Rassegne

Model of Management (Mo.Ma) for the patient with schizophrenia: crisis control, maintenance, relapse prevention, and recovery with long-acting injectable antipsychotics (LAIs)

Modello di Management (Mo.Ma) del paziente affetto da schizofrenia: controllo della crisi, mantenimento, prevenzione delle ricadute e recovery con gli antipsicotici LAI

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SUMMARY. Schizophrenia is a severe mental disease that affects approximately 1% of the population with a relevant chronic impact on social and occupational functioning and daily activities. People with schizophrenia are 2-2.5 times more likely to die early than the general population. Non-adherence to antipsychotic medications, both in chronic and first episode schizophrenia, is one of the most important risk factors for relapse and hospitalization, that consequently contributes to increased costs due to psychiatric hospitalization. Atypical long-acting injectable (LAI) antipsychotics can improve treatment adherence and decrease re-hospitalization rates in patients with schizophrenia since its onset. The primary goals in the management of schizophrenia are directed not only at symptom reduction in the short and long term, but also at maintaining physical and mental functioning, improving quality of life, and promoting patient recovery.

Aim. To propose a scientific evidence-based integrated model that provides an algorithm for recovery of patients with schizophrenia and to investigate the effectiveness and safety of antipsychotics LAI in the treatment, maintenance, relapse prevention, and recovery of schizophrenia.

Methods. After an accurate literature review we identified, collected and analyzed the crucial points in taking care schizophrenia patients, through which we defined the steps described in the model of management and the choice of the better treatment option.

Results. In the management model we propose, the choice of a second generation long acting antipsychotic, could allow from the earliest stages of illness better patient management, especially for young individuals with schizophrenia onset, a better recovery and significant reductions of relapse and health care costs. LAI formulations of antipsychotics are valuable, because they help patients to remain adherent to their medication through regular contact with healthcare professionals and to prevent covert non-adherence. Conclusion. The proposed schizophrenia model of management could allow better patient management and recovery, in which the treatment with LAI formulation is a safe and effective therapeutic option. This new therapeutic approach could change the cost structure of schizophrenia by decreasing costs with efficient economic resource allocation guaranteed from efficient diagnostic and therapeutic pathways.

KEY WORDS: Long-acting injectable antipsychotic drugs, LAIs, schizophrenia, recovery.

RIASSUNTO. La schizofrenia colpisce circa l’1% della popolazione e rappresenta un grave disturbo mentale con un notevole impatto anche sul funzionamento sociale, lavorativo e sulle attività della vita quotidiana. Le persone con schizofrenia hanno un tasso di mortalità superiore di 2-2.5 rispetto a quello della popolazione generale. La non aderenza ai farmaci antipsicotici è uno dei più importanti fattori di rischio per le ricadute e le ospedalizzazioni, sia nei pazienti con disturbo cronico sia al primo episodio, e conseguentemente contribuisce all’aumento dei costi sanitari. Gli antipsicotici atipici LAI possono migliorare l’aderenza al trattamento contribuendo a diminuire i tassi di ricaduta nei pazienti affetti da schizofrenia fin dall’esordio. Gli obiettivi primari nella gestione dei pazienti schizofrenici sono diretti, non solo alla riduzio-
ne dei sintomi nel breve termine, ma anche al mantenimento fisico e della funzionalità mentale, migliorando la qualità della vita e promuovendo il recupero del paziente. **Scope.** Proporre un modello integrato, basato sulle evidenze, che fornisca un algoritmo efficace per il recupero del paziente schizofrenico e indagare l'efficacia e la sicurezza degli antipsicotici LAI nel trattamento, nel mantenimento, nella prevenzione delle ricadute e nella recupero dei pazienti affetti da schizofrenia. **Conclusion.** Il modello di gestione della schizofrenia proposto potrebbe consentire un migliore recupero funzionale del paziente grazie alla scelta di iniziare il percorso terapeutico, fin dalle prime fasi del disturbo soprattutto se in giovane età e al primo episodio, con un farmaco atipico LAI. All'interno dei farmaci antipsicotici atipici la formulazione LAI rappresenta una scelta terapeutica sicura ed efficace nella gestione della schizofrenia fin dall'inizio della malattia. Questo nuovo approccio terapeutico potrebbe modificare la struttura dei costi della schizofrenia attraverso la loro riduzione e la ricollocazione delle risorse economiche, che verrà garantita da efficienti algoritmi diagnostico-terapeutici.

