Integrated treatment of schizophrenia

Il trattamento integrato della schizofrenia

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Summary

Psychosocial therapies play an important role in the treatment of schizophrenia. These therapies are aimed at improving the functioning of the patient in the community, which in turn can lead to clinical improvement, such as reduction in the number of relapses or hospitalizations. Substantial evidence supports the use of many psychosocial therapies in schizophrenia, including cognitive behavioral therapy, assertive community treatment, cognitive remediation and functional skills training.

The customization of pharmacological therapy in schizophrenia, besides the experience of the clinician and individual preferences of the patient, should be based on three sets of objective data: 1) clinical predictors of response to therapy; 2) predictable side effects of therapy; 3) pharmacogenetic and pharmacogenomic data.

It has been made a considerable effort to improve adherence to antipsychotic treatment through the development of drugs with better tolerability, in formulations that enable long-term administration of the drug, including injectable long-acting (depot) antipsychotics. In recent years the development of these formulations of atypical antipsychotics and the promising results obtained in clinical trials are changing the attitude toward these drugs, traditionally reserved for patients with repeated non-adherence to treatment.

Key words

Pharmacological treatment • Rehabilitative and psychosocial psychotherapy

Pharmacological treatment, rehabilitative and psychosocial psychotherapy

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Introduction

Schizophrenia is caused by complex interactions between biological, genetic and environmental factors; as a consequence, patients affected by the disorder should receive integrated treatments that include drugs and psychosocial therapy, care of physical health and treatment of comorbidities. In general, drugs are administered in the initial phases of schizophrenia when symptoms lead to an individual to consult psychiatric services. Psychosocial therapies are frequently not initiated until the appearance of uncontrolled symptoms. This model could change, however, once early diagnosis and timely therapeutic intervention become more common and non-pharmacological treatments can be initiated at an earlier stage. An integrated and multifaceted approach involving drugs, psychosocial interventions and attention to environmental circumstances can improve the outcomes of schizophrenia[1]. Thus, the psychiatrist should be part of a multidisciplinary team, composed of mental health professionals and other medical specialists, as well as providers of social services and other relevant entities (e.g. authorities who organise housing and employment).

Treatment with antipsychotics

Antipsychotics are a fundamental element of treatment of schizophrenia [2]. Undoubtedly, they are very effective in reducing the positive symptoms of schizophrenia. However, at present, the available antipsychotics have significant limitations (Table I); in particular, negative symptoms and cognitive alterations are not treated adequately, and many patients continue to present persistent psychotic symptoms. In addition, the lack of insight that accompanies schizophrenia is a partially unsolved problem. Clinical studies have consistently demonstrated that antipsychotics reduce positive symptoms such as delirium and hallucinations [3 4]. In this regard, large studies have demonstrated that second-generation agents are at least as efficacious (if not more so according to some studies) than first-generation antipsychotics, and that they are generally

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better tolerated with a reduced propensity to induce adverse effects such as motor symptoms; accordingly, they are associated with better compliance [3 5]. The safety profiles of older and newer agents, however, are significantly different [5].

Antipsychotics have been shown to be effective in the treatment of acute psychotic episodes [6]. About 85% of previously untreated patients show improvement of symptoms and 60% remain in remission at 3 years[7]. Effective, timely treatment of psychoses in the initial phases can avoid a long duration of untreated psychosis, which is associated with poorer clinical and social outcomes [8 9]. Maintenance therapy reduces the risk of relapse in patients with schizophrenia. An analysis of 65 clinical studies involving more than 6000 patients with schizophrenia demonstrated that maintenance treatment reduces the incidence of relapse and hospitalisation by around 60% (Fig. 1) [10]. It is important to highlight that this analysis also showed that the number needed to treat (NNT) of pharmacological therapy is related to adequate psychosocial therapy: under these conditions, in fact, treatment of only 3 patients for 7-12 months can prevent another relapse and treatment of 5 patients can prevent another hospitalisation [10].

In some patients, relapse can delay or halt progression of disease [11]. Moreover, by preventing relapse and improving insight, antipsychotics can assure a period of stability and facilitate the introduction of additional treatments such as psychosocial therapy [12]. There is evidence that the greater the improvement of symptoms after the start of pharmacotherapy, the greater the probability of a good response to psychosocial therapy [12].

Behavioural symptoms such as hostility and aggression are common in schizophrenia, and there is evidence that these symptoms are susceptible to antipsychotic drugs [13]. In general, good adherence to therapy seems to be associated with low levels of aggression, and persons with schizophrenia who adhere to therapy and are clinically stable do not seem to be more violent than the general population [13]. Suicidal behaviour is present in about 50% of affected individuals and about 5-10% of persons with schizophrenia commit suicide. Clinical studies with some antipsychotics have shown that they are associated with a reduction in suicidal behaviour [14].

Limitations of antipsychotics

The negative symptoms of schizophrenia, such as apathy, anhedonia and decreased emotional expression, can be present at the onset of disease and may represent the predominating symptoms; in fact, in around 70% of cases these symptoms develop before positive symptoms [3]. In reality, there is evidence to support the existence of a form of disease (deficit schizophrenia) that identifies a subgroup of patients characterised by the presence of primary and persistent negative symptoms [15]. The available antipsychotics have a limited effect on negative symptoms and are ineffective on primary and persistent symptoms [3]. This limitation is an important problem since negative symptoms are associated with compromised employment and social functioning, and are thus a significant obstacle in maintaining an independent life [16].

Almost all patients with schizophrenia have deficits in cognitive function, which affects domains such as verbal fluency, memory, attention, velocity of elaboration, ability to assign priorities and make decisions [3]. Such deficits present early in the course of disease, in general years before the appearance of overt psychosis, and are strong predictors of compromised social functioning and unfavourable outcomes. Unfortunately, currently-available antipsychotics have limited impact on the cognitive symptoms of schizophrenia: any improvements observed appear to be correlated with a reduction in other symptoms rather than to direct effects on cognitive ability [17 18].

Antipsychotics are associated with several collateral effects that can be severe and limit adherence to therapy, thus decreasing the possibility of recovery (Table II) [3]. Individual antipsychotics differ in their safety profile, but some adverse effects, such as motor symptoms and metabolic hormonal disorders, are common to all these

TABLE I.
Potential benefits and limitations of current antipsychotic medication (from Fleischhacker et al., 2014, modified) [1]. *Possibili benefici e limiti degli attuali farmaci antipsicotici (da Fleischhacker et al., 2014, mod.) [1].*

Benefits	Limitations
Reduction of positive symptoms	Limited efficacy against negative symptoms
Treatment of acute episodes	Inadequate treatment of cognitive impairment
Reduced risk of relapse	Troubling side effects or tolerability issues
Provision of stability and a platform for other treatments	Low acceptability to some patients • Poor adherence • Negative perceptions
Reduction of aggression and hostility	
Reduced suicidal behaviour	

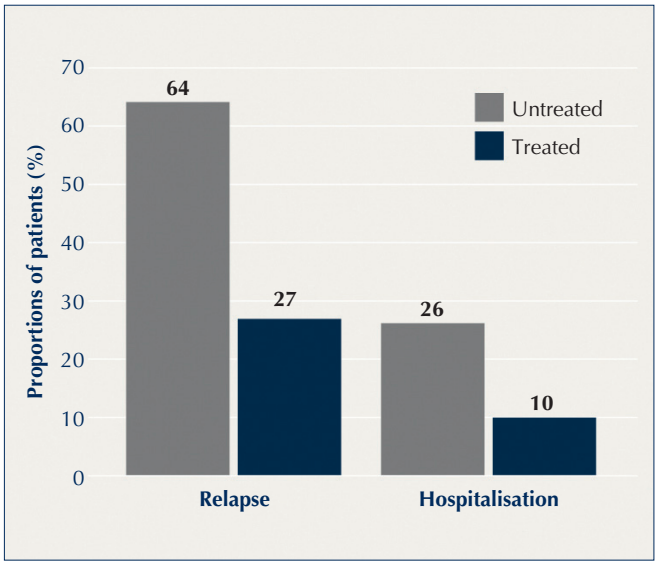


FIGURE 1.
Long-term treatment of schizophrenia (maintenance) significantly reduces the number of relapses (7-12 months) and the number of hospitalizations in patients with schizophrenia, compared with placebo (data from a combined analysis of 65 clinical trials) (from Leucht et al., 2012, modified) [10]. *La terapia antipsicotica a lungo termine (di mantenimento) riduce in maniera significativa il numero di recidive (a 7-12 mesi) e il numero di ricoveri nei pazienti con schizofrenia, rispetto al placebo (dati derivanti da un'analisi combinata di 65 trial clinici) (da Leucht et al., 2012, mod.)* [10].

drugs. In general, typical antipsychotics tend to have more motor effects, while several atypical antipsychotics can cause metabolic adverse effects; all first-generation antipsychotics and most second-generation antipsychotics can cause hyperprolactinaemia, with the exception of aripiprazole, clozapine and quetiapine. Motor symptoms influence movement and muscular tone and can lead to Parkinsonism (tremor and muscular rigidity) and muscle spasms (dystonia) as well as subjective and objective restlessness (akathisia). These symptoms are known collectively as acute extrapyramidal symptoms (EPS). Another EPS, which usually appears late in the course of treatment together with aging of the patient, is tardive dyskinesia, a symptom characterised by involuntary and repetitive movements of the limbs, trunk and more characteristically of the libs, tongue and jaw. Metabolic disorders include weight gain and changes in blood glucose, cholesterol and other lipids. These disorders can negatively influence the physical health of patients with schizophrenia. Other hormonal disorders, and in particular an increase in the levels of prolactin, can give rise to secondary problems such as sexual dysfunction.

