LONG-ACTING INJECTION ANTIPSYCHOTIC MEDICATIONS IN THE MANAGEMENT OF SCHIZOPHRENIA

Emilio Sacchetti[1,2], Heinz Grunze[3], Stefan Leucht[4], Antonio Vita [1,2]

[1] Department of Clinical and Experimental Sciences, University of Brescia; [2] Department of Mental Health, Spedali Civili, Brescia; [3] Institute of Neuroscience, Academic Psychiatry, University of Newcastle; [4] Department of Psychiatry and Psychotherapy, TU-München

Abstract

Antipsychotic drugs are recommended both for the treatment of the acute episodes and the prevention of recurrence of psychosis. Long-term goals of treatment of schizophrenia include relapse prevention, recovery, improved adherence to therapy and improved patients' quality of life. Antipsychotics in combination with other therapeutic interventions are considered essential for the achievement of these long-term goals.

However, relevant issues relating to the pharmacotherapy of schizophrenia still remain unresolved. Poor adherence to antipsychotic therapy is an important factor that contributes to possible inadequacy of treatment. A considerable effort has been put into the development of antipsychotic drugs with better tolerability, or in formulations that enable less frequent administration, including long-acting injectable (LAI) antipsychotics. In recent years, the development of these formulations with atypical antipsychotics and the promising results obtained in well conducted trials with these compounds are changing the attitudes towards these drugs, traditionally reserved to patients with long-term histories of non-adherence to treatment.

The discovery and development of antipsychotic drugs more than 50 years ago has significantly improved the quality of life of patients with schizophrenia and currently there is little doubt about the substantial benefits of antipsychotics [1]. Antipsychotic drugs are generally recommended for all stages of schizophrenia, for the treatment of acute episodes of psychosis and for the prevention of recurrence [2]. Important long-term goals of current treatment for schizophrenia include relapse prevention, recovery, improved adherence to therapy and improve 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, such as its premature termination or delayed access to treatment [1]. Poor adherence to antipsychotic therapy is another important factor that contributes to possible inadequacy of treatment [3]. 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,

Correspondence

Emilio Sacchetti

emilio.sacchetti@unibs.it

traditionally reserved to patients with long-term histories of non-adherence to treatment [4].

The importance of continuity of treatment

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, it is estimated that only 14-20% of patients will recover completely [2]. In addition, knowledge about the neurobiological basis of schizophrenia has provided evidence of the often progressive nature of the disease [5]. There is clear evidence indicating that the suspension of treatment is associated with a relapse in most cases [2]. It is also increasingly evident that early intervention in psychosis may have positive effects on the long-term course of illness, while a delayed access to mental health services in recent-onset schizophrenia seems to be associated with slower or incomplete recovery, an increased risk of recurrence and an overall poor outcome [6]. Continuity of treatment already in the early stages seems crucial and may alter the outcome of the disease. A study published by Robinson et al. [7] clearly showed that despite a generally good response to initial treatment, patients with a first episode of schizophrenia had a cumulative recurrence rate greater than 80% within five years. After the initial remission, discontinuation of antipsychotic medication was identified as a significant risk factor for recurrence, resulting in an almost five times increased risk.

There is a multitude of relapse prevention studies in schizophrenia in general, but so far only a few controlled clinical trials have evaluated the possibility of preventing relapse in patients suffering specifically from a first episode of schizophrenia. In one of these studies [8], 131 first episode patients in remission for at least six months were randomized to discontinue treatment or continue it, for the most part with lower doses of atypical antipsychotics, and were followed for 18 months. Discontinuation was associated with a significantly higher recurrence rate (43% *vs*. 21%, $p < 0.011$). A more recent randomized controlled trial (RCT) [9] compared continued maintenance therapy with intermittent treatment in patients with remitted first episode schizophrenia who received maintenance therapy for only one year. Recurrence rates were significantly higher in the group receiving intermittent treatment than in the group that received continuous maintenance treatment. In the light of these results, indicating the importance of continuous treatment from the early phases of the disease onwards, we might wonder whether a LAI antipsychotic should be used already after the first episode of schizophrenia. In this regard, a recent observational community cohort study conducted in Finland [10] 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. The authors reported that the use of LAI antipsychotic (haloperidol, risperidone, perphenazine, zuclopenthixol) was associated with substantially better outcomes than with the equivalent oral formulations.

