

Treatment of Schizophrenia with Long-Acting Injectable Antipsychotics

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INTRODUCTION

The characteristic symptoms of schizophrenia acute and chronic course, involve a range of cognitive, behavioral, and emotional dysfunctions, but no single symptom is pathognomonic of the disorder. It is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as one of the top ten illnesses contributing to the global burden of disease [1].

Characteristics of schizophrenia typically include positive symptoms such as hallucinations or delusions, disorganized speech, negative symptoms such as a flat affect or poverty of speech, and impairments in cognition including attention, memory and executive functions. A diagnosis of schizophrenia is based on the presence of such symptoms, associated with social or occupational dysfunction [2], for at least six months in the absence of another diagnosis that would better account for the presentation.

Individuals with schizophrenias may lack insight or awareness of their disorder and this symptom is the most common predictor of non-adherence to treatment, higher relapse rates, increased number of involuntary treatments, poorer psychosocial functioning, aggression, and a poorer course of illness.

Evidence from neuroimaging, neuropathological, and neurophysiological studies confirm that differences are evident in multiple brain regions between groups of healthy individuals and persons with schizophrenia. Differences are also evident in cellular architecture, white matter connectivity, and gray matter volume in a variety of regions such as the prefrontal and temporal cortices. Brain volume reductions with age are more pronounced in individuals with schizophrenia than in healthy individuals. Finally, individuals with schizophrenia appear to differ from individuals without the disorder in eye tracking and electrophysiological indices. Neurological soft signs common in individuals with schizophrenia include impairments in motor coordination, sensory integration, and motor sequencing of complex movements; left-right confusion; and disinhibition of associated movements [2].

PHARMACOLOGIC TREATMENT OF SCHIZOPHRENIA

The course of schizophrenia is characterized in about three quarters of the cases by phases of remission alternating with phases of relapse: after the first episode, in most of cases associated with discontinuation of antipsychotic treatment, while neurobiological basis of schizophrenia has provided evidence of the often progressive nature of the disease [3].

Early intervention in psychosis may have positive effects on the long-term course of illness, and delayed access to mental health services in recent onset schizophrenia seems to be associated with slower or incomplete recovery, increased risk of recurrence and an overall poor treatment outcome [4]. The study by Robinson et al. [5] showed that continuity of treatment in the early stages is crucial and may alter the outcome of the disease. Patients with a first episode of schizophrenia despite good response to early intervention had a cumulative recurrence rate greater than 80% within five years. Antipsychotic drugs are generally recommended for all stages of schizophrenia, for the treatment of acute episodes of psychosis and for the prevention of recurrence [6].

Long-term goals of current treatment for schizophrenia include relapse prevention, recovery and improved adherence to therapy and patients quality of life. Antipsychotics in combination with other therapeutic interventions are considered as essential for the achievement of these long-term goals. Several relevant issues relating to the pharmacotherapy of schizophrenia – especially when starting treatment and for how long to continue it – still remain unresolved and often result in an inadequacy of treatment for many patients [7].

Poor adherence to antipsychotic therapy is another important factor that contributes to possible inadequacy of treatment [8].

A considerable effort has been put into the development of antipsychotic drugs with better tolerability in order to improve adherence, or in formulations that enable less frequent, and by this a more reliable administration, including Long-Acting Injectable (LAI) antipsychotics. In recent years the development of these formulations of atypical antipsychotics and the promising results obtained in well conducted trials with these compounds are changing the attitude towards these drugs, usually reserved to patients with long-term histories of non-adherence to treatment [9].

DURATION OF PHARMACOLOGIC TREATMENT

Based on systematic review of Leucht et al. (2012), patients who have been stable on antipsychotics for the period of two to five years after an acute episode relapse more frequently if they are taken off medication than if they continue it [10].