Adherence to antipsychotic therapy is often low in persons with schizophrenia [5]: about 50% of patients are non-adherent to oral therapy [19], even if this percentage is higher in long-term studies. The main reasons for low adherence include:

- lack of information about the disease and its treatment;
- lack of improvement of psychotic symptoms;
- adverse effects (that resolve if the patient interrupts therapy);
- lack of knowledge about the need for treatment;
- economic difficulties (especially in countries in economic difficulty);
- complexity of treatment schemes;
- fear of discrimination;
- poor physician-patient relationship;
- lack of support by caregivers.

The lack of adherence to therapy is commonly associated with relapse, which often leads to hospitalisation; however, the association between adherence and hospitalisation can also depend on the fact that lack of adherence may represent a symptom of progression of disease [20]. The frequency of hospitalisation (often used as an indicator of severe relapse) is up to 400% higher in non-adherent patients than those who are adherent to therapy [21]. Moreover, non-adherent individuals have a greater probability of low overall function in the long term and to be

TABLE II.
Potential side effects of current antipsychotic medication (from Fleischhacker et al., 2014, modified) [1]. *Possibili effetti collaterali degli attuali farmaci antipsicotici (da Fleischhacker et al., 2014, mod.)* [1].

• Extrapyramidal symptoms – Slow, stiff movement and tremor (parkinsonism) – Abnormal muscle tone/muscle spasms (dystonia) – Involuntary movements (tardive dyskinesia) – Subjective experience of restlessness and restless movements (akathisia)
• Weight gain
• Metabolic disturbances – Changes in blood glucose levels – Increases in cholesterol and triglycerides
• Sedation
• A feeling of being ill-at-ease (dysphoria)
• Hormonal changes
• Sexual dysfunction
• Changes in the electrical activity of the heart (rare)
• Neuroleptic malignant syndrome (a rare but life-threatening neurological disorder)
• Agranulocytosis (very low levels of white blood cells, also life-threatening but rare)

more violent and attempt suicide more frequently than patients who are adherent to therapy.

Adherence to antipsychotic therapy can be improved through better understanding of the individual motivations for the lack of adherence and involving the patient in treatment decisions. One possible obstacle to adherence is the common practice of using polytherapy to control symptoms, which renders it difficult for patients to remember when to take various medications. Polytherapy, whenever possible, should be avoided. In addition, the use of long-lasting injectable formulations (depot) of antipsychotics may be associated with better adherence [22].

An individualised approach to therapy should be encouraged, which should also include patient preferences [1]. Drugs with tolerability and safety profiles that are adequate to the needs of the patient should be chosen (e.g., avoiding drugs that lead to weight gain if this represents a problem). Weight gain can be a significant problem in younger patients. About 25% of patients with a new diagnosis of schizophrenia are less than 18 years of age and can be particularly sensitive to side effects such as weight gain or menstrual cycle disorders associated with drug-induced hormonal changes. Careful and frequent monitoring of adverse effects should be carried out in all patients undergoing long-term therapy.

Antipsychotics are effective in reducing psychotic symptoms, but many patients show only partial response to treatment [3]. Even when patients obtain remission, few are completely free of symptoms. Moreover, up to one-third of patients affected by schizophrenia show a poor response to antipsychotics, and some develop resistance to treatment. Treatment resistance generally occurs with disease progression [23], but in about 10% of cases it is already evident after the first episode [19].

Psychosocial therapies

In addition to pharmacological therapy, psychosocial therapy also plays an important role in treatment of schizophrenia [1 24 25]. These therapies have the aim of improving the functioning of the patient in the community, which can also lead to clinical improvement, such as a reduction in the number of relapses or hospitalisations. The use of psychosocial therapies is supported by substantial evidence; these include cognitive behavioural therapy (CBT) for psychosis, in addition to cognitive remediation and functional skills training; other approaches also appear promising (Tables III, IV) [1 24 25]. Schizophrenia associated disabilities often involve several areas, and psychosocial therapies can be combined to confront a range of problems. For example, social skills training can be used as part of an integrated program that includes family psychoeducation, cognitive remediation and CBT.

Assertive community treatment

Assertive community treatment (ACT) is a model that was developed to improve the rate of relapse and hospitalisation following the transition from institutionalisation to territorial care in the USA starting in the 1980s [25]. This approach, aimed at a subgroup of patients who are strong users of services, involves a multidisciplinary team working in the community to provide a range of services comprising management of pharmacological therapy, practical support (e.g. housing) and rehabilitation. ACT is characterised by a high frequency of outpatient visits and a low number of patients (usually about 10) who are followed by each member of the team: these two characteristics obviously require considerable resources, even if it has been demonstrated that, for treatment of schizophrenia as for other psychological therapies, an increase in the time spent with the patient can contribute to achieving positive results [24 25]. Studies in several countries have demonstrated that ACT is associated with a lower incidence of homelessness and hospitalisation compared with standard care in patients who are frequent users of services [24-26]. One analysis revealed that, on average, there is a reduction in homelessness by 37% in patients undergoing ACT compared with standard care [26]. Even if ACT can help individuals with schizophrenia to live a stable life in the community, several studies have suggested that it has a relatively limited impact on other outcomes such as social functioning or employment. Recently, the OPUS study [27], carried out on patients with a first episode of schizophrenia, showed that ACT was superior to standard therapy in reducing both positive and negative symptoms and substance abuse, increasing overall patient satisfaction and adherence to therapy and in reducing the number of hospitalisations.

Cognitive-behavioural therapy

Psychotic symptoms can persist despite antipsychotic medications, which constitute a large obstacle to social recovery. CBT (a *talking* therapy that helps people manage their disease by changing their way of thinking and listening) directed towards psychotic symptoms aims to reduce their severity and consequent distress [24 25]. Many studies have demonstrated that this approach improves social functioning, reduces positive and negative symptoms and decreases mood disorders *vs* a control group. Other studies, however, have not demonstrated such improvements, and the effects of CBT on outcomes such as hospitalisation, depression, suicidal tendency and insight have not been clearly established [28]. A recent systematic review concluded that CBT does not offer a clear advantage over other psychosocial therapies such as family therapy and psychoeducation [29]. Evidence supporting the use of CBT is largely shown by studies in which partici-

TABLE III.
Many psychosocial interventions have been shown to improve outcomes in schizophrenia (evidence-based approaches), and others are being developed and evaluated (promising approaches) (from Fleischhacker et al., 2014, modified) [1]. *Molti interventi psicosociali hanno dimostrato di migliorare l'outcome nella schizofrenia (approcci evidence-based) e altri sono in fase di sviluppo e di valutazione (approcci promettenti) (da Fleischhacker et al., 2014, mod.)* [1].

Evidence-based approaches	Promising approaches
• Assertive community treatment	• Cognitive adaptive therapy
• Cognitive behavioural therapy for psychosis	• Healthy lifestyle intervention
• Cognitive remediation	• Interventions targeting older individuals
• Family therapy/psychoeducation	• Prodromal stage intervention
• Peer support and self-help strategies	• Social cognition training
• Social skills training	• Social rehabilitation (Clubhouse Model)
• Supported employment	
• Integrated treatment for coexisting substance abuse disorder	

TABLE IV.
Potential benefits of psychosocial therapies (from Fleischhacker et al., 2014, modified) [1]. *Possibili benefici delle terapie psicosociali (da Fleischhacker et al., 2014, mod.)* [1].

Intervention	Potential benefits
• Assertive community treatment	• Reduction in rates of homelessness and length of hospital stays
• Cognitive behavioural therapy for psychosis	• Decreases in both positive and negative symptoms and mood disturbances, and improved social functioning
• First episode intervention for psychosis	• Improvements in quality of life, social functioning and adherence
• Cognitive remediation	• Improvements in cognition and psychosocial functioning
• Family psychoeducation	• Some improvement in social functioning and family coping and empowerment
• Peer support and illness self-management training	• Enhancement of empowerment and ability to cope with the illness
• Social skills training	• Improvements in social functioning
• Supported employment	• Increases in employment rates, hours worked and wages earned. Gains in self-esteem and quality of life
• Integrated treatment for coexisting substance abuse disorder	• Reductions in substance use and arrests; improved functioning

pants received at least 16 sessions [6]: CBT requires specialist training and experience, and thus cost is an important consideration. An analysis by the National Institute for Health and Care Excellence (NICE), however, concluded that CBT likely has a good cost-efficacy ratio, since the costs are compensated by a decrease in hospitalisation [6].

