Use of long-acting antipsychotic medications: practical issues

L'uso di farmaci antipsicotici long-acting nella pratica clinica

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Summary

Introduction

Non-adherence to therapy is a significant problem in treatment of patients with a diagnosis of schizophrenia; the rate of non-adherence in psychiatric patients varies from 24% to 90%, with average of about 60%. This may be due to the lack of awareness of the disorder, weak conviction of the utility of therapy by the patient or family, complexity of treatment, or severity of side effects. To increase adherence to treatment formulations of extended-release injectable antipsychotics (long-acting injectable, LAI) have been developed that ensure a continuous supply of the drug with stable blood concentrations.

Objective

The objective of this review is to evaluate the advantages and disadvantages of LAI antipsychotics, the main guidelines, and attitudes of the physician and patient to their prescription and administration.

Methods

Review of the literature using PubMed. The keywords "antipsychotic long-acting", "LAI", "schizophrenia", "poor compliance" and "antipsychotic depot" were used.

Conclusions

Many authors agree on the poor use of LAI in clinical practice due to the lack of knowledge of the type of drug by both physicians and patients. A careful examination of guidelines may help to identify the ideal profile of patients who can benefit from LAI.

Key words

Antipsychotic long-acting • LAI • Schizophrenia • Poor compliance • Antipsychotic depot

Advantages and disadvantages of the use of long-acting antipsychotics

Extended-release (long-acting injection, LAI) antipsychotics represent a useful modality in clinical practice to cope with the problem of poor adherence to therapy. This has been defined as "the extent to which a person's behavior towards taking a medication or change a lifestyle consistent with the medical claims"[1]. A definition of non-adherence includes the failure to start a treatment program, premature termination of the treatment regimen and rejection or modification of the methods of administration prescribed. It comprises both intentional non-adherence (to not assume or change dosage according to individual decisions) from a unintentional non-adherence (e.g. forgetting to take the drug)[2].

Medina et al. [3] argues that adherence to treatment is a multifactorial phenomenon involving four types of factors: socio-demographic variables (age, sex, occupation, education level and social status); illness-related variables (type and severity of symptoms, illness insight, course of illness); treatment-related variables (dosage schedule complexity, frequency and intensity of side effects, length of treatment); and general patient values and attitudes (attitude towards illness). Cramer and Rosenheck [4] found that the rate of non-adherence in psychiatric patients ranges from 24% to 90%, with an average of around 60%, with potentially serious consequences, including, foremost, a high rate of relapse. The latter, together with rehospitalisation, as well as the possible long-term repercussions on the intellectual sphere and the risk of negative evolution of the disease, is associated with significant social cost. Patients with frequent relapses have more difficulty in social and occupational reintegration and often run the risk of being entirely at the expense of their families. As a result, family and social relationships

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and the quality of life of patients are inevitably destined to deteriorate over time [5].

Numerous studies have analysed the advantages and disadvantages of the use of LAI antipsychotics (Table I). LAI antipsychotics offer advantages over oral preparations such as the 'transparency' of adhesion [6], allowing the caregiver to be alerted promptly and take appropriate action if the patient does not follow therapy [7]. Another benefit related to LAI antipsychotics is the possibility of administration of the drug in a reliable manner, with reduced levels of peak plasma [8 9], with better tolerability and less frequent side effects [10 11], greater possibility of consent by the patient [12] and fewer relapses and rehospitalitation compared to oral treatment [8 13]. Peng et al. [14] have observed that in the 6 months prior to starting treatment with a LAI antipsychotic, 34% of patients had been hospitalised at least once, 7.5% twice and 1.4% three times. Six months after the transition to a LAI formulation, 14.3% were hospitalised once, 4.1% twice and 2% three times. The analysis of the costs incurred showed a significant reduction in the total cost of treatment, given the reduction in the total costs due to hospitalisations. Finally, administration of the drug by skilled health personnel reduces the risk of suicide associated with the ingestion of drugs at non-therapeutic doses [15].