LAI atypical antipsychotics in early psychosis

As for LAI atypical antipsychotics, there are currently very few data available on their use in first-episode schizophrenia.

An open-label study [11] conducted over two years in patients with first episode schizophrenia showed that those assigned to risperidone LAI had a significantly lower recurrence rate and a higher percentage of adherence compared to the control group treated with oral risperidone.

In another open-label study [12] conducted on patients with newly diagnosed schizophrenia or schizophreniform disorder, treatment for two years with risperidone LAI led to a remission in 64% of patients.

A RCT reported on the acceptance and the initial adherence outcomes with risperidone LAI treatment in patients with first episode schizophrenia [13]. Individuals who took risperidone LAI were significantly more likely to remain adherent at 12 weeks compared with patients treated with oral antipsychotics. These results support the feasibility and acceptability of LAI atypical antipsychotics as a treatment strategy already at the early stages of schizophrenia.

Duration of treatment

One of the open questions about how best to ensure the continuity of the treatment is the question of how long to treat patients in the maintenance phase of schizophrenia [1]. Based on evidence of clinical studies showing that even those 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 [14]. According to the guidelines of the Canadian Psychiatric Association [15] 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.
As in the treatment of other chronic diseases, a significant problem with continued long-term antipsychotic treatment is that of undesirable effects of drugs. In addition to the well-known neurological side effects of typical antipsychotics, there is clear evidence of metabolic side effects associated with some atypical antipsychotics [16]. Some studies have also suggested that chronic exposure to antipsychotics may contribute to the reduction of the volume of brain tissue founf in the disease [17]. However, one study [18] conducted in patients with newly diagnosed schizophrenia verified that prolonged treatment with long-acting 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; the study concluded that changing the adherence to risperidone may act on myelination and give reason for the better prognosis associated with the LAI antipsychotic than the oral formulation.
It is clear, however, that 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.

Adherence to treatment

One of the main factors that determine inadequate treatment and its untimely suspension is poor adherence to the treatment itself [3]. Poor adherence to medication is one of the most important problems in the treatment of patients with mental illness. The majority of hospital admissions are caused by some degree of non-adherence, although it is often unclear whether the non-adherence is causing a relapse or is a consequence of symptom worsening [19]. The percentage of patients with schizophrenia who are partially or completely non-adherent is estimated to vary between 40 and 60% [20].
Factors that contribute to poor adherence to drug therapy in schizophrenia are: patient-related factors (poor insight, depression, substance abuse), treatment-related factors (side effects, lack of efficacy, complexity of the regimen) and lack of support or therapeutic alliance with the doctor or the medical team [1]. Some of these factors can be acted upon by improving drug delivery strategies, such as with long-acting formulations. However, it should be kept in mind that for prompt recognition and correction of poor adherence educational efforts directed to patients and to medical staff are also extremely useful [21]. Poor adherence has been identified as an important risk factor for recurrence [3 22]. The use of LAI antipsychotics has been shown to improve adherence to treatment, leading to a lower percentage of drug withdrawal, relapse and hospitalization [23].

First generation and second generation antipsychotics

Although atypical antipsychotics are widely used, the debate over their alleged better tolerability compared to typical antipsychotics is still alive [24]. A meta-analysis by Leucht et al. [25] 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 meta-analysis provides data for individualised treatment based on efficacy, side effects, and cost. Moreover the results from another recent meta-analysis [26] suggest that, whereas individually SGAs were not consistently superior to FGAs, as a group, SGAs were associated with less relapse, overall treatment failure and hospitalization than FGAs, having a modest but clinically relevant effect size.
In recent years, the propensity of atypical antipsychotics to induce 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 [27]. Overall, the results of recent analyses 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 [2].

LAI antipsychotics

LAI antipsychotics were introduced over 40 years ago for reasons of potential advantages compared

Table I. Benefits of LAI antipsychotics.