Cognitive remediation

Cognitive remediation programs usually utilise exercises aimed at improving aspects related to cognitive function, often combined with teaching strategies to improve the results of such exercises; these can also include different ways to limit cognitive deterioration [24 25]. The majority of studies have revealed that this approach is effective in improving cognitive function, while its effects on psychosocial functioning have been quite variable [24 25]. Models for cognitive remediation differ greatly and the number of reliable studies in this area is rather limited. It has been suggested that cognitive remediation augments the effects of other types of psychotherapy and improves the capacity to learn new abilities. Moreover, there is very limited evidence that its use for 2 years is associated with a reduction in the loss of cerebral grey matter correlated with schizophrenia [30] and an increase in the number of connections between brain cells and functional networks [31]. In a meta-analysis on over 2000

patients, [32] a long-lasting, mild-moderate effect of cognitive remediation was seen on cognitive function and on overall functioning that did not depend on the methodology of the study (type of approach, duration, etc.). Cognitive remediation was more effective when patients were clinically stable, and greater significant differences were seen on functioning when cognitive remediation was carried out in combination with other forms of psychiatric rehabilitation [32].

Family psychoeducation

Many persons with schizophrenia live with their families, and as such family intervention (also known as family psychoeducation in the USA) can play an important role in care [24 25]. Education of patients and families about the nature of schizophrenia and the symptoms of the disease helps them to develop coping strategies, capitalise on their strengths and learn to take better care of oneself. Patients (and their families) treated with family intervention are better able to participate in shared decisional processes. Family psychoeducation offers a valuable opportunity for persons with schizophrenia, their families and healthcare providers to exchange their personal experiences about the disease and its treatment. It is important to highlight that family members can provide a continuity of care for persons with schizophrenia, even if the healthcare operators involved in treatment change over time. A psychoeducational approach aims to promote collaboration between the family and healthcare providers. Studies have consistently shown that psychoeducational approaches are effective in reducing the rates of relapse and hospitalisation and in improving social functioning [24 25]. There is also evidence that these benefits are long-lasting (> 5 years) [33]. Since according to other studies the effects of family psychoeducation tend to subside after about 2 years due to an extinguishing effect, it has been suggested that 'recall sessions' in a multifamily setting may be useful in reducing the economic impact [34]. An initial analysis demonstrated that relapse and hospitalisations can be reduced by about 20% when family members are included in treatment compared to traditional care [35]. In another study, the rate of relapse at 2 years was 40% in patients in whom families received psychotherapeutic intervention and 75% when families did not receive any intervention [36]. The greatest advantages of family psychoeducation seem to be present in persons with a first episode of psychosis or recent onset of schizophrenia. Moreover, the benefits of psychoeducation also extended to family members who referred reduced levels of stress, better family relationships and greater ability to cope with problems and responsibilities [28].

Group multifamily psychoeducation is another useful intervention based on the family. In this model, qualified personnel guide a group of individuals with schizophrenia and their families who are given information about the course of disease and treatment of psychotic disorders. Participants also undergo problem-solving exercises that are designed to specifically help them to deal with the difficulties associated with care of a person with a psychotic disorder [37]. A multifamily approach can significantly reduce the rates of relapse compared with monofamily psychoeducation, which already reduces the rates of relapse *vs* treatment with no family psychoeducation (Fig. 2) [38]. Moreover, the addition of multifamily group psychoeducation to therapy with antipsychotics doubles the effects of pharmacological therapy alone [38].

Paradoxically, however, providing information can increase self-stigma of persons with schizophrenia, inducing them to expect prejudice and discrimination. The potential impact of self-stigma is shown in the International Study of Discrimination and Stigma Outcomes, an international study carried out in 27 countries in which 64% of participants referred that they no longer looked for employment, training, or education, and almost 75% said they felt the need to hide their diagnosis because of predictable discrimination [39]. However, in the long-term, psychoeducation – supported by adequate antipsychotic and psychosocial therapies – seems to be effective in reducing the burden experienced by many people with schizophrenia and their families [28].

Mutual support and self-help strategies

Persons with schizophrenia and their caregivers have noteworthy and accurate comprehension of the problems

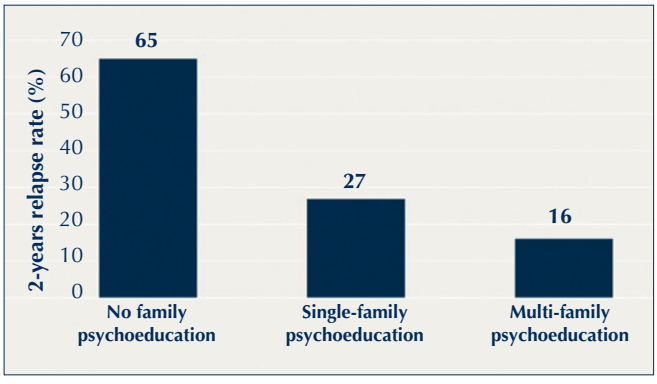


FIGURE 2.
Family psychoeducation reduces schizophrenia relapse rates, compared with treatment without family psychoeducation, and multifamily group psychoeducation is particularly effective (from Fiorillo et al., 2011, modified) [34]. *La psicoeducazione familiare riduce la percentuale di recidive di schizofrenia rispetto al trattamento senza psicoeducazione familiare, e la psicoeducazione multifamiliare di gruppo è particolarmente efficace (da Fiorillo et al., 2011, mod.)* [34].

associated with the disease. As a consequence, mutual support interventions can have an important role in the management of schizophrenia; this type of approach has been actively promoted in the USA and UK [40]. Mutual support groups, such as the National Alliance on Mental Illness (NAMI), the European Federation of Associations of Families of People with Mental Illness (EUFAMI) and the GAMIAN-Europe work together for affected individuals and caregivers. These groups can provide support in a number of different areas [40]. While peer-to-peer counselling seems to be useful when included as part of routine care, a self-help approach is generally more effective in other contexts (e.g., alcohol abuse or weight control) than in schizophrenia. However, in a recent report by the Schizophrenia Commission in the UK, 48% of patients with schizophrenia identified a self-help strategy as an important part of individual care [41]. There is also some evidence that self-help strategies can be useful in delaying hospital readmission, even if one study found no difference in clinical or social outcomes between individuals who participated in self-help groups compared with those who did not [42].

Social skills training

In persons with schizophrenia, problems in psychosocial functioning are related to disabilities in social skills that may be present before the onset of disease and persist if they are not addressed [24 25]. Social skills training can improve social proficiency, daily life, community functioning and other aspects of social functioning. The approach also has a small but significant effect on relapse [43]. The value of social skills training can be limited in some way to cognitive dysfunction in persons with schizophrenia [43]; however, its integration with cognitive remediation programs (or strategies aimed at improving attention and cognitive capacity), seem to be useful in improving the acquisition of social skills in patients with schizophrenia [44-46].

Supported employment

Schizophrenia can significantly reduce the ability of a person to work: on average, only 10-20% of persons affected with schizophrenia participate in the competitive workplace [24 25]. Persons with severe mental disorders such as schizophrenia are 6-7 times more likely to be unemployed than those without such disorders [47]. Data from the UK suggest that only 8% of persons with schizophrenia are employed, despite evidence that many would like to work [48]. Supported employment approaches can help persons with schizophrenia to obtain competitive employment, work longer and have higher salaries than persons without such support [26]. At least 50% of individuals who receive supported employment obtain a competitive job according to most studies [28]. The principal characteristics of such interventions are: focus on competitive employment; rapid search for work rather than a lengthy work training program; integration of psychiatric and employment services; emphasis on individual work preferences; continuous support in the workplace.

One of the most utilised supported employment models is Individual Placement and Support (IPS), according to which the only criterion for admission is the desire of the person to have a competitive job. The IPS model can produce notable savings in both social and healthcare costs, as well as potential benefits for the individual in terms of fewer hospital admissions and increased rates of employment [49]. Supported employment, however, has not been clearly demonstrated to improve long-term employment and economic independence in patients with schizophrenia. For this reason, it has been suggested that these strategies be adequately integrated with interventions such as CBT, cognitive remediation and social skills training [28].

Even if access to employment has a positive impact on mental health, the right type of employment must be considered: workplaces with low overall quality can cause stress, which can lead to psychological problems [47]. This is an important point since employers often have low expectations of persons with schizophrenia, and thus sometimes believe these individuals can only carry out jobs requiring low skill sets or with limited responsibility, or only volunteer work [48]. Retribution of work can be useful for persons with schizophrenia, even if this carries the additional risk of interrupting routine and consolidated habits.

Limitations of psychosocial therapy

Psychosocial therapy has some limitations that cannot be appreciated if symptoms are not well controlled and patients are not aware of their condition and the need to treat it. Involving the patient in the choice of treatment, for example, can be important in achieving a positive outcome: individuals who are highly motivated generally respond better to cognitive remediation than those who are less motivated [50]. Moreover, some persons affected with schizophrenia, if not treated with antipsychotics, can worsen when subjected to psychosocial interventions [51]. The costs of some therapies, such as CBT, can be prohibitive in countries in which adequate public healthcare resources are not available.