According to the guidelines of the Canadian Psychiatric Association [11], antipsychotic drugs for the treatment of a first episode of psychosis should be continued for at least two years after the first symptom remission, while one should observe a minimum of five years of stability without relapses before making a slow withdrawal of antipsychotic drugs over a 6-24 months in patients with a history of previous recurrences. A significant problem with continued long-term antipsychotic treatment are undesirable effects of drugs including neurological side effects of typical antipsychotics, and metabolic side effects associated with some atypical antipsychotics [12].

The reduction of the volume of brain tissue found in the disease may be caused by chronic exposure to antipsychotics according to study of Ho BC et al [13].

However, the prolonged treatment with LAI-risperidone was associated with stability of white matter volume, in contrast to a volume reduction observed in patients treated with the oral formulation of the same drug based on the study of Bartzokis G, et al.2011, [14] conducted in patients with early phase of schizophrenia diagnosis . This study also concluded that changing the adherence to LAI-risperidone may act on myelination and give reason for the better prognosis associated with the LAI antipsychotic than the oral formulation. The risk-benefit ratio of long term treatment should be carefully considered and that the clinician should be careful in prescribing the lowest dose of antipsychotic needed to control symptoms.

TREATMENT ADHERENCE AND SYMPTOM RELAPSE

Despite the recommendations from their psychiatrists, patients with schizophrenia discontinue their therapy often. Results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study indicate that up to 74% of patients with schizophrenia discontinued their therapy after 18 months; while 40% of patients after first episode schizophrenia discontinue medication during the first nine months [15,16] ,or up to 42% , one year after the disease onset, according to European First Episode Schizophrenia Trial (EUFEST) [17,18].

Discontinuation of treatment was also main risk factor associated with a significantly higher recurrence rate (43% vs. 21%, $p < 0.011$) in the study of 131 first episode patients in remission followed for 18 months [19].

Non-adherence with antipsychotic medications is a leading source of preventable morbidity in the community treatment of schizophrenia [20]. Approximately one-third of patients with schizophrenia chronic course of disease were noncompliant with their prescribed medication regimen [21] and findings suggests that non-adherence is one of the most important and main risk

factor that contribute inadequate treatment [22], relapse and readmissions [23]. The majority of hospital readmissions seems to be caused by non-adherence however, it is not clear yet whether the non-adherence is causing a relapse or is consequence of symptom worsening [24]. The high rate of non-adherence can be explained by poor insight into illness, cognitive deficits, and elevated substance abuse associated with schizophrenia, side effects caused by antipsychotics such as anhedonia and extrapyramidal symptoms [25], depression as outcome, lack of efficacy and therapeutic alliance with the doctor [7].

Clearly, the goal of treatment of schizophrenia patients should be to increase compliance with antipsychotic therapy, thereby decreasing the negative effects of untreated psychosis and—at the same time—to minimize the amount of antipsychotic-induced side effects. This goal may, in part, be achieved by the use of Long-Acting Injectable (LAI) or depot antipsychotics [26-28], leading to relapse and hospitalization decrease [29].

Clinical research and expert opinion [30] support the use of depot antipsychotics as a maintenance treatment for patients with a history of non-adherence with oral antipsychotics [31,32]. Moreover, LAI- antipsychotics should maximize pharmacokinetic coverage and minimize antipsychotic withdrawal symptoms resulting from non-adherence [33]. LAI-antipsychotics are not influenced by first-pass metabolism, decreasing the potential for drug-drug interactions and the slow rate of absorption, which leads to reductions in differences between Cmax (peak) and Cmin (trough) plasma levels [34], inducing less side effects (an important predictor of poor treatment compliance), relative to oral antipsychotics [35].

According to systematic review [36], not all LAI-antipsychotics are the same; for example, LAI- risperidone may be associated with equal or less side effects than oral risperidone, whereas fluphenazine enanthate and decanoate may be associated with equal or more side effects than oral fluphenazine. Randomized studies suggest that LAI-antipsychotics reduce risk of relapse when combined with additional interventions such as individual and family social therapy and/or a nurse available for home visits.