For patients, the biggest drawback of treatment with LAI antipsychotics is the fear of being monitored by their healthcare provider; in 1960, this new treatment modality was called "chemical cosh" or "chemical straitjacket", symbolising a form of treatment that is imposed on a patient who is prevented from expressing their rights or to choose treatment [16]. Attributes that may influence prescribing of long-acting formulations and patient acceptance include stigma [17], pain associated with injection[10] and embarrassment arising from the need to remove clothing for gluteal injections [18]. Although first generation depot antipsychotics that use oil-based formulations are associated with injection pain, aqueous-based formulations of LAI antipsychotics generally have good injection site tolerability. Furthermore, injection into the deltoid

TABLE I.
Advantages and disadvantages of long-acting medications. *Vantaggi e svantaggi di farmaci long-acting.*

Author	Year	Advantages	Disadvantages
Gerlach	1994	Ensures compliance Avoids first pass metabolism Stable plasma concentration of the drug Use the lowest effective dose Reduction in the rate of relapse	Delayed disappearance of side effects after suspension Feeling the patient to be controlled
Wistedt	1995	60% of patients are satisfied with LAI	Older patients complain about more side effects
Dencker et al.	1996	Relapse prevention	Patients think it is "forced treatment"
Ereshefsky et al.	2003	Reduced fluctuations in plasma drug levels	
McEvoy	2006	Release of safe medication Lack of peak plasma levels of the drug Increased evidence of poor compliance	Pain associated with injection
Jones	2006		Reactions at injection site
Emsley et al.	2008	Reduction in relapse rate The highest rate of remission Lower extrapyramidal symptoms	Increase in body mass index with risperidone
Johnson et al.	2009		Patients found to be controlled
Jaeger	2010		Stigma Patients feel limited in autonomy
Gopal et al.	2011	Improvement in scores on the Positive And Negative Syndrome Scale	Side effects of paliperidone: insomnia, nasopharyngitis, weight gain and prolactin
Tiihonen et al.	2011	Reduced hospitalisation rate	
Peng et al.	2011	Reduced hospitalisation rate Reduction of costs	
Geerts	2013		Side effects

muscle requires minimal removal of clothing. In addition to pain, other complications may also occur at the injection site, such as nodules, granulomas, muscle fibrosis, abscess formation and accumulation of the oil medium after repeated injections [19].
Other side effects may hamper treatment with LAI antipsychotics; tardive dyskinesia and extrapyramidal symptoms are the most feared, but are also related to metabolic disorders, weight gain, sexual dysfunction and sedation [20].
A further disadvantage that may restrict the use of LAIs in clinical practice is related to the delayed disappearance of side effects after the interruption of therapy [6].

Comparison of oral and long-acting antipsychotics: a critical analysis of clinical trials

Many studies have compared LAI antipsychotics with oral antipsychotics reaching variable results. The factors most frequently considered in this comparison are clinical effectiveness, rates of relapse and occurrence of extrapyramidal symptoms.
Some authors have shown greater effectiveness in terms of reducing the risk of therapeutic discontinuity [21 22], rehospitalisation [23] and improvement of symptoms [24] in patients treated with LAI antipsychotics. Conversely, Bai et al. [25] and Chue et al. [26], recruiting patients treated with risperidone LAI and with the equivalent oral formulation, showed no statistically significant differences in efficacy. A study conducted by Lily et al. [27] concluded that patients treated with olanzapine pamoate showed no differences in efficacy or side effects, but showed a significant reduction in the rate of rehospitalisation.
The benefits shown in several studies on the use of LAI antipsychotics, especially with regards to reduction in the rate of relapse [28-30], are challenged by the SOHO observational study that compared patients treated with oral olanzapine to those treated with first generation LAI antipsychotics [31]; the latter had a lower likelihood of achieving remission of symptoms and a higher risk of recurrence. Schooler et al. [32] showed no differences in relapse among patients treated with fluphenazine decanoate and those treated with oral fluphenazine; Rosenheck et al. [33], evaluating patients treated with risperidone LAI and oral, also came to the same conclusion.
One element that may limit the use of LAI antipsychotics in clinical practice is provided by evidence in the literature that confirm an increase in the onset of extrapyramidal symptoms in patients treated with a first-generation-LAI antipsychotic compared to the equivalent oral formulation [24 29 34]. Two studies that compared oral risperidone and risperidone LAI reached the opposite conclusions: Rosenheck et al. [33] revealed an increase in extrapyramidal symptoms, while Bai et al. [25] found that the LAI formulation led to a significant reduction of extrapyramidal symptoms.
In 2010, Leucht et al. [35] performed a meta-analysis comparing LAI and oral antipsychotic formulations in outpatients with a diagnosis of schizophrenic disorder and other related disorders (schizophreniform disorder, schizoaffective disorder and delusional). The authors used the register of the Cochrane Schizophrenia Group and Clinical Trials.gov including randomised controlled trials lasting at least 12 months. They evaluated the data on relapse, rehospitalisation due to worsening of psychopathology, non-adherence to treatment and discontinuation of therapy due to ineffectiveness of treatment, side effects, or other reasons. The results confirmed that the relapse rate was significantly reduced (21.6%) in patients treated with a LAI antipsychotic compared to those treated with oral medications (33.3%). No significant differences between the two groups in relation to the rate of rehospitalisation or discontinuation of therapy due to side effects or other reasons was seen. Considering specific reasons for discontinuation of therapy, fewer patients in the LAI group reported having suspended due to ineffectiveness of treatment (LAI 20.6% vs. oral 29.6%).
However, the validity of these results, as claimed by the authors themselves, may be questioned by confounding factors that may have increased or decreased the apparent superiority of LAIs; these include the small number of selected studies published over a period of about 30 years, with the inevitable heterogeneity of participants, methods and interventions, and finally the use, in some studies, of LAI formulations that differ from the equivalent oral medications.