Assuring drug delivery in patients who are unreliable pill takers or are drug reluctant - better adherence
Early identification of non-adherence
Providing a mechanism for monitoring adherence with injections
No need to remember to take medication every day
Regular interactions between patient and medical staff
Reduced relapse frequency and rehospitalization rates
Clear attribution of the cause of relapse or non-response, discriminating between non adherence or lack of response
Reduce the risk of accidental or deliberated overdose
Treating patients with more stable plasma concentrations than oral medications
Avoidance of first-pass metabolism - better relationship between dose and blood level of drug
Lower and less frequent peak plasma level - reduced side effects

vs. their oral counterparts, including their ability to improve compliance and to distinguish between non-adherence and lack of response, and to monitor the regular contact between patient and their caregivers, to reduce the risk of accidental or deliberate overdose, to achieve better bioavailability and obtain a more predictable correlation between drug dosage and plasma concentrations [20]. Table I summarizes the benefits of LAI antipsychotics.

LAI antipsychotics, however, 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 are used in the maintenance treatment of patients with schizophrenia, usually after clinical stabilization with oral antipsychotics. More recently, LAI formulations of atypical antipsychotics, including risperidone, olanzapine, paliperidone and aripiprazole, have been developed [28]. Table II lists the characteristics of available LAI antipsychotics.

Efficacy and safety of LAI *vs.* oral antipsychotics

Although it is reasonable to expect that LAI antipsychotics, may improve the clinical outcome of schizophrenia by improving adherence to treatment, the evidence obtained over the years of wide spread use of LAI typical antipsychotics is not completely clear [35 36]. On the other hand, systematic analyses of the effectiveness of the recently introduced LAI atypical antipsychotics are still in progress. A series of analyses and systematic reviews of the literature has been conducted to compare the effectiveness of LAI atypical antipsychotics to both typical and atypical oral antipsychotics [37-39].

A large metareview [35], including 8 Cochrane reviews of RCTs of individual LAI antipsychotics in patients with schizophrenia or schizophreniform disorder found recurrence rates and tolerability of LAI antipsychotics to be similar to the oral medications, while overall clinical improvement was significantly more frequent and marked with LAI than oral antipsychotics.

The results of a systematic review [36], carried out to compare LAI typical antipsychotics with typical and atypical oral antipsychotics, showed an overall higher clinical benefit of LAI typical antipsychotics, but these results were highly variable and inconclusive mainly because of the heterogeneity of methods and interventions used in the various studies.

In a systematic review and meta-analysis of 10 RCTs of at least 12 months duration, published between 1975 and 2010, including a total of 1,700 patients, a significant reduction in relapse rate (21.6% *vs*. 33.3%, RR 0.70, 95% CI 0.57 to 0.87, p = 0.0009) and rate of dropouts for inefficacy of LAI antipsychotics compared to typical oral antipsychotics was demonstrated [37].

Another systematic review of studies published between 2000 and 2011 [38] that compared the efficacy of LAI and oral antipsychotics on relapse, hospitalization and discontinuation of drug for any cause in schizophrenia revealed a clear difference between observational studies (4 prospective and 4 retrospective), which showed a significant benefit for the LAI formulations (prospective studies: RR = 0.62, 95% CI 0.48-0.81, p < 0.001; retrospective studies: RR = 0.56, 95% CI 0.44 to 0.71, p < 0.001), and RCTs (5 studies), which showed a non-significant difference favouring LAI formulations (RR = 0.89, 95% CI 0.64 to 1.22, p = 0.416). The authors of this meta-analysis concluded that the study design may affect considerably the results obtained: in particular, the controlled clinical trials, while avoiding the confounding factors and selection bias often present in observational studies, do not take into account the characteristics and variability of setting of real world treatment.

In a recent meta-analysis by Kishimoto et al. [39] of 21 RCTs (n = 5,176 patients), LAI antipsychotics did not reduce relapse compared with oral antipsychotics in

schizophrenia patients. The exceptions were first-generation LAI antipsychotics, mostly consisting of fluphenazine-LAI studies, which were superior to oral antipsychotics regarding relapse and hospitalization. Considering these findings and in order to evaluate the real world effectiveness of LAI compared with oral antipsychotics, the authors underline the need of large and long pragmatic trials, which better represent common clinical practice.