First-generation long-acting injectable (depot) antipsychotics (AP1G) used for the treatment of schizophrenia since 1960, resulted in a significant decrease in the number of patients relapses, length and frequency of hospitalizations [37].

However, when oral second-generation antipsychotics (AP2G) were introduced thirty years later, psychiatrists prescribed them for long term therapy of schizophrenia and started to switch LAI -antipsychotics first generation (AP1G) to oral Antipsychotics second generation (AP2G), as they were seen as more efficient and better tolerated [38]. This trend persisted for many years, despite evidence to suggest from meta-analyses and naturalistic studies that depot AP1G were more effective in reducing schizophrenic relapses than oral AP2G [39].

The same finding was later logically replicated also for Long-acting injectable, LAI- AP2G [40-43].

When considering the length of subsequent prophylactic treatment after the first episode of schizophrenia, not only its efficacy but also the profile or severity of adverse events of the given antipsychotic must be taken into account. Moreover, it should be taken into consideration that approximately 20% of first-episode patients will never experience a subsequent exacerbation of schizophrenia; irrespective of whether they receive or the type of therapy they receive [44].

The current guidelines on schizophrenia treatment, consider depot or Long-acting injectable antipsychotics as drugs of choice for long-term therapy in patients who are non-adherent with antipsychotic medication [45-47].

Although patients with schizophrenia are often willing to use depot or LAI-antipsychotics, these preparations are today prescribed only for approximately 20% of them [48-50], or up to 30% in United States [30,31].

Systematic surveys of specific studies indicate that patients treated with depot antipsychotics show only a 24% non-adherence rate while they are sufficiently covered by medication for 91% of the total therapy time [51-53].

FIRST VS SECOND GENERATION OF ANTIPSYCHOTICS IN FIRST EPISODE SCHIZOPHRENIA-CURRENT KNOWLEDGE

Instead of guessing whether patients will accept LAI therapy or not, psychiatrists should offer this form of treatment as a routine choice to all appropriate patients with schizophrenia, including first-episode subjects. Selection between long-term injectable therapy and oral medication should be based on educational and therapeutic dialogue of the psychiatrist and the patient who can then in turn discuss the potential benefits and disadvantages of the proposed therapeutic strategy [54,55].

Recent studies show that LAI- AP2G therapy is effective and also acceptable for schizophrenia first-episode patients [56,57].

LAI- AP2G has been used in clinical practice for several years. Nowadays, LAI-AP2G is reserved mainly for patients with long-term course of schizophrenia who show low adherence to oral medication. The studies performed especially with LAI-risperidone in patients with first episode or early stage of schizophrenia clearly indicated that this form of therapy could be effective and well tolerated [58,59].

These findings, which clearly favor the LAI form of risperidone in early stage of disease, conflict with a number of recent studies of patients with chronic course of schizophrenia that showed no advantage for relapse prevention [60].

Poor awareness of having a psychotic disorder accompanied by poor awareness of the need for medication is the norm in the early phase of schizophrenia while LAI- antipsychotic medication were well accepted by patients with a recent first episode of schizophrenia leading to better medication adherence, greater relapse prevention, and better psychotic symptom control than

oral antipsychotic medication. The superiority of LAI-risperidone extends beyond preventing psychotic symptom return also leading to better maintenance of intracortical myelination [61], as well as improved cognitive functioning [62].

If the improved psychotic symptoms such as control, cognition, and intracortical myelination can be replicated in longer longitudinal studies of patients with a first episode of schizophrenia, it would suggest that the use of LAI antipsychotics early in schizophrenia can modify the trajectory of the disorder and lead to better long-term outcomes. This possibility would be a “game changer” for the field [63].

The debate over the alleged better tolerability of atypical antipsychotics compared to typical antipsychotics is still alive [64], while meta-analysis by Leucht et al. 2009, [65] compared the effectiveness of nine atypical or Second Generation Antipsychotics (SGAs) with First Generation Antipsychotics (FGAs) in patients with schizophrenia. The authors found that four of SGAs were better than FGAs for overall efficacy, with small to medium effect sizes (amisulpride, clozapine, olanzapine and risperidone). The other SGAs were not more efficacious than the FGAs, even for negative symptoms. Authors concluded that SGAs differ in many properties and are not a homogeneous class.