**PAROLE CHIAVE:** Antipsicotici long-acting iniettabili, LAI, schizofrenia, recupero.

**INTRODUCTION**

**Epidemiology of schizophrenia: impact on social and occupational functioning**

Schizophrenia is a severe, chronic psychiatric disorder affecting about 1% of the general population. It is associated with social and occupational functioning decline and characterized by positive symptoms, representing an excess or distortion of normal functions, negative symptoms, a reduction of normal functions, and cognitive symptoms. Schizophrenia-associated impairment tends to persist in many patients, thus impacting considerably their independent personal, social, and occupational lives and constituting a major source of disability. Cognitive impairment persistently reduces patients' ability to engage and maintain social and professional relationships. The main reason for unimproved functional outcome is that the treatment of those aspects that are most strongly related to it, i.e., cognitive dysfunction and negative symptoms, is currently unsuccessful. The best predictor of long-term functioning is poor first-three-post-diagnosis-years functioning. This is most prominent for unemployment, which is associated with duration of untreated psychosis (DUP) and prevalent negative symptoms. Early intervention in psychosis is a comprehensive and evidence-based approach aimed at detection and treatment of psychotic symptoms in their early stages, so to reduce the long-term adverse impact of psychosis and prevent relapses. It focuses on people with ultra-high risk for psychosis and those with initial psychotic symptoms. Even incompletely recovered patients may achieve a sufficiently satisfactory quality of life, provided they receive adequate support. The switch from an oral to a LAI antipsychotic formulation may benefit patients' quality of life, independently from initial response, thus paving the way to recovery. After the acute phase of treatment for a first psychotic episode, guidelines usually indicate that subsequent maintenance antipsychotic medication should continue for at least 1 year, but consensus is lacking regarding the total duration of treatment if the patient remains asymptomatic. A 5-year observational study of patients with first-episode psychosis indicated that stopping antipsychotic medication increased relapse rates 5-fold compared with continued treatment. Annual discontinuation rates for oral antipsychotics in first-episode schizophrenia were as high as 42% in the European First Episode Schizophrenia Trial (EUFEST). However, the risk of relapse needs to be weighed against the likelihood and severity of adverse effects caused by antipsychotic medication and the fact that about 20% of first-episode patients experience only a single episode of psychosis. The commonest cause of relapse and hospitalization in schizophrenia is poor adherence to oral medication.

**The issue of the lack of adherence to antipsychotic medication**

Non-adherence to medication is a major challenge for patients treated for schizophrenia; adherence problems are among the most frequent causes of relapse and rehospitalization. Despite the availability of effective antipsychotic treatment, adherence to antipsychotic treatment in the long run is low. Failure to comply with treatment is frequent in patients with schizophrenia. Between ½ to ¾ of patients do not comply with prescription. Some non-adherence is not due to willful refusal to take medication, but rather to patient forgetfulness, which can worsen by illness sequelae, such as disorganization or lack of insight. Cannabis use is a risk factor for non-adherence to medication and dropout from treatment. It should be recalled that schizophrenia and cannabis abuse frequently co-exist, but the causality of their relationship is far from clear. In addition, stigma can also play a role, as can adverse effects, cost and lack of perceived efficacy. Also, given that adherence may decrease in 25-80% of patients during treatment, non-adherence could substantially impact healthcare costs, an issue that still awaits accurate evaluation.

**Health Economics aspects**

Epidemiological data show mental illness to occur both in more- and in less-economically developed countries. Mental disorders are known to have major consequences for longevity, quality of life, and productivity for both patients and caregiver. Mental health disorders are inversely correlated with household income; this might indicate that mental illness negatively affects patients and their families productivity or, as some authors discussed, that a low socio-economic status increases the risk of mental health problems. Schizophrenia, the most chronic and disabling of major mental illnesses, is included among the first ten causes worldwide of long-term disability, with a wide ranging and long-lasting impact for people suffering from the illness, their families and society as a
whole\textsuperscript{29,31}. In the USA, its direct and indirect costs are estimated to amount to $62,700,000,000\textsuperscript{32}. Similarly, in Europe the total cost related to schizophrenia and other psychotic disorders was estimated at €93,900,000,000; 69% of this amount is due to indirect costs\textsuperscript{33}. Direct and indirect costs are high because schizophrenia is a chronic, lifelong condition with frequent relapses after onset, that occurs most frequently in young age\textsuperscript{34,35}. In terms of direct costs, their main drivers in Italy were estimated to be hospitalization and residential cost (71% of total direct cost per patient), followed by semi-residential services (13%), antipsychotic and other drugs (8%) and outpatient services (8\%).\textsuperscript{36,37} Despite the availability of effective antipsychotic drugs for the treatment of acute and chronic treatment of schizophrenia, more than 80% of patients relapse within 5 years, and suicide occurs in about 10% of cases\textsuperscript{38,39}. Increased relapse during the post-onset period (16% in the first year after diagnosis, 50% at 2 years and 70% at 5 years\textsuperscript{39,40}) means, in clinical and management terms, high hospitalization rates and, in economic terms, increased costs per treated individual. The most common cause of relapse in treated schizophrenia is poor adherence to oral medication\textsuperscript{41,42}. Non-adherence contributes to a substantial increase in the cost of schizophrenia\textsuperscript{34,35}. It is estimated that non-adherence accounts for approximately 40% of re-hospitalization costs for patients with schizophrenia in the 2 years following their discharge from an inpatient treatment facility\textsuperscript{43}. Consequently, efficacious interventions and a correct integrated management of schizophrenia patients are essential to increase adherence, prevent relapse, and restore social functioning, so to improve long-term prognosis and reduce costs.

Early treatment with Long Acting Injectable (LAI) antipsychotics represents an effective tool for improving adherence\textsuperscript{39,47} and should have a positive economic impact reducing the main important direct cost of the total economic burden of disease (hospitalization). For example, if an efficacious treatment with fair adherence reduces by only 5% re-hospitalization, the estimated mean cost reduction per patient in Italy would be €146 per year\textsuperscript{48} that multiplied for approximately 180,000 patients treated\textsuperscript{48,49} would correspond to a total direct cost reduction of €26.2 million per year. In Italy, it was estimated that the most important costs related to schizophrenia are indirect and correspond to 70% of the total economic burden per patient\textsuperscript{40}. Unemployment rate in schizophrenia is more than double than the one in the general population\textsuperscript{41,42} and 51% of these subjects obtain a disability pension in Italy\textsuperscript{43}. Indirect costs represents the key economic aspects in the management of schizophrenia patients. In fact, another important objective of pharmacological intervention in the stable phase of the disease is to prevent relapse and help keeping the patient stable enough to ensure a life as normal as possible; this would allow to continue the process of recovery\textsuperscript{44,45}. This would translate into reduced absenteeism and for patients with a job and increase the possibility to find a job for those who are unemployed.