Efficacy and safety of the individual LAI atypical antipsychotics

Risperidone LAI: despite some studies have demonstrated significant reductions in recurrence rates with the risperidone LAI formulation compared to the oral one [37 40-42] other studies have not confirmed this superiority [43-45]. The diverging results might be due to differences in quality, type of design and methods of the various studies [1].

Olanzapine LAI: the efficacy and tolerability of olanzapine LAI (olanzapine pamoate) was assessed by two randomized, double-blind, controlled trials, one compared to placebo [46], the other compared to oral olanzapine [47]. In the former 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. The latter demonstrated a higher efficacy and tolerability of olanzapine LAI compared to oral olanzapine in the maintenance treatment of up to 24 weeks duration.

In an 8-week randomized, double-blind, placebo-controlled trial [48], olanzapine LAI improved the level of functioning in acutely ill patients with schizophrenia. In a recent 2-year, open-label, randomized study of olanzapine LAI, outpatients with schizophrenia maintained or improved their baseline level of functioning over time, but results did not significantly differ between olanzapine LAI and oral olanzapine [49].

Paliperidone LAI: several studies have demonstrated the greater efficacy of paliperidone LAI (paliperidone palmitate) compared to placebo and its non-inferiority compared to risperidone LAI in improving the scores of the PANSS in schizophrenia patients with acute symptomatology and a delay in time to recurrence in stabilized patients [50-52]. It should be noted that paliperidone LAI 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 [53].

More recently, the LAI formulation of aripiprazole has been approved by EMA for the maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole [34]. The clinical efficacy of aripiprazole LAI was established in two randomized, double-blind, controlled studies conducted in patients with schizophrenia. In one study [54], aripiprazole LAI 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 [55], the recurrence rate with aripiprazole LAI 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 aripiprazole LAI as an acute treatment in patients with schizophrenia, a 12 weeks double-blind RCT [56] was performed. The authors found that aripiprazole LAI improved symptoms and functioning in patients with acute schizophrenia, with acceptable safety and tolerability.

Current and recommended use of LAI antipsychotics

Current guidelines [2 14 15] generally recommend LAI antipsychotics for the maintenance treatment of schizophrenia among other available treatment options and/or when it is necessary to improve adherence to medication.

LAI antipsychotics can also be considered for the acute phase of schizophrenia if there is a repeated history of non-adherence or poor adherence [14], while data on the potential of new LAI formulations in the first episode of schizophrenia still appear to be too limited to represent the basis for specific recommendations [57]. However, many experts believe that these guidelines are too restrictive and that we should widen the indication of LAI antipsychotics in the treatment of schizophrenia [19]. With the increasing availability of effective and well tolerated LAI atypical antipsychotics, international guidelines should consider at which stage of the disease LAI atypical antipsychotics should be used, and which patients may benefit from treatment with such compound.

Another fact that has emerged from a number of surveys conducted in several Western countries, including Italy, is the relative lack of use of LAI antipsychotics even in patients who could clearly benefit from it. This finding may be explained by the number of misunderstandings and prejudices prevalent among physicians, patients and caregivers. LAI antipsychotics are gener-

Table II. Characteristics of LAI antipsychotics drugs.

Agent	Formulation	Release mechanism	Available doses	Injection site (IM) according to SPC	Starting modalities	
Fluphenazine decanoate [29]	Sesame oil solution (insoluble in water)	Prodrug: hydrolysis by esterases	25 mg/mL vials	Gluteal	Several strategies for the LD. OS not necessary	
Haloperidol decanoate [30]	Sesame oil solution (insoluble in water)	Prodrug: hydrolysis by esterases	50 mg/mL, 100 mg/mL vials	Gluteal	Several strategies for the LD. OS not necessary	
Risperidone LAI [31]	Aqueous suspension; risperidone encapsulated into biodegradable microspheres	Microspheres: diffusion and erosion	12.5, 25, 37.5 or 50 mg	Deltoid or gluteal	It is required a period of 3 weeks of overlap with oral risperidone	
Olanzapine pamoate [32]	Micro-crystalline salt of olanzapine and pamoic acid suspended in aqueous solution	Dissociation into olanzapine and pamoic acid	210, 300 or 405 mg	Gluteal	Several strategies for the LD	
Paliperidone palmitate [33]	Nanocrystal molecules in aqueous suspension	Poorly soluble in water: hydrolysis by esterases, dissociation into paliperidone and palmitic acid	39, 78, 117, 156 or 234 mg	Deltoid or gluteal	Initial injection on day 1 and day 8. OS not necessary	
Aripiprazole monohydrate [34]	Aqueous suspension; lyophilized powder of aripiprazole monohydrate crystals	Poorly soluble in water: crystals particles dissociate, with slow and prolonged dissolution and absorption	300 or 400 mg	Gluteal	OS is necessary for 2 weeks	