The results from another recent meta-analysis [66], suggest that individually SGAs were not consistently superior to FGAs, as a group, SGAs were associated with less relapse, readmissions and overall treatment failure than FGAs, having a modest but clinically relevant effect size. In recent years, the atypical antipsychotics inducing of weight gain and changes in glucose and lipid metabolism raised doubt about their alleged advantage over typical antipsychotics, leading to a reconsideration of the positioning of some atypical antipsychotics in the treatment of schizophrenia [67].

Nevertheless, analysis of the recent results comparing typical and atypical antipsychotics demonstrate the high heterogeneity of the two classes of drugs, which does not allow any generalization, the choice of medication should be made on the basis of a careful assessment of each case, and of the various treatment options available [68].

Although the data available are limited many experts recommend prescribing LAI-AP2G (especially LAI-risperidone or alternatively paliperidone palmitate) in the early stages of schizophrenia, particularly in patients who benefited from the original oral molecule in the past and agree to receive long-term injection treatment. Early application of LAI-AP2G can significantly reduce the risk of relapses in future and thus improve not only social and working potential of patients with schizophrenia but also their quality of life [69].

LONG ACTING INJECTABLE VS ORAL ANTIPSYCHOTICS

Long-Acting Injectable (LAI) formulations of antipsychotic medications were developed to improve adherence, to reduce the frequency of daily medication where the patient must only

decide to have an injection administered once or twice monthly. Pharmacokinetically, LAI-antipsychotics provide a more stable steady-state concentration of medication in the blood compared with daily oral dosing.

LAI antipsychotics were introduced for reasons of potential advantages compared to oral antipsychotics, including their ability to improve compliance and to distinguish between non-adherence and lack of response, to monitor the regular contact between patient and their caregivers, to reduce the risk of accidental or deliberate overdose, and to achieve better bioavailability in obtaining a more predictable correlation between drug dosage and plasma concentrations [70].

In the study of Hogarty et al. (1979), comparison of oral and LAI fluphenazine, demonstrated that relapse rates were notably worse for patients taking the oral formulation, but this was not apparent until after at least a year of treatment [71].

In the observational community cohort study in Finland [72], the administration of depot AP1G and LAI-risperidone resulted in reduction of the risk of rehospitalization by 50% or 65%, respectively, compared with oral formulations of the same antipsychotics. This study investigated the risk of rehospitalization and medication discontinuation in a nationwide cohort of 2,588 consecutive patients with schizophrenia who were hospitalized for the first time between 2000 and 2007, and indicated the importance of LAI-antipsychotic use after the first episode of schizophrenia, reporting that LAI-antipsychotic (haloperidol, risperidone, perphenazine, zuclophenthixol) treatment was associated with substantially better outcomes than with the equivalent oral formulations. Regarding this study the prevention of schizophrenia relapse is crucial and indicate LAI treatment [72].

Time-to-relapse in patients with clinically stable schizophrenia treated with oral risperidone, olanzapine, or a typical antipsychotic was significantly longer when switched to treatment with LAI-risperidone [73-75].

Convincing data showing the superiority of LAI over Oral Antipsychotics (OAPs) is needed to support the use of LAI- antipsychotics, meanwhile meta-analysis of Kishimoto et al.2012, [76] find that LAI-antipsychotics were associated with significantly lower relapse rates than OAPs. The meta-analysis in 2011 collected outpatient in Randomized Controlled Trials that compared LAI-antipsychotics with OAPs medications and lasted for at least 12 months (10 studies, n=1700), and analysis found that patients on LAI-antipsychotics are 30% less likely to relapse compared with those on OAPs medications. The other meta-analysis by the same research group in 2014 used a broader set of inclusion criteria, including inpatient and outpatient studies of at least 6-month duration, and included two new large studies that did not find an overall advantage for LAI-antipsychotics over OAPs medications. Contrary to the earlier study, this second meta-analysis (21 studies, n=5176) concluded that LAI-antipsychotics did not significantly reduce rates of relapse [60].