Efficacy, adherence and good management are important not only from a clinical perspective, but also for their economic impact. A new treatment approach would change the cost structure of schizophrenia by decreasing costs (especially in terms of hospitalization and indirect costs) with efficient economic resource allocation guaranteed from efficient diagnostic and therapeutic pathways.

### METHODS

We searched the PubMed database using the following search strategy “(antipsychotic* OR neuroleptic*) AND (long-acting OR depot OR LAI OR once monthly OR prolonged release) AND (“randomized controlled trial” OR double-blind)”. Reference lists of identified articles were reviewed for additional relevant publications. Included were double-blind, randomized controlled trials (RCTs) of any LAI antipsychotic versus placebo or comparators.

### RESULTS

Our search strategy yielded 271 records on April 6, 2016; of these, 30 were reviews and excluded, but their reference lists were hand-searched for the identification of other potential studies to include. We finally included in our discussion of the efficacy and safety of LAIs 16 studies that are cited in that section. Table 1 roughly summarizes the evidence obtained from these studies. No other papers emerged after having searched the reference lists of retrieved literature. For a thorough review we recommend the paper by Graffino et al.\textsuperscript{53}.

#### Strategies to prevent relapses and to reduce hospitalization by improving medication adherence

Relapse prevention is critical, as psychopathology and social functioning can worsen with psychotic episodes in schizophrenia\textsuperscript{44}. Guidelines for the management of schizophrenia recommend improving medication adherence as a strategy to reduce hospitalization rates and costs in patients with schizophrenia\textsuperscript{45}. Long-acting injectable anti-psychotics provide an opportunity to improve medication adherence\textsuperscript{21,56,57} and reduce hospitalization rates compared to treatment with oral formulations. Relapse prevention and identifying treatments to assist patients may reduce the risk of cognitive and functional declines across the lifespan in patients with schizophrenia.

#### The issue of recovery in schizophrenia: is it feasible in studies of recently introduced antipsychotics?

It is widely accepted that some patients with schizophrenia may have a favorable prognosis. Symptoms can abate over time, and some patients with schizophrenia may attain fair outcomes in some clinical and functioning outcomes. While remission is usually well defined in terms of clinical symptoms\textsuperscript{58}, recovery involves also regaining the pre-onset functioning in the social interaction, physical activity/independence (autonomy), leisure and work domains. The benefits of an early intervention program for psychosis support higher recovery rates at substantially lower personal and economic costs\textsuperscript{59,60}. Extensive scientific literature supports the clinical benefits of antipsychotics for early intervention or treatment of first-episode psychosis\textsuperscript{61}. A recent systematic review and meta-analysis found that second-generation LAIs were superior to first-generation LAIs for relapse prevention\textsuperscript{63}. In addition, LAIs are effective for treating first-
Table 1. Summary of studies using atypical LAI antipsychotics