G: gauge; IM: intramuscular; LD: loading dose; OS: oral supplementation; SPC: Summary of Product Characteristics; TW: thin wall; UTW: ultra-thin wall.

ally considered as old and coercive drugs, and used to be reserved for patients with poor adherence, and have often been associated with a reduced involvement of the mental health staff in patient care [58]. Some psychiatrists consider them to be "a last resort" treatment, to be used when all other pharmacological therapies have failed, and reserve them for patients who have already presented with multiple episodes.

The high cost of LAI atypyical antipsychotics represent a further major obstacle to the prescription of these formulations. However, recent pharmacoeconomic studies have shown that LAI atypical antipsychotics may constitute a superior therapeutic strategy also from the economic point of view, if the various direct and indirect cost items of patients' care are taken into account [59].

Practical recommendations on the use of LAI atypical antipsychotics

There is large consensus among specialists that the optimal use of new formulation LAI require a substantial change in the general attitude towards the treatment with depot antipsychotics [1 19]. LAI atypical an-

	Injection interval	Dose range	T max	T ½ (multiple dosing)	Supply	Needle supplied or recommended	Storage	Monitoring post injection
	2-4 weeks	12.5-100 mg	0.3-1.5 days	14 days	Available in multi-dose vials	21 G	Refrigeration is not required; room temperature (15-30°C)	No
	4 weeks	50-200 mg	3-9 days	21 days	Available in multi-dose vials	21 G	Refrigeration is not required; room temperature (15-30°C)	No
	2 weeks	12.5-50 mg	21 days	3-6 days	Must be reconstituted: vial with microspheres and syringe with 2 ml of diluent	Deltoid: 21 G 1-inch (25 mm) UTW; Gluteal: 20 G 2-inch (50 mm) TW	Refrigeration is required; (2-8°C)	No
	2-4 weeks	150-405 mg	7 days	30 days	Must be reconstituted	19 G (38 or 50 mm)	Refrigeration is not required; room temperature (15-30°C)	Yes (3 hours)
	4 weeks	39-234 mg	13 days	25-49 days	Pre-filled syringes	Deltoid: 23 G 1-inch (25 mm) or 22 G 2 ½-inch (according to patient weight) Gluteal: 22 G 1 ½-inch (38 mm)	Refrigeration is not required; room temperature (15-30°C)	No
	4 weeks	300 or 400 mg	6.5-7.1 days	29.9-46.5 days	Must be reconstituted	21 G 1 ½-inch (38 mm) in non-obese patients; 21 G 2-inch (50 mm) in obese patients	Refrigeration is not required; room temperature (15-30°C)	No

tipsychotics should also be considered as a potential first choice and should be used for suitable patients whenever treatment is indicated in the long-term and not just for patients with poor adherence [2 19 60]. An effective pharmacological maintenance therapy is the starting point for success of multimodal treatment and rehabilitation programs for people suffering from schizophrenia. It is general expert consensus that oral antipsychotics should be initiated as soon as possible in patients with a newly and firmly diagnosed schizophrenia [2]. Even though the data on the effectiveness of LAI atypical antipsychotics in this area are still limited, it can be assumed that they are at least as favorable as oral antipsychotics. In patients with an acute exacerbation of schizophrenia, in which the treatment guidelines propose treatment with oral antipsychotics, the use of LAI atypical antipsychotics should be considered when these exacerbations are due to prior repetitive non-adherence or poor adherence [1].

Finally, it is worth recalling that the switch from an oral antipsychotic to a LAI formulation requires specific strategies to maintain or improve the therapeutic efficacy and to minimize the effects of a potential cholinergic or histaminergic rebound [61].