LAI- antipsychotics have also some limitations, such as slow dose titration, a greater time required to reach steady state, and side effects persisting for a while if they have to be suspended for safety concerns. Traditionally, LAI formulations were used in the maintenance treatment of patients with schizophrenia, usually after clinical stabilization with oral antipsychotics. More recently, LAI formulations of atypical antipsychotics, including olanzapine, paliperidone and aripiprazole, have been developed [77,78].

Table 1: Characteristics of older LAI antipsychotics drugs.

Agent	Vehicle	Formulation	Dosing interval	Injection site Pain/reaction	T-max
Phluphenazine	Ester(decanoate)	Sesame seed oil	2-5weeks	+++	0,3-1,5days
Phlupentixol	Ester(decanoate)	viscol oil	2-4weeks	+++	3-5 days
Haloperidol	Ester(decanoate)	Sesame seed oil	4weeks	+++	3-9days
Zuclopenthixol	Ester decanoate)	viscol oil	2-4weeks	++++	3-5days

Inadvertent intravascular injections: + minimal, ++ low, +++ moderate, ++++high

Table 2: Characteristics of newer LAI antipsychotic drugs.

Agent	Vehicle	Formulation	Dosing interval	Injection site Pain/reaction	T-max
Risperidon	Microspheres	Water	2 weeks	+	21 days
Paliperidone	Ester(palmitate)	Water(nanosuspension)	4 weeks	++	13 days
Olanzapine	Salt(pamoate)	Water(microcrystalline suspension)	2-4weeks	++	7 days
Aripiprazol	Lyophil(crystal)	Water(nanosuspension)	4 weeks	++	6,5-7 days

Inadvertent intravascular injections: + minimal, ++ low, +++ moderate, ++++high

EFFICACY AND SAFETY OF THE LAI –SECOND GENERATION (ATYPICAL) ANTIPSYCHOTICS

The use of Long-Acting Injectable Antipsychotics (LAIs) is an important option [79].

In practice, patients and clinicians are sometimes reluctant to use LAI-antipsychotics because of stigma, needle pain, time constraints, side effect concerns, and cost [80].

Risperidone LAI: despite some studies have demonstrated significant reductions in recurrence rates with the risperidone LAI formulation compared to the oral one [43], treatment adherence is generally better with LAI-risperidon, which likely confers a substantial impact to better effectiveness maintenance, but other studies [81-83], have not confirmed this superiority.

Olanzapine LAI: the efficacy and tolerability of olanzapine LAI (olanzapine pamoate) was assessed by two randomized, double-blind, controlled trials, one compared to placebo (84),the

other compared to oral olanzapine [85]. LAI-olanzapine was significantly more effective than placebo in reducing scores on the PANSS (Positive And Negative Syndrome Scale); however, with a higher rate of side effects due to weight gain and alteration of lipid metabolism. LAI -olanzapine compared to oral olanzapine showed higher efficacy and tolerability in the maintenance treatment of up to 24 weeks duration, in an 8-week randomized, double-blind, placebo controlled trial [86].

LAI-olanzapine improved the level of functioning in acutely ill patients with schizophrenia. In a recent open-label, randomized study of LAI-olanzapine, outpatients with schizophrenia maintained or improved their baseline level of functioning over time [87].

Paliperidone LAI: several studies have demonstrated the greater efficacy of LAI-paliperidone (paliperidone palmitate) compared to placebo and its non-inferiority compared to LAI-risperidone in improving the scores of the PANSS in schizophrenia patients with acute symptomatology and a delay in time to recurrence in stabilized patients [88-90].

LAI-paliperidone has a relatively neutral metabolic profile, resulting in only limited weight gain and no effects on glucose and lipid metabolism, both in short and long-term studies [91].