<table>
<thead>
<tr>
<th>Author(s), year</th>
<th>Study type</th>
<th>LAIs involved</th>
<th>Objective</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauriello et al., 2008&lt;sup&gt;70&lt;/sup&gt;</td>
<td>8-week double-blind comparison vs. placebo</td>
<td>Olanzapine pamoate</td>
<td>Assess efficacy and safety</td>
<td>Olanzapine LAI significantly reduced PANSS scores and improved CGI scores, but also induced more weight gain</td>
</tr>
<tr>
<td>Kane et al., 2010&lt;sup&gt;71&lt;/sup&gt;</td>
<td>24-week double-blind comparison between various olanzapine doses and oral olanzapine (open)</td>
<td>Olanzapine pamoate, various doses</td>
<td>Assess efficacy and safety</td>
<td>Olanzapine LAI was comparable with oral olanzapine for efficacy and side effects, but had more side effects related to injection reactions</td>
</tr>
<tr>
<td>Leucht et al., 2011&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Systematic review, meta-analysis</td>
<td>Multiple</td>
<td>Compare LAIs to oral formulations</td>
<td>LAIs significantly reduced relapse rates</td>
</tr>
<tr>
<td>Lambert et al., 2012&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Observational</td>
<td>Risperidone microspheres</td>
<td>Assess efficacy and safety</td>
<td>Improved functioning and reduced illness severity in Australian patients with schizophrenia or schizoaffective disorder after two years of risperidone LAI</td>
</tr>
<tr>
<td>Grimaldi-Bensouda et al., 2012&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Cohort study</td>
<td>Risperidone microspheres</td>
<td>Compare hospitalization rates between risperidone LAI use and no risperidone LAI use</td>
<td>Risperidone LAI use reduced hospitalization rates</td>
</tr>
<tr>
<td>Barnett et al., 2012&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Pharmaco-economic</td>
<td>Risperidone microspheres</td>
<td>Cost-effectiveness of introducing risperidone LAI in patient care</td>
<td>Introduction of risperidone LAI did not reduce hospital or total health care cost or improve outcomes</td>
</tr>
<tr>
<td>Witte et al., 2012&lt;sup&gt;72&lt;/sup&gt;</td>
<td>8-week randomized, double-blind comparison of various olanzapine LAI doses vs. placebo</td>
<td>Olanzapine pamoate</td>
<td>Quality of life assessment</td>
<td>All quality of life assessments improved and correlated inversely with PANSS score severity</td>
</tr>
<tr>
<td>Gilday and Nasrallah, 2012&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Review</td>
<td>Paliperidone palmitate</td>
<td>Efficacy and safety</td>
<td>Paliperidone LAI is safe and efficacious in both acute and maintenance settings</td>
</tr>
<tr>
<td>Kane et al., 2012&lt;sup&gt;79&lt;/sup&gt;</td>
<td>52-week maintenance; comparison between aripiprazole LAI and placebo</td>
<td>Aripiprazole monohydrate</td>
<td>Efficacy and safety; Kaplan-Meier survival curves to impending relapse</td>
<td>Aripiprazole LAI was effective and safe; prolonged significantly time to impending relapse, compared to placebo</td>
</tr>
<tr>
<td>Fleischhacker et al., 2014&lt;sup&gt;76&lt;/sup&gt;</td>
<td>38-week noninferiority comparison between various doses of aripiprazole LAI and oral aripiprazole</td>
<td>Aripiprazole monohydrate, two doses, one effective and one placebo (50 mg/month)</td>
<td>Efficacy; Kaplan-Meier survival curves to impending relapse</td>
<td>Aripiprazole LAI was noninferior to oral aripiprazole and prolonged significantly time to impending relapse, compared to 50 mg/month aripiprazole LAI</td>
</tr>
<tr>
<td>Ascher-Svanum et al., 2014&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Randomized open study of olanzapine LAI vs. oral olanzapine</td>
<td>Olanzapine pamoate</td>
<td>2-year follow-up of quality of life</td>
<td>Improvement or maintenance of quality of life; no difference between oral and LAI</td>
</tr>
<tr>
<td>Fu et al., 2014&lt;sup&gt;74&lt;/sup&gt;</td>
<td>13-week, double-blind, double-dummy study of paliperidone and risperidone LAIs and oral risperidone</td>
<td>Paliperidone palmitate and risperidone microspheres</td>
<td>Efficacy and safety</td>
<td>All three treatments had similar efficacy and side effect profiles</td>
</tr>
</tbody>
</table>

(Continued)
episodes of psychosis and for early initiation of treatment for schizophrenia. \(^{64}\)

We intend to propose a scientific evidence/guideline-based model that provides an algorithm for standard treatment, rehabilitation and recovery investigating the efficacy and safety of antipsychotics LAI in treatment, maintenance, relapse prevention and recovery in schizophrenia.

### Efficacy and safety of atypical LAI antipsychotics

Some investigations showed significant reductions in recurrence rates with the risperidone LAI formulation compared to the oral one \(^{60,67}\), while others failed to confirm this superiority \(^{68,69}\). The efficacy and tolerability of olanzapine LAI (olanzapine pamoate) was assessed in two randomized, double-blind, controlled trials, one compared to placebo \(^{70}\), the other to oral olanzapine \(^{71}\). In the placebo-controlled, randomized, double-blind trial \(^{72}\), olanzapine LAI improved the level of functioning in acutely ill patients with schizophrenia after 8-weeks. 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 \(^{73}\). 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 PANSS scores in schizophrenia patients with acute symptomatology and in inducing a delay in time to recurrence in stabilized patients \(^{74}\). 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 \(^{75}\). 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 \(^{76}\). Found aripiprazole LAI to be not inferior to its oral counterpart, while a further study, carried-out in Asian countries established that the two formulations were comparably well tolerated \(^{77}\). The clinical efficacy of aripiprazole LAI was established in two randomized, double-blind, controlled studies conducted in patients with schizophrenia in an acute \(^{78}\) and in a maintenance setting \(^{79}\). The efficacy and safety of aripiprazole LAI in the maintenance of stabilized schizophrenia were comparable to those of oral aripiprazole \(^{79}\). Aripiprazole LAI was also found to be efficacious and safe for patients experiencing an acute schizophrenia episode \(^{80}\). Superior improvements on clinician-rated health-related quality of life and a favorable tolerability profile suggest greater overall effectiveness for aripiprazole vs. PP \(^{80}\). Pharmacological (dynamic/kinetic) and dosage-related measures of LAI antipsychotic drugs are compared in Table 2.

### DISCUSSION

Schizophrenia is a chronic and disabling condition that requires long-term pharmacological and nonpharmacological management. This is multidimensional and can involve integrated psychosocial interventions, including family therapy and individual psychotherapy, social interventions like case management and psychosocial support, professional rehabilitation, establishing a network of social relations and motivation to engage in pleasurable activities. This may require a team working in harmony with the same aim, i.e., to benefit the patient and increase his/her quality of life.

