerability.

The availability of both deltoid and gluteal formulations of LAI medication could therefore facilitate patient acceptance and long-term adherence to injectable antipsychotic medication. No or mild administra-

tion site pain, minimal risk of embarrassment/damage to the therapeutic relationship and some sedation but no other side effects were ideal features of LAI antipsychotics were identified. Furthermore, injection into the deltoid muscle requires minimal removal of clothing as it seems that patients prefer.

A survey of physicians and nurses from around Europe also revealed that the deltoid site may improve acceptance of LAI antipsychotics and be preferred by their patients. In fact seems that the deltoid administration may reduce social embarrassment associated with LAI antipsychotics and it has been considered as more respectful to the patient [27].

Predictably, the reviewed information revealed that SGA-LAIs have safety profiles consistent with their oral parent formulations. However, they seem to also show unforeseen and worrisome safety signals. Indeed, the routine use of olanzapine-LAI in clinical practice could be limited not only by the well-known risk of postinjection syndrome, whose clinical management remains a matter of concern, but also by the risk of worsening of psychosis. The reviewed information seems to suggest that worsening of psychotic symptoms and depression could also be associated with both risperidone-LAI and paliperidone palmitate. The leading cause of death among patients enrolled in risperidone-LAI studies was suicide [28].

Patients with schizophrenia are known to have a shorter life expectancy than the general population [29]; likely linked to the increased incidence of cardiovascular risk factors as well as metabolic comorbidities reported. Anyway, an early initiation of continuous treatment may benefit patients, as a lack of AP treatment has been associated with greater all-cause mortality.

Conclusion

As second-generation antipsychotic long-acting injections (SGA-LAIs) are rapidly replacing depot first-generation antipsychotics as first-line agents in treating schizophrenia spectrum disorders, a systematic review of their adverse effects is timely.

Second-generation antipsychotic drugs in their long acting formulations are an obvious benefit to the clinician in managing a complex disabling disorder such as schizophrenia. Although has been reported, the adverse reactions from the injection of such molecules, it can not and should not be an impediment to their use since there are benefits in terms of preventing relapses and therefore better quality of life for patients. In fact, the aim of treating schizophrenia can not only be to control symptoms in acute phases, but it must necessarily be a pattern of maintaining response over time.

Conflict of interest

Guido Di Sciascio was a consultant and/or speaker in symposia sponsored by Arcapharma, Angelini, Janssen-Cilag, Otsuka, Polifarma. Claudia Palumbo and Salvatore Calò: none.

Take home messages for psychiatric care

- Nonadherence to antipsychotic medications is an enormous challenge for clinicians and patients in the treatment of schizophrenia
- The formulation of LAIs as a method of delivering antipsychotics can be used to improve adherence, to decrease the chance of a patient's illness relapsing, and improve their recovery
- The choice of LAI should be individualised to each patient, taking into account both efficacy and tolerability specific to the patient, practicalities, patient preference and cost
- It has been shown good tolerability and almost no interruption due to adverse effects of LAIs

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