Aripiprazol LAI: this formulation of aripiprazole has been approved by EMA for the maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole while the clinical efficacy of LAI-aripiprazol was established in two randomized, double-blind, controlled studies conducted in patients with schizophrenia. In one study [92], LAI-aripiprazol was found to be non-inferior to oral aripiprazole for both the relapse rate and the PANSS change after 26 weeks of treatment. In the other study [93], the recurrence rate with LAI-aripiprazole at 52 weeks was 5.03 times lower than with placebo. The main adverse events observed in the two clinical trials were: weight gain (9.0%), akathisia (7.9%), insomnia (5.8%), and pain at the injection site (5.1%).

Furthermore, to evaluate the efficacy of LAI-aripiprazole as an acute treatment in patients with schizophrenia, a 12 weeks double-blind RCT [94], was performed. The authors found that LAI-aripiprazole improved symptoms and functioning in patients with acute schizophrenia, with acceptable safety and tolerability.

Current guidelines [10,11,68] generally recommend LAI-AP2G for the maintenance treatment of schizophrenia among other available treatment options.

LAI-AP2G antipsychotics can also be considered for the acute phase of schizophrenia if there is a repeated history of non-adherence or poor adherence [10], while data on the potential of new LAI formulations in the first episode of schizophrenia still appear to be limited to represent the basis for specific recommendations [95].

Early intervention and continuity of treatment are decisive for achieving long-term remission, preventing a malicious course of the disease and reducing the costs and the burden of the disease. Traditionally, LAI have been reserved for non-adherent patients who have already experienced multiple episodes, the availability of new LAI-AP2G drugs, with a better tolerability than the

earlier typical depot antipsychotics in terms of extra pyramidal side effects, provides the option of extending such treatment to young patients in the early stages of disease [96].

LAI formulations have been marked mainly for patients with low insight into the illness and poor adherence to the therapy, however if the target population for LAI-AP2G would be extended to include also patients with better insight and apparent adherence, readmission rate should decrease. Of course, this would apply only to patients who are willing to use these products on an outpatient basis. However, many experts believe that these guidelines should widen the indication of LAI- AP2G in the treatment of schizophrenia [79].

CONCLUSION

The clinical decision to initiate injection antipsychotic medications appears to rest on a clinical assessment of the risks and consequences of poor medication adherence. Patients at greater risk, specifically those who have a history of persistent non-adherence and those admitted for inpatient care during their last episode of non-adherence, were more likely to be started on injections.

Studies results suggest that efforts are needed to improve access of depot antipsychotic medications to cognitively impaired patients [97], as psychopathology and social functioning can worsen with repeated psychotic episodes in patients with schizophrenia [98,99].

A series of double-blind prospective studies confirmed the importance of LAI-antipsychotics treatment in preventing of chronic or relapsing schizophrenia, especially its use in first-episode schizophrenia.

The prescribing of LAI-antipsychotics for out-patient maintenance therapy continued to grow worldwide, although the use varied considerably in different countries.

It seems that the use of LAI- AP2G after a first episode of schizophrenia has notable advantages for clinical outcomes. The key clinical advantages are apparently owing to the more consistent administration of the LAI-AP2G, which should be offered earlier in the course of illness.

RECOMMENDATIONS

LAI-antipsychotics are better to consider in patients with recent-onset schizophrenia and those with risk factors for medication non-adherence such are the history of non-adherence, severe psychotic symptoms, substance abuse, cognitively impaired patients, patients with ambivalence or negative attitudes towards medications, and poor insight.

When selecting an LAI- antipsychotic, considering a patient's preferences, health status, experience with prior antipsychotic medication trials, and the side-effect profiles of different medications, is crucial.

The effectiveness of newer LAI-antipsychotics and older LAI-antipsychotics seems to be similar, except side effects.

And finally, oral clozapine rather than LAI-antipsychotics should be tried for those whose clinical instability is due to treatment-resistant illness rather than medication non-adherence.

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