The design of studies aimed at investigating the efficacy of psychosocial therapies is not always as robust as the methodology applied to clinical studies for authorisation of a new drug. Thus, precisely planned, randomised controlled studies with adequate enrolment are needed in order to make strict recommendations regarding the use of these treatments.

Individualisation of treatment in schizophrenia

A. Rossi

Introduction

In spite of significant progress in understanding the nature of the disease, schizophrenia remains a challenging condition to treat. Schizophrenia is characterised by high morbidity and mortality: available treatments are inadequate, with variable efficacy, and are associated with several adverse effects. In spite of these obstacles, however, the availability of a wide range of individualised treatments, rehabilitative services and social support can effectively promote recovery of persons with schizophrenia [52] (Fig. 3). In reality, even if current antipsychotic treatments are not completely sufficient, they can nonetheless significantly reduce the burden of disease and improve daily life of patients. Towards this end, critical evaluation of the considerable amount of available information on antipsychotics and their individualised use is essential, and further efforts are needed to answer clinically important questions [53-57]. In clinical practice, decisions about the best antipsychotic with which to initiate treatment – or switch to another following treatment failure – is essentially an empirical process, since there is a limited amount of data in this regard on guiding treatment choices. In fact, while it is believed that the available antipsychotics have an efficacy that is broadly similar in treatment of schizophrenia [5], they differ significantly in their adverse event profiles. Given the notable variability in the pharmacokinetics of drugs and response to treatment in individual patients, it is worthwhile highlighting that efficacy is generally equivalent between groups of patients, although this is not necessarily the case when considering the single patient. At present, it is not possible to predict which antipsychotic is optimal for any given patient. There is no drug or dose that is valid for all patients, even if it seems that there is a dose range for optimal efficacy. Decisions about the choice of antipsychotic often follow a process of trial and error that includes careful monitoring of response and adverse effects, prompt evaluation of the risk-benefit ratio and when needed prudent switch to another drug [56] (Table V).

In general, typical or first-generation antipsychotics are effective in improving positive symptoms, but often cause motor symptoms or EPS that can be irreversible in the case of tardive dyskinesia. The most recent atypical or second-generation antipsychotics can improve both positive and negative symptoms and are less frequently associated with EPS and tardive dyskinesia than first-generation agents. However, weight gain, metabolic alterations and cardiovascular effects are associated with some second-generation antipsychotics (clozapine, olanzapine, thioridazine, risperidone, quetiapine for weight gain and metabolic effects; ziprasidone for increasing the QTc interval) have caused significant concern (Tables VI-X).

In spite of the progress made in psychopharmacology, many patients with schizophrenia interrupt or switch antipsychotics for lack of efficacy and/or treatment-adverse events, and a large proportion of patients remain symptomatic despite treatment. Individualisation of pharmacological treatment in schizophrenia, in addition to clinical experience and patient preference, should be based on three types of objective data: 1) clinical factors predictive of response to therapy; 2) predictable adverse effects of therapy; 3) pharmacogenetic and pharmacogenomic data.

Clinico-demographic variables and prevalent clinical dimension as predictive factors of response to therapy

The factors that influence variability of response to therapy with antipsychotics have not been clarified, thus rendering it difficult to develop effective treatment strategies for individual patients. The identification of clinical factors associated with outcomes in the treatment of schizophrenia would be of significant advantage in clinical practice. In fact, early identification of patients with poor response would allow avoiding ineffective treatments and associated adverse effects. Moreover, since some predictive factors can be corrected for, their individuation could provide a specific objective for treatment. Lastly, better understanding of factors related to response to therapy could help to better comprehend the physiopathology of the disease. However, to date studies that have attempted to identify factors associated with response to therapy have been largely negative. Nonetheless, some clinico-demographic variables have been associated with pharmacological response, including sex, duration of disease and duration of untreated disease, age of onset, comorbidity with other psychiatric disorders and substance abuse [58].

In recent years, data have emerged that associate differences in clinical response to pharmacotherapy in relation to the prevalent clinical dimension of the patient. The available data indicate that the presence of prevalent positive symptoms is associated with good response to antipsychotic therapy. A recent study, for example, demonstrated that response to pharmacological treatment is directly proportional to the severity of positive symptoms, showing that psychotic symptoms respond better to medical therapy [59].

The negative dimension is more difficult to treat, and if prevalent, is associated with poor long-term prognosis [60]. Olanzapine, aripiprazole and risperidone are more effec-

tive than haloperidol in treating the negative symptoms of schizophrenia, confirming data on the greater efficacy of atypical antipsychotics on this dimension [61 62].

The severity of disorganised thought in patients with schizophrenia is associated with poor long-term prognosis [63]. Moreover, the prevalence of symptoms of disorganised thought in patients with schizophrenia is predictive of response to antipsychotic therapy [64]. Disorganised thought and the positive dimension respond better to treatment with neuroleptics, even if recent data have demonstrated that disorganised thought responds better to atypical antipsychotics [65].

One of the biggest problems in the treatment of schizophrenia is recovery or at least maintenance of cognitive function. It is known that the severity of cognitive deficits is one of the most important predictive factors in long-term outcomes in schizophrenic disorders [66]. The available data are in fair agreement in sustaining that new antipsychotics are more effective than neuroleptics on cognitive function in schizophrenia [67]. It is still unclear, however, to what degree the effects of second-generation antipsychotics have on the cognitive dimension in schizophrenia, and especially if there are statistically significant differences between second-generation agents [68]. Moreover, whether or not the effects of atypical antipsychotics on cognitive function are generalised or concentrated on specific areas is still debated [68].

There is limited information on correlations between depression and outcomes in patients with schizophrenia. The available data suggest that atypical antipsychotics are not only not inferior to first-generation antipsychotics in this regard [69], but that at least some (amisulpride, aripiprazole, clozapine, olanzapine and quetiapine) seem to be more effective in treatment of depression in schizophrenia [4].

The presence of aggressive impulses is strongly correlated with suicidal behaviour in patients with schizophrenia [70]. While aggression is well controlled even by typical antipsychotics, there is much evidence showing that atypical antipsychotics, and in particular clozapine, improve impulsive behaviour and especially self-harm [14].

Predictable adverse effects of therapy

Current guidelines [53 55] recommend that the safety profile of the drug is a critical factor in the choice of antipsychotic in patients with schizophrenia. In reality, adverse effects of antipsychotics are a crucial aspect of therapy since they are the major cause of discontinuation of therapy. Adverse effects, therefore, can complicate and un-

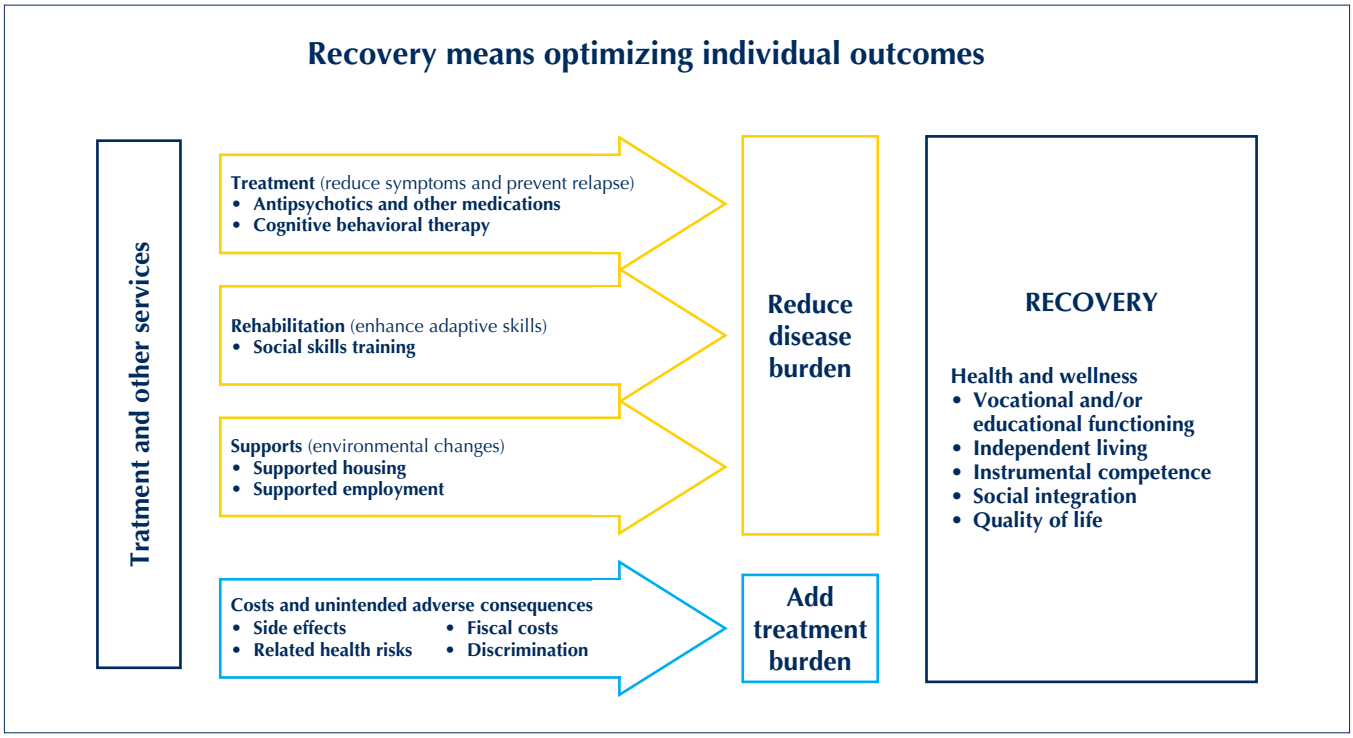


FIGURE 3.
Healing can be obtained by optimizing individual treatment (from Tandon et al., 2006, modified) [52]. *La guarigione può essere ottenuta ottimizzando il trattamento individuale (da Tandon et al., 2006, mod.)* [52].