Comparison of first- and second-generation LAI antipsychotics

A comparison of the first- and second-generation LAI antipsychotics was performed by Taylor [36] (2009), in particular with regards to side effects. Haloperidol decanoate is primarily associated with a dose-dependent increase of prolactin levels in blood[37]. Perphenazine decanoate, like other first generation antipsychotics, is associated with the onset of extrapyramidal symptoms ,and the prevalence of concomitant use of anticholinergic drugs varies from 29% to 55%[38]. Finally, zuclopenthixol typically causes extrapyramidal symptoms and alterations, usually mild, involving the autonomic nervous system such as postural dizziness and blurred vision [39].
The first-generation LAI antipsychotics are associated with an increased risk of extrapyramidal symptoms and more frequent occurrence of acute and chronic local reactions at the injection site, especially when used at high doses [40].
Regarding second-generation antipsychotics, risperidone is associated with a reduction in the rate of onset of mo-

tor disorders, but increased risk of metabolic syndrome and hyperprolactinaemia[41]. The use of olanzapine is also limited by the risk of post-injection syndrome for which patients should be observed for at least 3 hours to verify the possible occurrence of signs and symptoms consistent with overdose[42]. These reactions occurred in 0.1% of injections and in approximately 2% of patients, characterised by sedation and/or delirium (confusion, disorientation, agitation, anxiety and other symptoms of impaired cognition) extrapyramidal symptoms, dysarthria and ataxia.

Guidelines

The guidelines of the National Institute for Health and Clinical Excellence (NICE) UK 2009 suggest considering LAI antipsychotic medication for individuals with schizophrenia who prefer such treatment after an acute episode or when necessary to prevent hidden non-adherence (whether intentional or unintentional) to antipsychotic drug therapy as a clinical priority. Given the nature of the disorder, the frequency and consequences of psychotic relapses and the high percentage of non-adherence to prescribed therapy, psychoeducational intervention is proposed as an integral part of the treatment, almost obligatory, and consider LAI antipsychotics for all patients starting treatment [43].

According to the American Psychiatric Association (APA, 2004), LAI medication may be taken into consideration for the acute phase of schizophrenia in case of assessed, repeated poor or non-adherence to drug treatment [44].

A cornerstone of the scientific debate concerns the identification of the correct moment in which to introduce LAI drug therapy. On the one hand, the Texas Medication Algorithm Project recommends the use of a LAI antipsychotic at any stage of the disease in patients who are not adequately adhering to drug treatment [45]; on the other hand, however, the recent Guidelines of the British Association for Psychopharmacology claim that the role of LAI in the first episode remains uncertain on the basis of the absence of long-term research that compare oral antipsychotic treatment with LAI formulations [46].

A good reason to start treatment with LAI antipsychotic drugs in first-episode patients derives from the fact that numerous studies have confirmed that they are associated with a reduction in the relapse rate compared to oral medications; a relapse in the first few years of the disease is very frequent and the alternating nature of the disease causes neurotoxicity, which is also correlated with structural brain alterations, such as an increase in the volume of the cerebral ventricles and cortical atrophy [47]. Another advantage may be the overall improvement of quality of life, with greater opportunities for social reintegration, employment and relationships.