Conclusions

In conclusion, the recent emergence of LAI formulations of atypical antipsychotics has increased the treatment portfolio available for individualized and personalized treatment of schizophrenia, a long neglected key aspect in the management of patients with mental illness. 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 drugs, with a better tolerability than the earlier typical depot antipsychotics in terms of extrapyramidal side effects, provides the option of extending such treatment to young patients in the initial stages of schizophrenia. This is particularly relevant considering the risk of relapse after discontinuation of treatment and the devastating consequences of a relapse. Further education of doctors and patients is needed to consider LAI antipsychotics from a new perspective: not any more as drugs of last resort, but rather a first step to achieve continuity of treatment and clinical remission. More well-designed long-term studies in first episode patients will be needed to confirm the preliminary, yet encouraging results with LAI formulations of atypical antipsychotics.

References

1 Altamura AC, Aguglia E, Bassi M, et al. *Rethinking the role of long-acting atypical antipsychotics in the community setting*. Int Clin Psychopharmacol 2012;27:336-49.

2 Jääskeläinen E, Juola P, Hirvonen N, et al. *A systematic review and meta-analysis of recovery in schizophrenia*. Schizophr Bull 2013;39:1296-306.

3 Haddad PM, Brain C, Scott J. *Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies*. Patient Relat Outcome Meas 2014;5:43-62.

4 Stahl SM. *Long-acting injectable antipsychotics: shall the last be first?* CNS Spectr 2014;19:3-5.

5 Vita A, De Peri L, Deste G, et al. *Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies*. Transl Psychiatry 2012;20:e190.

6 Penttilä M, Jääskeläinen E, Hirvonen N, et al. *Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis*. Br J Psychiatry 2014;205:88-94.

7 Robinson DG, Woerner MG, Alvir JM, et al. *Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder.* Am J Psychiatry 1999;156:544-9.

8 Wunderink L, Nienhuis FJ, Sytema S, et al. *Guided discontinuation versus maintenance treatment in remitted first- episode psychosis: relapse rates and functional outcome.* J Clin Psychiatry 2007;68:654-61.

9 Gaebel W, Riesbeck M, Wölwer W, et al.; German Study Group on First-Episode Schizophrenia. *Relapse prevention in first-episode schizophrenia-maintenance vs. intermittent drug treatment with prodrome-based early intervention: results of a randomized controlled trial within the German Research Network on Schizophrenia*. J Clin Psychiatry 2011;72:205-18.

10 Tiihonen J, Haukka J, Taylor M, et al. *A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia*. Am J Psychiatry 2011;168:603-9.

11 Kim B, Lee SH, Choi TK, et al. *Effectiveness of risperidone long-acting injection in first-episode schizophrenia: in naturalistic setting*. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1231-5.

12 Emsley R, Oosthuizen P, Koen L, et al. *Remission in patients with first-episode schizophrenia receiving assured antipsychotic medication: a study with risperidone long-acting injection.* Int Clin Psychopharmacol 2008;23:325-31.

13 Weiden PJ, Schooler NR, Weedon JC, et al. *A randomized controlled trial of long-acting injectable risperidone vs. continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome*. J Clin Psychiatry 2009;70:1397-406.

14 Leucht S, Tardy M, Komossa K, et al. *Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis*. Lancet 2012;379:2063-71.

15 Canadian guidelines. *Clinical practice guidelines. Treatment of schizophrenia*. Can J Psychiatry 2005;50:7S-57S.

16 Newcomer JW. *Metabolic considerations in the use of antipsychotic medications: a review of recent evidence*. J Clin Psychiatry 2007;68(Suppl 1):20-7.

17 Ho BC, Andreasen NC, Ziebell S, et al. *Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia*. Arch Gen Psychiatry 2011;68:128-37.

18 Bartzokis G, Lu PH, Amar CP, et al. *Long-acting injection versus oral risperidone in first-episode schizophrenia: differential impact on white matter myelination trajectory*. Schizophr Res 2011;132:35-41.

19 Kane JM, Garcia-Ribera C. *Clinical guideline recommendations for antipsychotic long-acting injections*. Br J Psychiatry 2009;52(Suppl):S63-7.

20 Olivares JM, Pinal B, Cinos C. *Comparisons of long-acting antipsychotics injection and oral antipsychotics in schizophrenia*. Neuropsychiatry 2011;1:275-89.