Efficacy, adherence and good management are important not only from a clinical perspective, but also for their economic impact. A new treatment approach would change the cost structure of schizophrenia by decreasing costs (especially in terms of hospitalization and indirect costs) with efficient

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**Table 1.**

<table>
<thead>
<tr>
<th>Author(s), year</th>
<th>Study type</th>
<th>LAIs involved</th>
<th>Objective</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al., 2014 (^{64})</td>
<td>12-weeks, double-blind aripiprazole LAI vs. placebo</td>
<td>Aripiprazole monohydrate</td>
<td>Efficacy and safety</td>
<td>Reduced symptoms and LAIs involved episode psychosis and for early initiation of treatment for schizophrenia (^{64}).</td>
</tr>
<tr>
<td>Buckley et al., 2015 (^{80})</td>
<td>Comparison of LAIs with SGAs</td>
<td>Multiple SGA LAIs</td>
<td>Show any difference in outcome or treatment adherence</td>
<td>LAIs did not differ from SGAs on any outcome measure</td>
</tr>
<tr>
<td>Ishigooka et al., 2015 (^{77})</td>
<td>52-week noninferiority comparison between aripiprazole LAI and oral aripiprazole (1:1 randomized)</td>
<td>Aripiprazole monohydrate</td>
<td>Efficacy; Kaplan-Meier survival curves to impending relapse</td>
<td>Aripiprazole LAI was noninferior to oral aripiprazole for both efficacy and safety</td>
</tr>
<tr>
<td>Naber et al., 2015 (^{79})</td>
<td>Head-to-head comparison of two LAI antipsychotic drugs, open</td>
<td>Aripiprazole monohydrate and paliperidone palmitate</td>
<td>Quality of life; clinician-rated efficacy</td>
<td>Aripiprazole LAI better than paliperidone LAI on quality of life and clinician-rated improvement; less side effects with aripiprazole LAI</td>
</tr>
</tbody>
</table>

**Abbreviations:** LAIs = long-acting injectable antipsychotic drugs; PANSS = Positive and Negative Syndrome Scale for Schizophrenia; SGAs = second generation antipsychotic drugs.
economic resource allocation guaranteed from efficient diagnostic and therapeutic pathways.

Integrated care pathways (PDTA) and management models (Mo.Ma) are government tools that can enhance the different actors to define the best pathway for the schizophrenia patients optimizing clinical and the healthcare outcomes and resources.

In mental health and schizophrenia disease these aspects are particularly important due to the complexity of the diagnosis, treatment and case management. The complexity of the diagnosis is related to the presence of a variety of signs and symptoms, the treatment needs to be coordinated between the clinical and psychosocial aspects, and lastly the case management requires to structure processes in which different actors take part (various specialties, professions and hospital-territory).

The clinical pathway reported in Fig. 1 has been recently proposed to summarize current Guidelines and optimize resources and costs. Our proposed model focuses on the right part of the algorithm, marked as Mo.Ma intervention area and will be detailed further on.

<table>
<thead>
<tr>
<th>LAI</th>
<th>Formulation</th>
<th>Release mechanism</th>
<th>Dose</th>
<th>Available doses</th>
<th>T max</th>
<th>Interval Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone LAI</td>
<td>Aqueous suspension, risperidone encapsulated in biodegradable microspheres</td>
<td>Diffusion and erosion of microspheres</td>
<td>12.5-50 mg</td>
<td>12.5, 25, 37.5 or 50 mg</td>
<td>21 days</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>Micro-crystalline salt of olanzapine and pamoic acid suspended in aqueous solution</td>
<td>Dissociation in olanzapine and pamoic acid</td>
<td>150-405 mg</td>
<td>210, 300 or 405 mg</td>
<td>7 days</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>Nanocrystal molecules in aqueous suspension</td>
<td>Poorly soluble in water: hydrolysis by esterases, dissociation in paliperidone and palmitic acid</td>
<td>39-234 mg</td>
<td>39, 78, 117, 156 or 234 mg</td>
<td>13 days</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Aripiprazole Monohydrate</td>
<td>Aqueous suspension; lyophilized powder of aripiprazole monohydrate crystals</td>
<td>Poorly soluble in water: crystals particles dissociate, with slow and prolonged dissolution and absorption</td>
<td>300 or 400 mg</td>
<td>300 or 400 mg</td>
<td>6.5-7.1 days</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Mo.Ma evidence-based model algorithm for standard treatment, rehabilitation and recovery

People with schizophrenia face a number of challenges in managing their lives and disease, including lack of insight into their illness and cognitive deficits that interfere with treatment adherence – both psychosocial and pharmacologic. These challenges increase the risk of relapse, with each relapse resulting in significant personal and economic costs.
### Table 3. Key performance indicators for validating organization quality and process