TABLE V.
Steps to achieve optimum outcomes with currently available antipsychotics (from Bruijnzeel et al., 2014, modified) [56]. *Passaggi per ottenere un outcome ottimale con i farmaci antipsicotici attualmente disponibili (da Bruijnzeel et al., 2014, mod.)* [56].

1. Considerations in selecting the best antipsychotic for a particular patient
• Equivalent efficacy across agents
• Individual variability in response
• No good predictor of individual response to different agents
• Different agents have different side effects
• Different patients have different vulnerabilities and preferences
2. Proper antipsychotic trial sequence
• Begin with systematic 6-10 week trial of one antipsychotic with optimal dosing
• If inadequate response, follow with systematic trial of monotherapy with one or more other antipsychotics at adequate dose and duration
• If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic
• Follow with a trial of clozapine, if not tried before
• Only then consider other strategies (e.g., antipsychotic polypharmacy)
3. Good practice guidelines for ongoing antipsychotic treatment
• Measurement-based individualized care
• Repeated assessment of efficacy using reliably defined treatment targets (facilitated by use of standard rating scales)
• Careful assessment of adverse effects
• Care consistent with health monitoring protocols
• Standard protocols customized to individual vulnerabilities/needs and specific agent
• Ongoing collaboration with patien tin decision-making

TABLE VI.
A summary of the first-generation and second-generation antipsychotic medications (from Xu Q, et al., 2013, modified) [81]. *Riassunto delle caratteristiche dei farmaci antipsicotici di prima e di seconda generazione (da Xu Q, et al., 2013, mod.)* [81].

	First-generation antipsychotic medications	Second-generation antipsychotic medications
Main content	Butyrophenones, phenothiazines thioxanthenes	Clozapine, olanzapine, risperidone, quetiapine, ziprasidone, etc.
Calming effect	Powerful	Weaker (except clozapine)
Receptor targets	Narrow, mainly D2 receptors	Multitarget, D2 receptors and serotonin receptors
High prolactin	Common	Less common(except risperidone)
Efficacy	Good	Equivalent or superior
Positive symptoms	Good efficacy	Good efficacy
Negative symptoms	Weaker efficacy	Better efficacy
Cognitive symptoms	Weaker efficacy	Better efficacy
Extrapyramidal symptoms	Serious	Light
Tardive dyskinesia	Common	Rare
Effective dose	Large dosage	Generally small
Compliance	Bad	Better
Weight gain	Obvious	More obvious(except ziprasidone)
Metabolic syndrome	Common, higher risk	Rare, lower risk

TABLE VII.
Recommendations for the antipsychotic treatment in the acute phase of schizophrenia (from Hasan et al., 2012, modified) [53].
Raccomandazioni per la scelta del farmaco antipsicotico nella fase acuta della schizofrenia (da Hasan et al., 2012, mod.) [53].

Antipsychotic agent	Category of evidence[a]	Recommendation[b]
Olanzapine	A	1
Quetiapine	A	1
Risperidone	A	1
Clozapine[1]	A	2
Haloperidol	A	2
Amisulpride	B	2
Aripiprazole	B	2
Ziprasidone	B	2
Asenapine[2]	F	–
Iloperidone[2]	F	–
Paliperidone[2]	F	–
Lurasidone[2]	F	–
Sertindole[2]	F	–
Zotepine[2]	F	–

[a] Category of evidence: Category of evidence where A = full evidence from controlled studies. [b] Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. [1] Clozapine is highly effective in the treatment of first-episode patients, but because of its side effect profile it should be considered as recommendation grade 2. [2] It can be assumed that these antipsychotics are effective in the treatment of first-episode schizophrenia, but we could not identify any study to give an evidence-based recommendation.

TABLE VIII.
Recommendations for the antipsychotic treatment in relapse phase of schizophrenia (from Hasan et al., 2012, modified) [53].
Raccomandazioni per la scelta del farmaco antipsicotico nella recidiva della schizofrenia (da Hasan et al., 2012, mod.) [53].

Antipsychotic agent	Category of evidence[a]	Recommendation[b]
Amisulpride	A	1
Asenapine[1]	A	1/2
Aripiprazole	A	1
Clozapine[2]	A	1/2
Haloperidol	A	2
Iloperidone[1]	A	1/2
Olanzapine	A	1
Paliperidone[1]	A	1/2
Quetiapine	A	1
Risperidone	A	1
Sertindole[1,3]	A	1/2
Ziprasidone	A	1
Lurasidone	B	3
Zotepine	B	3

[a] Category of evidence: Category of evidence where A = full evidence from controlled studies. [b] Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. [1] These drugs are not approved for the treatment of schizophrenia in all countries and therefore it should be generally considered as recommendation grade 2 in these countries. [2] Clozapine is highly effective in the treatment of multi-episode patients, but it is only recommended as second line treatment due to its special side-effect profile (see main text). [3] Sertindole has a safety rating of 1, but due to its cardiovascular side effect profile the use is restricted in some countries. In these countries, it should be considered as recommendation grade 2 for legal reasons.

dermine treatment with antipsychotics in various ways. In fact, adverse effects can cause or worsen the symptoms associated with schizophrenia, including positive, negative, cognitive symptoms and agitation, [71] and can also contribute to increased risk for other mental disorders [72]. Lastly, adverse effects are subjectively difficult to tolerate and can compromise the quality of life. Most adverse effects caused by antipsychotics are due to their action on neurotransmitter systems and anatomic regions that are different from those involved in their therapeutic effects [73]. Adverse effects are both class- and agent-specific and are often dose-related: these include neurological, cardiovascular, anticholinergic and antiadrenergic effects in addition to weight gain, metabolic disorders involving glucose and lipids and sexual dysfunction [53 73] (Table XI). Adequate treatment of adverse effects, especially during long-term treatment of schizophrenia, can affect adherence and therefore improve outcomes [74]. Neurological adverse effects such as EPS tend to be more frequently associated with typical antipsychotics, while metabolic effects (weight gain, hyperlipidaemia, diabetes) are more frequently associated with atypical antipsychotics [75]. In recent years, particular attention has been given to metabolic adverse effects, also because it has been demonstrated that metabolic syndrome is more common in patients with schizophrenia than in the general population. An alternative classification has been proposed for antipsychotics based on metabolic risk, in which they are divided in: a) antipsychotics with high metabolic risk (clozapine, olanzapine, thioridazine, risperidone, quetiapine); b) antipsychotics with low metabolic risk (ziprasidone, fluphenazine, haloperidol, aripiprazole, amisulpride). In particular, among atypical antipsychotics aripiprazole, ziprasidone and amisulpride have a neutral effect on weight gain and lipid metabolism, while aripiprazole and amisulpride do not increase the risk of developing type 2 diabetes [76].

TABLE IX.
Recommendations for the antipsychotic treatment of negative symptoms in schizophrenia (from Hasan et al., 2012, modified) [53].
Raccomandazioni per la scelta del farmaco antipsicotico nel trattamento dei sintomi negativi della schizofrenia (da Hasan et al., 2012, mod.) [53].

	Primary negative symptoms		Secondary negative symptoms	
Antipsychotic agent	Category of evidence[a]	Recommendation[b]	Category of evidence[a]	Recommendation[b]
Amisulpride	A	1	A	1
Asenapine[1]	F	–	B	3
Aripiprazole	C3	4	A	1
Clozapine	C3	4	A	1
Haloperidol[2]	F	–	A	1
Iloperidone	F	–	F	–
Lurasidone	F	–	B	3
Olanzapine	A	1	A	1
Paliperidone[1]	F	–	A	1
Quetiapine	B	3	A	1
Risperidone	F	–	A	1
Sertindole[1,3]	F	–	A	1/2
Ziprasidone	B	3	A	1
Zotepine	D	5	A	1

Primary negative symptoms are considered a core symptom of schizophrenia, whereas secondary negative symptoms are a consequence of positive symptoms (e.g. social withdrawal because paranoid ideas), depressive symptoms (e.g. post-psychotic of antipsychotic-induced depression) or environmental factors (e.g. social understimulation due to hospitalism) (Carpenter et al. 1985). [a] Category of evidence: Category of evidence where A = full evidence from controlled studies. [b] Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. [1] These drugs are not approved for the treatment of schizophrenia in all countries and therefore it should be generally considered as recommendation grade 2 or lower in these countries. [2] Haloperidol is the most commonly used FGA across all studies. Please see the main text for other FGAs. [3] Sertindole has a safety rating of 1, but due to its cardiovascular side effect profile the use is restricted in some countries. In these countries, it should be considered as recommendation grade 2 or lower for legal reasons.