21 Vita A, Barlati S, Sacchetti E. *Non-pharmacological strategies to enhance adherence and continuity of care in schizophrenia*. In: Sacchetti E, Vita A, Siracusano S, et al., editors. *Adherence to antipsychotics in schizophrenia*. Milan: Springer 2014, pp. 99-137.

22 Leucht S, Heres S. *Epidemiology, clinical consequences, and psycho- social treatment of nonadherence in schizophrenia*. J Clin Psychiatry 2006;67(Suppl 5):3-8.

23 Kaplan G, Casoy J, Zummo J. *Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia*. Patient Prefer Adherence 2013;7:1171-80.

24 Hartling L, Abou-Setta AM, Dursun S, et al. *Antipsychotics in adults with schizophrenia: comparative effectiveness of first-generation versus second-generation medications: a systematic review and meta-analysis*. Ann Intern Med 2012;157:498-511.

25 Leucht S, Corves C, Arbter D, et al. *Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis*. Lancet 2009; 3;373:31-41.

26 Kishimoto T, Agarwal V, Kishi T, et al. *Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics*. Mol Psychiatry 2013;18:53-66.

27 Zhang JP, Gallego JA, Robinson DG, et al. *Efficacy and safety*

of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2013;16:1205-18.

28 Morrissette DA, Stahl SM. *Optimizing outcomes in schizophrenia: long-acting depots and long-term treatment*. CNS Spectr 2012;17(Suppl 1):10-21.

29 Moditen® Depot, Riassunto caratteristiche del prodotto http://www.bmscanada.ca/static/products/en/pm_pdf/MODECATE_EN_PM.pdf

30 Haldol® Decanoas, Riassunto caratteristiche del prodotto https://www.janssen.com.au/files/Products/Haldol_PI.pdf?44e085a0074766d87996f89c96d5c3e6

31 Risperdal®, Riassunto caratteristiche del prodotto http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Risperdal_Consta_30/WC500008170.pdf

32 ZypAdhera®, Riassunto caratteristiche del prodotto: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/000890/WC500054429.pdf

33 Xeplion®, Riassunto caratteristiche del prodotto: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_ _Product_Information/human/002105/WC500103317.pdf

34 Abilify Maintena®, Riassunto caratteristiche del prodotto: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_ _Public_assessment_report/human/002755/WC500156105.pdf

35 Adams CE, Fenton MKP, Quraishi S, et al. *Systematic meta-review of depot antipsychotic drugs for people with schizophrenia*. Br J Psychiatry 2001;179:290-9.

36 Haddad PM, Taylor M, Niaz OS. *First-generation antipsychotic long-acting injections v. oral antipsychotics in schizophrenia: systematic review of randomised controlled trials and observational studies*. Br J Psychiatry 2009;195:s20-8.

37 Leucht C, Heres S, Kane JM, et al. *Oral versus depot antipsychotic drugs for schizophrenia- - a critical systematic review and meta-analysis of randomised long-term trials*. Schizophr Res. 2011;127:83-92.

38 Kirson NY, Weiden PJ, Yermakov S, et al. *Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs*. J Clin Psychiatry 2013;74:568-75.

39 Kishimoto T, Robenzadeh A, Leucht C, et al. *Long-acting injectable vs. oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials*. Schizophr Bull 2014;40:192-213.

40 Grimaldi-Bensouda L, Rouillon F, Astruc B, et al. Does long-acting injectable risperidone make a difference to the real-life treatment of schizophrenia? Results of the Cohort for the General Study of Schizophrenia (CGS). Schizophr Res 2012;134:187-94.

41 Suzuki H, Gen K. *The influence of switching from haloperidol decanoate depot to risperidone long-acting injection on the clinical symptoms and cognitive function in schizophrenia.* Hum Psychopharmacol 2012;27:470-5.

42 Lambert T, Emmerson B, Hustig H, et al.; e-STAR Research Group. *Long-acting risperidone in Australian patients with chronic schizophrenia: 24-month data from the e-STAR database*. BMC Psychiatry 2012;26:12-25.