<table>
<thead>
<tr>
<th>KPI</th>
<th>How to measure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early intervention</strong></td>
<td></td>
</tr>
<tr>
<td>• Patient age at first care plan after the first episode</td>
<td>Average age of first contact with the Mental Health Department (MHD)</td>
</tr>
<tr>
<td>• Early multi-professional evaluation for clinical and psychosocial problems</td>
<td>Number of MHD contact onset patients receiving multi-professional evaluation/Number of MHD contact onset patients</td>
</tr>
<tr>
<td>• Intensity of territorial assistance for early patient</td>
<td>Average contacts per patient per month</td>
</tr>
<tr>
<td>• Intensity of territorial assistance for families of early patient</td>
<td>Average MHD interventions targeted for family per month</td>
</tr>
<tr>
<td>• Rehabilitative interventions and support at work</td>
<td>Patients treated in the MHD with at least four operations on basic skills, interpersonal and social/Patients treated in the MHD</td>
</tr>
<tr>
<td><strong>Management of the acute phase</strong></td>
<td></td>
</tr>
<tr>
<td>• Acute Psychiatric Care Unit (APCU) re-admissions within 30 days of discharge</td>
<td>N° of APCU re-admissions within 30 days of discharge</td>
</tr>
</tbody>
</table>
| • Ongoing treatment with antipsychotic drugs in the following period of acute episode | Number of patients who receive an antipsychotic drug in the acute phase and in which there is no interruption of drug therapy  
  a) for at least 90 days  
  b) for at least 180 days  
  c) or at least 365 days divided by the number of patients at the beginning of antipsychotic drug treatment |
| • Dyslipidemia control in patients of antipsychotic drugs treatment initiation | Number of patients at the beginning of antipsychotic treatment, with at least two controls of blood glucose, cholesterol, and triglyceride levels in the 12 weeks following initiation of therapy / Number of patients treated with antipsychotic |
| • Patients who receive a psychiatric examination in MHD within 14 days of discharge in APCU | Number of patients who receive a psychiatric examination in MHD within 14 days of discharge in APCU/Number of patients discharged from APCU                                                                 |
| • Territorial treatment continuity after discharge from the APCU    | Number of patients discharged from APCU with at least one contact with the MHD per month in the six months following discharge/Number of patients discharged from APCU                                           |
| **Continuous treatments and long-term treatment**                  |                                                                                                                                                                                                              |
| • Intensity of patient territorial assistance                        | Number of patients with more than five territorial interventions in MHD/Number of patients in contact with MHD                                                                                             |
| • Treatment maintenance with LAI antipsychotic drug                 | Number of patients who continued the LAI antipsychotic drugs therapy with  
  a) for at least 90 days  
  b) for at least 180 days  
  c) for 365 days divided from the first prescription in the year divided by Number of patients with antipsychotic drug treatment |
| • Periodic monitoring of blood hyperlipidemia in patients on treatment with antipsychotic drugs | Patients receiving continued treatment with antipsychotic drugs with constant monitoring of safety / Patients receiving continued treatment with antipsychotic drugs |
| • Unagreed treatment conclusion                                     | Number of patients who leave treatment with antipsychotic/ Number of patients with at least one contact with MHD                                                                                             |
| • Housing and Employment support                                    | Continuous and long-term treatments/ Number of patients receiving in MHD setting at least five socialization, expressive, motor and practical interventions |
| **Cognitive Remediation Therapy**                                   | Number of patients that improve neurocognitive abilities and executive functioning which leads to improved social functioning                                                                             |
| • Housing support and employment support                            | Number of patients, no employees, entered into business activities or character supported by MHD / Number of patients not employed with at least one contact with the MHD in the year |

*Mo. Ma for the patient with schizophrenia*

*Riv Psichiatr 2016; 51(2): 47-59*
A wide variety of antipsychotic agents is available, with the drugs having broadly similar efficacies in terms of producing reductions in symptoms and in the risk of relapse. Therefore, antipsychotic choice is commonly guided by tolerability issues and individual patient factors, including past medical history, past response to drugs, past experience of adverse events, concurrent medical conditions or comorbidities, and individual patient preference. However, their success depends also on treatment adherence. The use of atypical LAI formulations of antipsychotic drugs is suitable to overcome medication non-adherence. Relapse prevention is considered a major treatment aim in schizophrenia. Relapse itself represents an important predictor of subsequent relapse, while multiple relapses have been associated with poorer long-term outcome. Relapse rates decrease by over 50% after maintenance antipsychotic treatment. Three RCTs support relapse prevention by LAI aripiprazole in schizophrenia, two versus oral and one versus placebo. The latter has also shown efficacy in the acute treatment of schizophrenia. Psychiatric hospitalization rates were significantly lower when patients were treated with aripiprazole LAI, compared with oral anti-psychotic therapy. In a head-to-head comparison study, treatment with aripiprazole LAI showed superior improvements to paliperidone palmitate (PP) on health-related quality of life, improvements in symptoms and functioning, and a favorable tolerability profile, as shown by fewer important AEs and lower all-cause discontinuation rates; taken together, these data suggest greater overall effectiveness for aripiprazole LAI vs. paliperidone palmitate. In predefined analyses, significantly greater improvements with aripiprazole LAI vs. PP were consistently shown in patients ≤35 years, indicating that younger patients may be particularly responsive to aripiprazole LAI. Aripiprazole LAI may show a favorable metabolic profile and was generally well tolerated. Of 12 analyzable drugs, aripiprazole ranked fourth for limiting weight gain and fifth for limiting EPS and sedation, best for limiting prolactin increase and prolactin levels, and second best drug for limiting QTc prolongation. The better tolerability profile of aripiprazole regarding metabolic alterations and prolactin increase suggests that aripiprazole LAI may target those patients for which these issues are a particular concern. The safety profile of aripiprazole LAI was comparable to that of oral aripiprazole and consistent with the one reported for oral aripiprazole in previous registration maintenance studies. Studies confirm that aripiprazole LAI choice is reasonable for younger, first episode patients, who showed more benefit than multi episode patients with schizophrenia. Patients with obesity are also likely to benefit more from aripiprazole LAI. For patients with a chronic disorder that had previously responded to other antipsychotics and who have florid positive symptoms, other LAIs may be preferable.
We are tempted to conclude that the sooner you intervene, the better (Figure 3). So we propose a model that integrates all current notions about schizophrenia, its insidious onset and prodrome, the worsening course in the absence of timely treatment, and the negative impact of hospitalizations and nonadherence, we call this Mo.Ma (Model of Management). The model in current psychiatric practice may be implemented according to the algorithm found in Figure 2. Considering both clinical and pharmacoeconomic aspects\textsuperscript{82,87} we here propose this updated treatment algorithm, by which the choice of a LAI antipsychotic may occur soon after diagnosis of schizophrenia, especially for patients with poor awareness of illness and poor insight; this algorithm will allow us to deal with patients from the very first presentation of psychosis to full-blown schizophrenia. LAIs are traditionally reserved for patients at later stages of psychosis; however their use is currently advocated for early episodes of schizophrenia, so to further improve outcomes like recurrence, hospitalization rate, and consequences of lack or less than optimal treatment\textsuperscript{88,89}. The results of a similar study will tell us whether there is a need for change in our current practices. Outcomes should include efficacy and safety matters, but also patient-focused measures such as quality of life, functioning, satisfaction with treatment and attitudes towards the use of drugs.