An argument against the use of LAI antipsychotics in first episode patients is the uncertainty of diagnosis. In fact, if the clinician suspects a brief psychotic disorder, psychotic disorder not otherwise specified (NOS) or schizophreniform, the recommended duration of treatment should be shorter and a greater percentage of patients may have a chance of complete psychopathological recovery compared to patients with a diagnosis of schizophrenic disorder [48].

In the 10th edition of The Maudsley prescribing guidelines (2009) before starting treatment with an LAI formulation, for first-generation antipsychotics, the administration of an initial small test dose is recommended with the aim to reveal any sensitivity of the patient to the oily solution and onset of extrapyramidal symptoms. The test dose of a second-generation LAI antipsychotic is not recommended because they have little tendency to cause extrapyramidal symptoms and the aqueous medium used is not associated with allergic reactions. These guidelines also recommend starting treatment with the lowest therapeutic dose, to prescribe the dose at the longest interval allowed and to stabilise the dose only after a period of careful assessment; moreover, adding a drug with an oral formulation during treatment with a LAI can be useful, although this may be complicated by the occurrence of side effects [49].

The main conclusions consistent with the guidelines are the consideration of drug therapy in LAI formulation as maintenance therapy in stable patients who show poor adherence to treatment and suggest, however, the choice of LAI as an autonomous decision of the patient, in terms of personal comfort [50].

Current guidelines for the treatment of schizophrenia, however, have been criticised as too conservative and vague [51]. These cannot replace clinical knowledge that aims at improving the overall health of the patient; they remain, however, points of reference for efficacy, safety and tolerability [52].

Attitudes of the physician and patient in the use of LAI antipsychotics

The attitude of patients and psychiatrists toward LAI antipsychotics has been evaluated by several authors. Waddell and Taylor [53] published a review examining this attitude considering 12 studies. Of the 5 studies that analyze the attitudes of patients, one highlighted the positive opinion towards the use of LAIs, 2 of these had a negative opinion and 2 were neutral. Of the 7 studies that assessed the attitudes of health in relation to LAIs, 4 showed a positive attitude to the use of LAIs, 2 a negative attitude and one was neutral. A study conducted by Heres et al. [54] showed a positive attitude to treatment with LAI antipsychotics; only 23% of patients taking a LAI for the first time

considered it acceptable therapy, compared to 45% of those who had previously taken a LAI and compared to 73 % who were taking one in a continuous manner. This indicates that the preference for LAI increases with the familiarity with the drug and duration of treatment.
The study by Patel et al. [55] noted that 69% of psychiatrists surveyed believe that the benefits of therapy outweigh the negative aspects of LAI antipsychotic, while a minority of specialists consider them to be stigmatising and outdated. Srividya et al. [56 57] reported experiences and opinions of patients and psychiatrists towards treatment with LAI conducting focus groups. The focus groups conducted by psychiatrists yielded 4 main themes: limited knowledge about and experience with LAIs; attitudes toward LAIs (beliefs about negative perceptions of patients regarding LAIs, personal bias against needles and consensus about some advantages of LAIs); prescribing practices around LAIs (generally seen as a last-resort option for patients with a history of non-adherence); and pragmatic barriers to using LAIs (e.g., cost, storage and staffing). From the focus groups conducted with patients diagnosed with schizophrenia four prevalent themes emerged: lack of knowledge of the formulation, subjective perception about treatment regarding the mode of administration and side effects, high costs of LAI injections considered as a significant disadvantage and issues arising from the coercive context in which the LAI may be prescribed.
The main problem that emerges from the focus groups is the need for increased training and retraining of health personnel and patient involvement in the choice of treatment, as well as the need for clearer communication and information on LAI antipsychotic therapy [58].

Conclusions

There are no similar opinions on the use and the benefits of treatment with LAIs in clinical practice in terms of psychopathology and improving appearance of side effects. There is unanimous opinion, however, in attributing an important role to LAIs in improving patient adherence to drug treatment.
We still need to determine the ideal profile of the patient who should begin treatment with a LAI in order to achieve good clinical outcome. The criteria to be taken into consideration include adherence to treatment, attitude of the psychiatrist, relatives and/or patient towards antipsychotic treatment, awareness of the disease by the patient, patient's medical history, especially relapses, previous treatment with antipsychotic drugs, number of previous hospitalisations, duration of illness, presence of positive symptoms and/or negative side effects associated with the treatment. We must also consider demographic characteristics such as age, sex, ethnicity, education and possible history of substance abuse.
The ideal candidate for treatment with LAI antipsychotics should be a patient that chooses this drug therapy, who however has unsatisfactory adherence to the treatment and needs to follow a treatment plan that ensures adequate control of the disorder, in order to determine a lower number of relapses and hospitalisations, with a global improvement of the quality of life [59].