43 Buckley PF, Schooler NR, Goff DC, et al.; the PROACTIVE Study. *Comparison of SGA Oral Medications and a Long-Acting Injectable SGA: the PROACTIVE Study.* Schizophr Bull 2014 May 27. pii: sbu067 [Epub ahead of print].

44 Barnett PG, Scott JY, Krystal JH, et al.; CSP 555 Research Group. *Cost and cost-effectiveness in a randomized trial of long-acting risperidone for schizophrenia*. J Clin Psychiatry 2012;73:696-702.

45 Nielsen J, Jensen SO, Friis RB, et al. *Comparative effectiveness of risperidone long-acting injectable vs. first-generation antipsychotic long-acting injectables in schizophrenia: results from a nationwide, retrospective inception cohort study*. Schizophr Bull 2014 Sep 1. pii: sbu128 [Epub ahead of print].

46 Lauriello J, Lambert T, Andersen S, et al. *An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long- acting injection in acutely ill patients with schizophrenia*. J Clin Psychiatry 2008;69:790-9.

47 Kane JM, Detke HC, Naber D, et al. *Olanzapine long-acting injection: a 24-week, randomized, double- blind trial of maintenance treatment in patients with schizophrenia*. Am J Psychiatry 2010;167:181-9.

48 Witte MM, Case MG, Schuh KJ, et al. *Effects of olanzapine long-acting injection on levels of functioning among acutely ill patients with schizophrenia*. Curr Med Res Opin 2012;28:315-23.

49 Ascher-Svanum H, Novick D, Haro JM, et al. *Long-term functional improvements in the 2-year treatment of schizophrenia outpatients with olanzapine long-acting injection*. Neuropsychiatr Dis Treat 2014;20;10:1125-31.

50 Fu DJ, Bossie CA, Sliwa JK, et al. *Paliperidone palmitate versus oral risperidone and risperidone long-acting injection in patients with recently diagnosed schizophrenia: a tolerability and efficacy comparison*. Int Clin Psychopharmacol 2014;29:45-55.

51 McEvoy JP, Byerly M, Hamer RM, et al. *Effectiveness of paliperidone palmitate vs. haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial*. JAMA 2014;311:1978-87.

52 Markowitz M, Fu DJ, Levitan B, et al. *Long-acting injectable paliperidone palmitate versus oral paliperidone extended release: a comparative analysis from two placebo-controlled relapse prevention studies*. Ann Gen Psychiatry 2013;12:22.

53 Gilday E, Nasrallah HA. *Clinical pharmacology of paliperidone palmitate, a parenteral long-acting formulation for the treatment of schizophrenia*. Rev Recent Clin Trials 2012;7:2-9.

54 Fleischhacker WW, Sanchez R, Perry PP, et al. *Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study*. Br J Psychiatry 2014 Jun 12. pii: bjp.bp.113.134213 [Epub ahead of print].

55 Kane JM, Sanchez R, Perry PP, et al. *Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study*. J Clin Psychiatry 2012;73:617-24.

56 Kane JM, Peters-Strickland T, Baker RA, et al. *Aripiprazole once-monthly in the acute treatment of schizophrenia: findings from a 12-week, randomized, double-blind, placebo-controlled study*. J Clin Psychiatry 2014 Aug 19 [Epub ahead of print].

57 Jeong HG, Lee MS. *Long-acting injectable antipsychotics in first-episode schizophrenia*. Clin Psychopharmacol Neurosci 2013;11:1-6.

58 Besenius C, Clark-Carter D, Nolan P. *Health professionals' attitudes to depot injection antipsychotic medication: a systematic review*. J Psychiatr Ment Health Nurs 2010;17:452-62.

59 Achilla E, McCrone P. *The cost effectiveness of long-acting/extended-release antipsychotics for the treatment of schizophrenia: a systematic review of economic evaluations*. Appl Health Econ Health Policy 2013;11:95-106.

60 Manchanda R, Chue P, Malla A, et al. *Long-acting injectable antipsychotics: evidence of effectiveness and use*. Can J Psychiatry 2013;58(5 Suppl 1):5S-13.

61 Newcomer JW, Weiden PJ, Buchanan RW. *Switching antipsychotic medications to reduce adverse event burden in schizophrenia: establishing evidence-based practice*. J Clin Psychiatry 2013;74:1108-20.