Pharmacogenetic and pharmacogenomic data

The basis of individualised medicine consists in the presupposition that the unique characteristics of an individual have a significant role in the choice of the most appropriate therapy. Such characteristics include genetic alterations and epigenetic modifications, clinical symptoms, modification of biomarkers and environmental factors. The objectives of personalised medicine are to predict an individual's susceptibility to disease, obtain accurate diagnosis and determine efficacy and favourable response to treatment [77]. In particular, the aim of pharmacogenetics is to predict which patients will benefit from a certain drug based on genetic information in order to provide tailored treatment that will optimise reduction in symptoms and minimise adverse effects of the drug [78 79].

Pharmacogenetic studies are concentrated on the main pathways of molecules hypothesised to be involved in the mechanism of action (pharmacodynamics) and on enzymes that metabolise antipsychotics (pharmacokinetics). It is known since the 1960s that dysfunction of the dopaminergic system is at the basis of the physiopathology of schizophrenia. Dopamine has different subtypes of receptors (D1 to D5), but only D2, D3 and D4 have been extensively studied by pharmacogenetics [78 79]. In reality, a number of studies have evaluated the relationship between response to antipsychotic drugs and genetic variations in dopamine receptors. Another area of research involves the pharmacokinetics of antipsychotics, and in particular on the family of cytochrome P450 enzymes that metabolise most of these drugs. Variants in genes that code for these enzymes can lead to an increase or decrease in the metabolism of antipsychotics that can alter plasma levels of the drug. In the last 15 years, many variants of genes have been studied in relation to response to antipsychotic drugs [78 79]. The majority of pharmacogenetic studies on antipsychotics have investigated selected candidate genes, focusing on polymorphisms in genes that code for receptors of the dopamine and serotonin systems, in addition to genes that code for enzymes that metabolise antipsychotics such as COMT and CYP2D6 [78 79]. A number of phar-

TABLE X.
Choice of treatment in the acute phase of schizophrenia (from Lehman et al., 2004, modified) [54]. *Scelta del farmaco nella fase acuta della schizofrenia (da Lehman et al., 2004, mod.)* [54].

	Consider Medication From			
Patient profile	**Group 1: first-generation agents**	**Group 2: risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole**	**Group 3: clozapine**	**Group 4: long-acting injectable antipsychotic agents**
First episode		Yes		
Persistent suicidal ideation or behavior			Yes	
Persistent hostility and aggressive behavior			Yes	
Tardive dyskinesia		Yes; all group 2 drugs may not be equal their lower or no tardive dyskinesia liability	Yes	
History of sensitivity to extrapyramidal side effects		Yes, except higher doses of risperidone		
History of sensitivity to prolactin elevation		Yes, except risperidone		
History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia		Ziprasidone or aripiprazole		
Repeated nonadherence to pharmacological treatment				Yes

macogenetic studies have attempted to identify genes that may be involved in inter-individual differences in adverse events induced by antipsychotics, although the results are inconsistent [78 79].

Pharmacogenetics involves the use of genomic techniques, such as genotyping, sequencing, gene expression, genetic epidemiology, transcriptome, proteomics, metabolome and bioinformatics to study drugs in clinical use, and apply high-throughput systemic approaches to accelerate the discovery of markers for response to therapy that may be related to the drug's target, its metabolism or course of disease [80 81]. Pharmacogenomics is different from pharmacogenetics as the former studies a wide range of genes that may be involved in the response to a drug, while the latter primarily examines specific candidate genes. For many drugs, interindividual differences are mainly due to single nucleotide polymorphisms (SNP) in genes that code for enzymes that metabolise or transport drugs and/or are targets of the drug (e.g. enzymes, receptors and defective proteins that alter metabolic pathways, leading to expression of the phenotype of the disease) [80].

The use of these techniques in disorders of the central nervous system is an extremely complicated process since the majority of neuropsychiatric disorders, including schizophrenia, are complex pathologies that involve many different genes. In addition, it is highly unlikely that a single pharmacological agent can reverse multifactorial mechanisms associated with neuronal dysfunction of most processes of the central nervous system with a complex phenotype that involves mood, personality, behaviour, cognition and functioning. Treating such a heterogeneous clinical picture generally requires the administration of a combination of diverse drugs [80].

Clinico-pharmacological management of the patient with schizophrenia

A. Fagiolini, A. Altamura, P. Rocca

Introduction

The discovery and development of antipsychotics started more than 50 years ago and has profoundly improved the quality of life of many patients with schizophrenia. As such, there is little doubt on the benefits (and disadvantages) of antipsychotics [82]. Antipsychotic drugs are generally recommended in all phases of schizophrenia, from treatment of acute episodes to prevention of relapse [83]. The important long-term objectives of treatment plans for schizophrenia include improving adherence to therapy,

TABLE XI.
Main side effects of typical and atypical antipsychotics (from Marder et al., 2004, modified) [73]. *Principali effetti collaterali degli antipsicotici tipici e atipici (da Marder et al., 2004, mod.)* [73].

Drug	EPS	Increased prolactin	Increased weight	Hyperglycemia	Hyperlipidemia	QTc prolongation	Sedation	Hypotension	Anticholinergic effects
Perfenazine	++	++	+	+(?)	+(?)		+	+	
Haloperidol	+++	+++	+				++		
Clozapine			+++	+++	+++		+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	+	
Olanzapine			+++	+++	+++		+	+	++
Quetiapine			++	++	++		++	++	
Ziprasidone						++			
Aripiprazole							+*		

* Sedation is indicated with higher doses of therapeutic range.

rehabilitation through psychosocial interventions – that involve patients and often even family members – and improving the quality of life. A combination of antipsychotics with other types of intervention is very important in achieving these long-term objectives.
Several important questions regarding pharmacotherapy of schizophrenia – in particular when to initiate treatment and how long to continue it – are still unresolved and often lead to inadequacy of therapy for many patients (e.g. premature discontinuation or delayed access to pharmacological therapy) [82]. Poor adherence to pharmacological therapy is an important aspect that contributes to inadequate treatment [84]. Considerable efforts have been made to improve adherence by developing antipsychotics with better tolerability in formulations that enable prolonged administration of the drug, including long-acting injectables, also known as depot antipsychotics. In recent years, these formulations of atypical antipsychotics have shown promising results in clinical trials that have led to changes in attitudes towards these drugs, which were traditionally reserved for patients with recurrent poor adherence to treatment [82 85].

The continuity of treatment

In about 75% of cases, the course of schizophrenia is characterised by a remission phase that alternates with relapses; after the initial episode, it is estimated that only 14-20% of patients can completely recover [83]. Moreover, knowledge of the neurobiological bases of schizophrenia has provided evidence regarding the potentially progressive nature of the disease. There is clear evidence indicating that interruption of treatment is associated with relapse in the majority of cases [83]. In addition, it is increasingly evident that early treatment is associated with less destructive psychotic episodes, while delayed access to mental health services in recent onset schizophrenia seems to be associated with slower and incomplete recovery, increased risk of relapse and poorer prognosis. Continuity of treatment in the initial phases appears to be crucial and can modify long-term prognosis. A study by Robinson [64] clearly showed that in spite of a good overall response to initial treatment, patients with a first episode of schizophrenia had a rate of relapse that was > 80% at 5 years. Following initial remission, discontinuation of the antipsychotic was identified as a significant factor for relapse, increasing the risk by almost 5-fold.
To date only a few controlled clinical trials have evaluated the possibility of preventing relapse, which is seen in 41-79% of cases at 12 months after dose reduction or discontinuation of treatment [11] (Table XII) in patients with a first episode of schizophrenia. In one of these studies [86], 131 patients with a first episode in remission for at least 6 months were randomised to gradual discontinuation of therapy or to continue treatment, consisting in the majority of cases of low doses of antipsychotics, and followed for 18 months. Discontinuation of therapy was associated with a significantly higher rate of relapse (43% *vs* 21%, $p < 0.011$). A more recent randomised controlled trial [87] compared the efficacy of additional maintenance therapy to intermittent treatment in prevention of relapse in patients with a first episode of schizophrenia in remission and who had been on maintenance therapy for at least one year. The percentage of relapses was significantly higher in the group receiving intermittent treatment than in those undergoing continuous maintenance therapy. Both these trials further highlight the importance of continuous maintenance treatment in patients with a first episode, even after one year in remission.
In light of results that indicate the importance of continu-