Conflict of Interest
Prof. A. Rossi, dr. P. Stratta, dr. A. Collazzoni, dr. S. Patriarca and dr. M. Ragusa have not received any grant.

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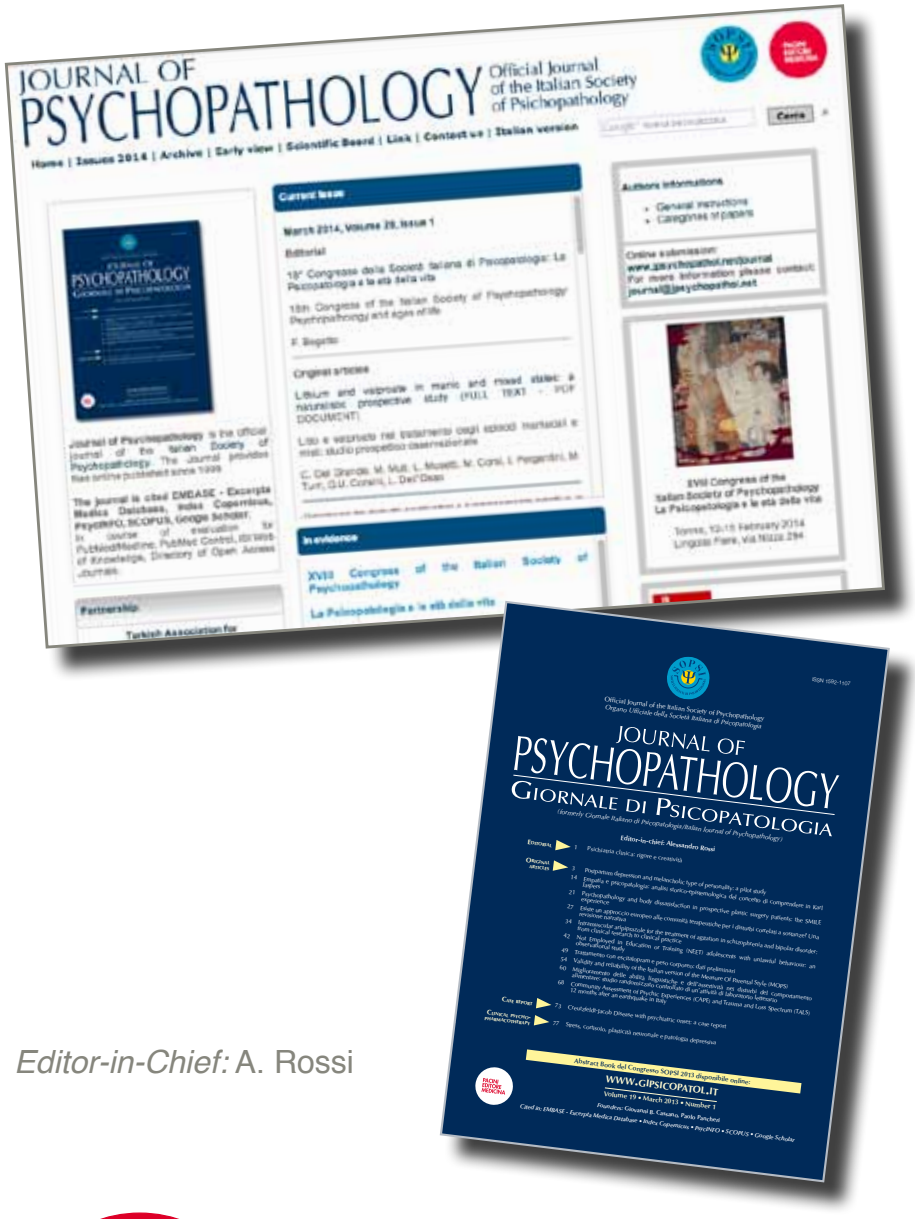

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