A set of indicators (KPI) can be selected to validate organization quality and process, so to monitor the correct adoption of clinical pathways (Figure 4)\textsuperscript{90}.

**PERSPECTIVES**

Applying the model we propose is desirable to obtain:
- Reducing hospitalizations by increasing adherence
- Reduction medication dosages
- Improve compliance to other drugs
- Increase subjective well-being
- Improve social functioning (recovery)
- Reducing health care costs
- Reducing Social costs
LIMITATIONS
Since this was a selective, nonsystematic review, we might have not included in our discussion some significant papers. Furthermore, since we endorse a strong, ground-breaking viewpoint, we might not concur with the bulk of literature; however, we identified some papers that are in line with this viewpoint, so this paper may be added to theirs and constitute the core of a new approach to the early treatment of schizophrenia.

CONCLUSIONS
Schizophrenia affects approximately 1% of the population, and is a severe mental illness with a chronic impact on social and occupational functioning and daily activities. Schizophrenia, is the most chronic and disabling of mental illnesses and is included among the first ten causes worldwide of long-term disability, with a wide ranging and long-lasting impact for people suffering from the illness, their families and society as a whole.29-31

The primary goals in the management of schizophrenia are directed not only at symptom reduction in the short and long term, but also at maintaining physical and mental functioning, improving quality of life, and promoting patient recovery.37,38

Efficacious interventions and a correct integrated management of schizophrenia patients are essential to increase adherence, prevent relapse, and restore social functioning, so to improve long-term prognosis and reduce costs. Early treatment with LAI antipsychotics represents an effective tool for improving adherence39,47 and should have a positive economic impact reducing the main important direct cost of the total economic burden of disease (hospitalization).

Figure 3. Treatment algorithm according to Mo.Ma (Model of Management of schizophrenia patient with LAI atypical antipsychotics) principles.

*Aripiprazole choice is reasonable for younger, first episode patients, who showed more benefit than multiepisode episode patients with schizophrenia.80 Patients with obesity are also likely to benefit more from aripiprazole LAI86. For patients with a chronic disorder that had previously responded to other antipsychotics and who have florid positive symptoms, other LAIs may be preferable.

**Assessment: psychopathological picture, metabolic profile, side effects, age, network, patient preference, stigma, attitude toward therapeutic drugs, compliance/adherence, insight: into having a disorder, into the need for intervention, into the need for taking this particular medication.
The proposed schizophrenia model of management, already in place in the Mental department of the board members, allowed better patient management and recovery, where aripiprazole LAI formulation represents a new safe and effective long-acting treatment option for the management of schizophrenia. The efficacy of aripiprazole LAI as maintenance treatment for schizophrenia has been demonstrated in three RCTs. Aripiprazole LAI was superior to placebo, and non-inferior to oral aripiprazole, in delaying the time to (impending) relapse, as well as in reducing relapse rates. The actual benefit of aripiprazole LAI over oral medications in clinical practice may even be greater than the one shown in RCTs, since patient willingness to participate and a protected research environment can increase treatment adherence. Since patients seen in everyday practice are likely to show poor adherence, the increased compliance fostered by LAI formulations will probably increase the gap between LAI and oral aripiprazole.

In the model of management we propose, the cost structure of schizophrenia could also change by decreasing costs with efficient economic allocation governed from efficient diagnostic and therapeutic pathways. The cost-saving effect of aripiprazole LAI compared to other antipsychotics has to be investigated in a real life setting; however, data emerging from recent publications and congress abstracts suggest that the use of aripiprazole LAI will lower health care costs more than other antipsychotics and other LAI at least compared to paliperidone palmitate.

Acknowledgments: The authors wish to thank Ms Mimma Ariano, Ms Ales Cascarino, Ms Teresa Prioresci, and Ms Susanna Rospo, Librarians of the Sant’Andrea Hospital, School of Medicine and Psychology, Sapienza University, Rome, for rendering precious bibliographic material accessible, as well as their Secretary Lucilla Martinelli for her assistance during the writing of the manuscript.