TABLE XII.
Studies reporting symptom recurrence rates after treatment reduction/discontinuation after a single episode of psychosis (from Emsley et al., 2013, modified) [11]. *Studi che riportano le percentuali di recidiva dopo riduzione/sospensione del trattamento a seguito di un singolo episodio di psicosi (da Emsley et al., 2013, mod.) [11].*

Authors	Sample size	Treatment duration	Symptom recurrence rates					Comparator recurrence rate
			9 months	12 months	18 months	24 months	36 months	
Kane et al.	28	Not specified		41%				0%
Crow et al.	120	Not specified				62%		46%
Gitlin et al.	53	3 months in remission		78%		96%		-
Wunderink et al.	161	6 months in remission			43%			21%
Chen et al.	178	12 months +		79%				41%
Gaebel et al.	44	12 months		57%				4%
Boonstra et al.	20	12 months min remission	82%					12%
Emsley et al.	33	24 months		79%		94%	97%	-

ous early treatment, the question can then be asked if long-acting antipsychotics (LAI) should be used in first-episode schizophrenia; at present, there are only limited data to answer this question [88 89]. A two-year open-label study [90] in patients with a first episode of schizophrenia demonstrated that those assigned to long-acting risperidone had a significantly lower rate of relapse and better adherence than those treated with an oral formulation of risperidone. In another open-label study [91] on patients with schizophreniform disorder or schizophrenia at diagnosis, treatment for 2 years with risperidone LAI was associated with remission in 64% of patients.

Duration of therapy

An open question concerns the optimal means of ensuring continuity of treatment, and in particular for how long maintenance treatment should continue in patients with schizophrenia that is in remission [82]. On the basis of clinical evidence and studies demonstrating that a 5-year period following an acute episode represents the period in which patients are particularly susceptible to relapse, maintenance therapy should last for at least 2 to 5 years [92]. According to the guidelines of the Canadian Psychiatric Association [93], for treatment of a first psychotic episode antipsychotics should be continued for at least 2 years following the initial remission of symptoms, while a minimum of 5 years of stability without relapse and adequate functioning should be observed before considering gradual discontinuation of the antipsychotic over a period of 6-24 months [74].
As in the treatment of other chronic diseases, a relevant problem of long-term, continuous antipsychotic treatment is adverse effects. In addition to the well-known neurological adverse effects of antipsychotics, there is good evidence that some atypical antipsychotics are associated with adverse metabolic effects. Some studies in animal models have suggested that chronic exposure to antipsychotics can contribute to a reduction in the volume of cerebral tissue associated with the disease [94]. However, a study [95] carried out in patients with recent diagnosis showed that prolonged treatment with long-acting risperidone was associated with a stable volume of white matter, in contrast to a reduction in volume observed in patients treated with the oral formulation of risperidone; the study concluded that modification of adherence with long-acting risperidone may act differently on the process of myelinisation, which would explain the better prognosis associated with the long-acting formulation compared with the oral formulation.
It is thus clear that the risk-benefit ratio of long-term treatment should be carefully evaluated and that care must be taken in prescribing the lowest dose of antipsychotic for effective control of symptoms.

Adherence to treatment

One of the main factors that leads to inadequate treatment and early discontinuation is poor adherence to therapy [84]. In fact, poor adherence is one of the most important problems in treatment of patients with mental disorders. The majority of hospital admissions are due to non-adherence, even if it is often not clear if non-adher-

ence was the cause or consequence of relapse [96]. The percentage of patients that are partially or completely non-adherent to therapy has been estimated to be between 40% and 60% [97].
The factors that contribute to poor adherence to pharmacotherapy for schizophrenia are related to the patient (low insight, depression, substance abuse), treatment (adverse effects, poor efficacy, complexity of therapeutic regimen) and lack of support or therapeutic alliance with the medical team [82 98 99] (Table XIII). Some of these factors can be overcome by improving the strategies used to administer the drug, such as long-acting formulations. However, it should always be considered that for early recognition and intervention of poor adherence, better education of patients and training of healthcare providers is extremely important. Poor adherence has been identified as an important risk factor for relapse [84 100]. The use of LAI antipsychotics has been demonstrated to improve adherence to therapy, and is associated with fewer treatment discontinuations, relapses and hospitalisations [101].

Typical and atypical antipsychotics

Even if atypical antipsychotics are widely used, there is continued debate regarding their tolerability, which is presumed to be better than first-generation agents. In recent years, the propensity of atypical antipsychotics to induce weight gain and metabolic alterations in glucose and lipids has raised doubts about their advantages over typical antipsychotics. For this reason, the role of some atypical antipsychotics in treatment of schizophrenia has been reconsidered. Taken together, the results of recent analyses comparing typical and atypical antipsychotics has demonstrated a high level of heterogeneity between the two classes of drugs that does not allow for any general conclusions to be drawn. The choice of drug should thus be made on an individualised basis considering the available therapeutic options [53 74 83 102].

Long-acting injectable antipsychotics (LAI)

LAI antipsychotics were introduced over 40 years ago because of their numerous potential advantages over oral formulations, including the possibility to monitor compliance and distinguish poor adherence from lack of response, regular contact with the patient and caregiver, reduced risk of accidental or deliberate overdose, better bioavailability and more predictable correlation between dose and plasma levels [97].
However, LAI antipsychotics have several limitations such as slow dose titration, longer time to reach steady state levels and sustained adverse effects if discontinued for problems related to tolerability. Traditionally, LAI formulations are used in maintenance treatment of patients with schizophrenia, generally following clinical stabilisation with oral antipsychotics. LAI formulations of atypical antipsychotics have been developed for risperidone, olanzapine, paliperidone and, more recently, for aripiprazole: at present, there are 10 LAI formulations, 6 first-generation and 4 second-generation [103].
Even if it is reasonable to expect that LAI antipsychotics can improve adherence to therapy and clinical outcomes, the clinical evidence obtained over the years regarding such benefits is not entirely clear, while the analysis of more recently introduced LAI antipsychotics is in progress. A series of analyses and systematic reviews has been carried out to indirectly compare the efficacy of LAI antipsychotics with oral formulations of both typical and atypical antipsychotics [104-108].
A large systematic meta-review [104], covering 8 Cochrane reviews of randomised clinical trials of individual typical LAI antipsychotics in patients with schizophrenia or schizophreniform disorder showed that the rates of relapse and tolerability profiles are similar for oral and LAI formulations, while general clinical improvement was significantly higher for LAI compared with oral formulations.
A recent systematic review [105], including studies with different designs and comparing typical LAI antipsychotics with atypical oral formulations, indicated that the LAI antipsychotics had greater clinical benefit than oral formulations, although the results were variable and inconclusive mainly because of the heterogeneity in methods and interventions used in the various studies. In addition, a recent publication [109] confirmed that studies using different methodologies may give different results, and that studies on LAI antipsychotics may be an example of a situation where conventional randomised trials may not be the gold standard: in fact, these types of studies tend to increase adherence to treatment and therefore lead to underestimation of the possible benefits of LAI antipsychotics compared with the corresponding oral formulations. A significant reduction in the rates of relapse (21.6% *vs* 33.3%, RR 0.70, 95% CI 0.57-0.87, p = 0.0009) and dropouts for inefficacy of typical LAI antipsychotics compared to oral antipsychotics was reported in a systematic review and meta-analysis of 10 long-term RCT lasting at least 12 months published between 1975 and 2010, for a total of 1,700 outpatients [106].
Another systematic review of studies published between 2000 and 2011 [107] compared the efficacy of LAI and oral antipsychotics on relapse, hospitalisation and all-cause discontinuation of therapy in schizophrenia revealed a clear difference between observational studies (4 prospective and 4 retrospective), which showed a significant advantage for LAI formulations (prospective: RR = 0.62,

TABLE XIII.
Factors associated with non-adherence (from Kane et al., 2013, modified) [99]. *Fattori associati con la mancata aderenza (da Kane et al., 2013, mod.)* [99].