Financial & Competing Interests Disclosure: In the past three years, Paolo Girardi has received research support from Lilly, Janssen, Angelini, and Springer Healthcare, and has participated in Advisory Boards for Lilly, Otsuka, Pfizer, Schering, and Springer Healthcare and received honoraria from Lilly and Springer Healthcare. All other authors of this paper have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

REFERENCES
25. Hughes DA, Bagust A, Haycox A, Walley T. Accounting for non-
compliance in pharmacoeconomic evaluations. Pharmacoeco-
severity, and unmet need for treatment of mental disorders in the
World Health Organization World Mental Health Surveys. JA-
27. Golberstein E, Busch SH. Mental Health, Determinants of. In:
Culyer A (ed). Encyclopedia of Health Economics. United
28. Yeo RA, Martinez D, Pommy J, et al. The impact of parent socio-
economic status on executive functioning and cortical morphol-
gy in individuals with schizophrenia and healthy controls. Psy-
29. Cortesi PA, Mencacci C, Luigi F, et al. Compliance, persistence,
costs and quality of life in young patients treated with antipsy-
chotic drugs: results from the COMETA study. BMC Psychiatry
30. Rössler W, Salize HJ, van Os J, Riecher-Rossler A. Size of burden
of schizophrenia and psychotic disorders. Eur Neuropsychophar-
31. Knapp M, Mangalore R, Simon J. The global costs of schizophre-
the brain in Europe 2010. Eur Neuropsychopharmacol 2011; 21:
718-9.
34. Hasan A, Falkai P, Wobrock T, et al. World Federation of Soci-
eties of Biological Psychiatry (WFSBP) Guidelines for Biological
Treatment of Schizophrenia. Part 3: Update 2015 Manage-
ment of special circumstances: Depression, Suicidality, substance
use disorders and pregnancy and lactation. World J Biol Psychi-
35. Hasan A, Falkai P, Wobrock T, et al. World Federation of Soci-
eties of Biological Psychiatry (WFSBP) guidelines for biological
treatment of schizophrenia, part 2: update 2012 on the long-term
treatment of schizophrenia and management of antipsychotic-in-
duced side effects. World J Biol Psychiatry 2013; 14: 2-44.
36. Degli Esposti L, Sangiorgi D, Mencacci C, et al. Pharmaco-utili-
sation and related costs of drugs used to treat schizophrenia and
bipolar disorder in Italy: the IBIS study. BMC Psychiatry 2014;
14: 282.
Giovanna M. I costi della schizofrenia in Italia: i risultati di un’analisi condotta nell’ASL della Provincia di Pavia, Giornale
39. Patel MX, Taylor M, David AS. Antipsychotic long-acting injec-
following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999; 56: 241-7.
41. 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 Adher-
42. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, et al. Medication
nonadherence and treatment outcome in patients with schizo-
phrenia or schizoaffective disorder with suboptimal prior re-
43. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data
to assess the relationship of medication adherence with hospital-
44. Thieda P, Beard S, Richter A, Kane J. An economic review of com-
pliance with medication therapy in the treatment of schizo-
45. Knapp M, King D, Pugner K, Lapuerta P. Non-adherence to an-
tipsychotic medication regimens: associations with resource use
46. Weiden PJ, Olsson M. Cost of relapse in schizophrenia. Schizophr
47. Kane JM. Treatment strategies to prevent relapse and encourage
study: point and one-year prevalences of psychiatric disorders in
an Italian community sample using clinical interviewers. Psycho-
ther Psychosom 2004; 73: 226-34.
Centri di Salute Mentale, dei Centri Diurni e delle Strutture Re-
sidenziali psichiatriche del Lazio. ASP Regione Lazio, 2014.
costs of schizophrenia in community psychiatric services in Italy.
The GISIES study. Interdisciplinary Study Group on the Eco-
51. Garattini L, Barbui C, Clemente R, et al. Direct costs of schizo-
phrenia and related disorders in Italian community mental health
services: a multicenter, prospective 1-year follow-up study.
in Italian community psychiatric services. Pharmacoeconomic-
s 2001; 19: 1217-25.
jective antipsychotics in the treatment of schizophrenia: a re-
54. Kane JM, Kishimoto T, Correll CU. Assessing the comparative
effectiveness of long-acting injectable vs. oral antipsychotic med-
ications in the prevention of relapse provides a case study in
cumparative effectiveness research in psychiatry. J Clin Epide-
55. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM.
Maintenance treatment with antipsychotic drugs for schizophren-
56. Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for
a change in focus. JAMA Psychiatry 2013; 70: 1107-12.
57. Hasan A, Falkai P, Wobrock T, et al. World Federation of Soci-
eties of Biological Psychiatry (WFSBP) guidelines for biological
treatment of schizophrenia, part 2: update 2012 on the long-term
treatment of schizophrenia and management of antipsychotic-in-
duced side effects. World J Biol Psychiatry 2013; 14: 2-44.
current intervention in psychosis cost-effective over the long term?
60. Sertetti A, Mandelli L, Bajo E, et al. The socio-economical bur-
den of schizophrenia: a simulation of cost-offset of early inter-
vention program in Italy. Eur Psychiatry 2009; 24: 11-6.
61. Cocchi A, Mapelli V, Meneghelli A, Prei A. Cost-effectiveness of
treating first-episode psychosis: five-year follow-up results from an
Italian early intervention programme. Early Interv Psychiatry
63. Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CU.
Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-
64. Stevens GL, Dawson G, Zummo J. Clinical benefits and impact
of early use of long-acting injectable antipsychotics for schizo-
65. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S.
Oral versus depot antipsychotic drugs for schizophrenia— a criti-
cal systematic review and meta-analysis of randomised long-
Mo.Ma for the patient with schizophrenia