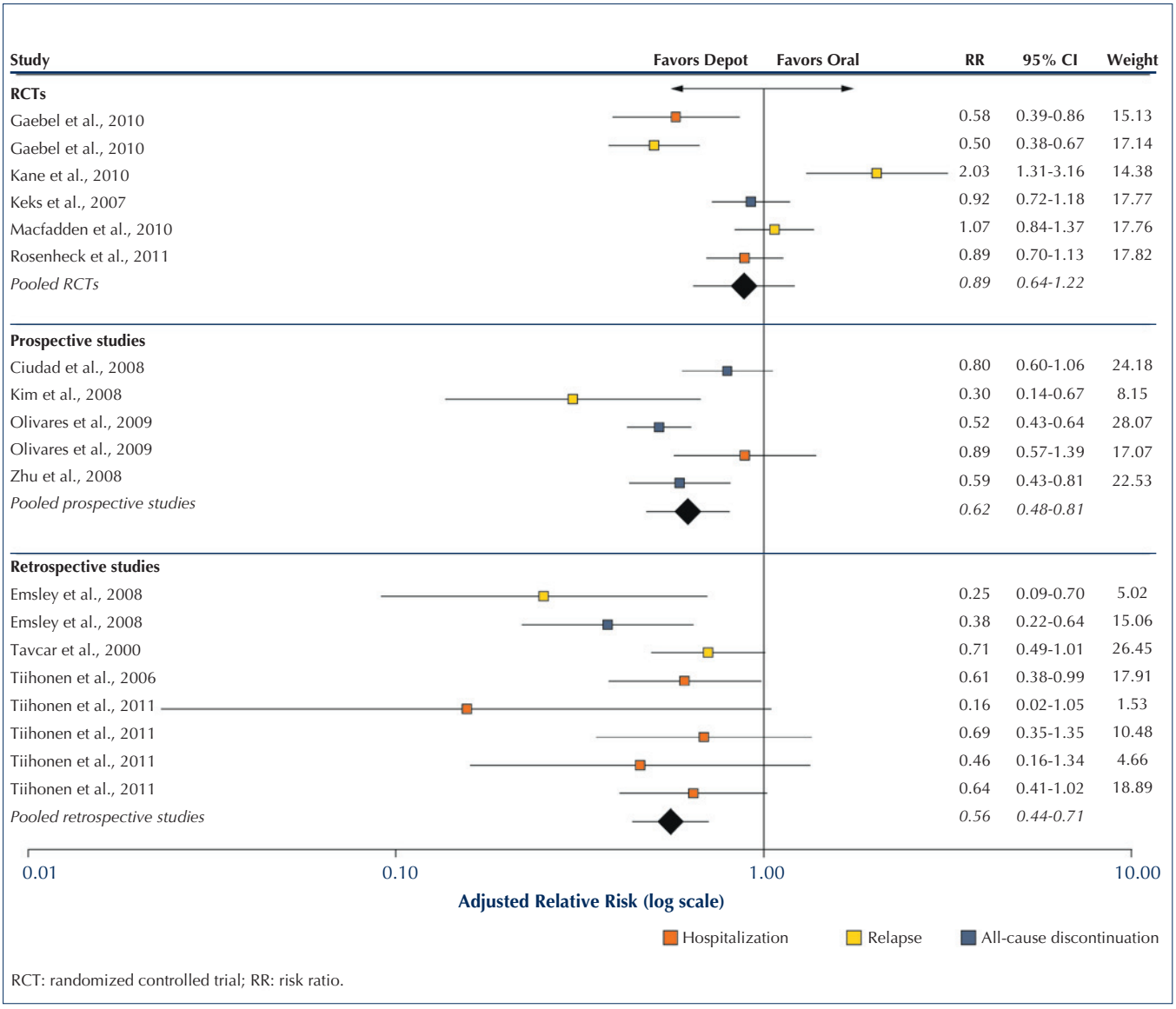
Patient characteristics	**Provider/system/treatment characteristics *(continued)***
Sex, age, race	Duration of treatment (past and expected)
Education	Complexity of administration
Socio-economic status	Accessibility and cohesion of services
Knowledge	Access to care
Perceived need for treatment (insight)	Continuity of care
Motivation	Reimbursement
Beliefs about treatment risks and benefits	Ability to monitor adherence
Past experiences/"transference"	Provision of psychoeducation
Past history of adherence	Availability of trained psychosocial treatment specialists
Self-stigma	Evaluation of obstacles to adherence
Illness characteristics	Access to alternative formulations (e.g., long-acting injectable antipsychotics)
Illness duration (first episode, chronic)	Complexity of administration
Illness phase (acute, maintenance, etc.)	
Symptom type and severity (e.g., negative symptoms, depression, demoralization)	**Family/caregiver characteristics**
Cognitive function	Nature of relationship
Lack of insight	Perceived need for treatment (insight)
Substance use	Beliefs about treatment risks and benefits
Comorbidities	Knowledge, beliefs, attribution
Degree of refractoriness	Involvement in psychoeducation
Potential for relatively asymptomatic intervals or "spontaneous remission"	Involvement in adherence monitoring
	Stigma
Medication characteristics	Environmental characteristics
Efficacy (consider different domains)	Physical environment
Effectiveness	Level of supervision
Adverse effects (of relevance for the patient)	Orderliness
Delivery systems/formulation	Safety and privacy
Dosage frequency	Stigma
Cost/access	Extrafamilial support system
Provider/system/treatment characteristics	**Other resource characteristics**
Therapeutic alliance	Financial
Frequency and nature of contact with clinicians	Transportation

95% CI 0.48-0.81, $p < 0.001$; retrospective: RR = 0.56, 95% CI 0.44-0.71, $p < 0.001$), and randomised controlled studies (5 trials), which showed a non-significant difference favouring LAI formulations (RR = 0.89, 95% CI 0.64-1.22, $p = 0.416$) (Fig. 4). The authors of this meta-analysis concluded that in this type of comparison the trial design can considerably influence the results, probably since controlled clinical studies, even if avoiding confounding factors and possible selection bias associated with observational studies, are not reflective of a real-world treatment setting.

A meta-analysis of 13 randomised trials on 6,313 patients [108] compared efficacy and safety of second-generation LAI antipsychotics to placebo and oral antipsychotics. It was found that LAI antipsychotics were more effective than placebo [$p < 0.001$ for PANSS (positive and negative syndrome scale) score] and at least as effective and safe than oral antipsychotics.

Efficacy and safety of individual LAI antipsychotics

For risperidone LAI, despite studies that have demonstrated significant reduction in relapse with LAI formulations over oral formulations, other studies have not confirmed this superiority [82 106 110 111]. It is likely that the differences in results are related to dissimilarities in the quality, design and methodologies of various studies [82].



RCT: randomized controlled trial; RR: risk ratio.

FIGURE 4.
Meta-analysis of adjusted risk ratios, by study design (from Kirson et al., 2013, modified) [107]. *Meta-analisi del rischio relativo standardizzato, a seconda del disegno dello studio (da Kirson et al., 2013, mod.)* [107].

The efficacy and tolerability of olanzapine LAI (olanzapine pamoate) has been investigated in two randomised, double-blind, studies, one versus placebo [112] and the other versus oral olanzapine [113]. In the former, olanzapine was found to be significantly more effective that placebo in reducing the PANNS score, but with weight gain and alterations in lipid metabolism. The second study demonstrated the efficacy of olanzapine LAI in maintenance treatment up to 24 weeks.

Several studies have demonstrated that paliperidone LAI (paliperidone palmitate) is more efficacious than placebo and is non-inferior to risperidone LAI in improving the PANSS score in patients with symptomatic acute schizophrenia or in delaying the appearance of relapse in patients with stable disease [114 115]. Paliperidone LAI has been demonstrated to have a metabolic profile similar to other second-generation antipsychotics; moreover, as in the case of olanzapine LAI and risperidone LAI, its use has been associated with worsening of psychosis in some patients [116].

More recently, the EMA has approved aripiprazole LAI for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole [117]. The clinical efficacy of aripiprazole LAI has been established in two

randomised, double-blind clinical studies in patients with schizophrenia. In the first [118], aripiprazole LAI was shown to be non-inferior to oral aripiprazole considering both the rate of relapse after 26 weeks and improvements in the PANSS score. In a previous study [119], aripiprazole LAI was associated with a risk of relapse at 52 weeks that was 5.03 fold lower than placebo. The most common adverse events observed in the two studies were: weight gain (9.0%), motor symptoms (7.9%), insomnia (5.8%) and injection site pain (5.1%). In particular, injections site reactions were generally mild to moderate and self-limiting; injections site pain appeared at a median of 2 days after injection and lasted for a median of 4 days. Aripiprazole LAI was associated with a greater frequency of EPS (18.4 %) than oral aripiprazole (11.7%); motor symptoms were the most frequent adverse effect and generally appeared around 10 days after the first injection and lasted for a median of 56 days, while Parkinsonism was slightly less frequent (6.9%). In the study by Fleischhacker [118], weight gain ≥7% *vs* baseline and last visit was 9.5% in the group treated with aripiprazole LAI and in 11.7% the oral aripiprazole group; weight loss ≥7% from baseline values to last visit was seen in 10.2% of patients treated with aripiprazole LAI and 4.5% of patients in the aripiprazole oral group. In a previous study by Kane [119], weight gain ≥ 7% was seen in 6.4% of patients treated with aripiprazole LAI and 5.2% of subjects in the placebo group; weight loss ≥ 7% was seen in 6.4% in the aripiprazole LAI group and 6.7% of patients in the placebo group; the mean change in weight from baseline to last visit was -0.2 kg for LAI and -0.4 kg for placebo (p = 0.812).

Quality of life, functioning and treatment satisfaction of patients with LAI antipsychotics

Quality of life is an important parameter in evaluating the benefits of treatment, especially in chronic diseases. Studies that have examined patients switching from an oral to LAI formulation of an antipsychotic have reported significant improvements in the quality of life, overall functioning and treatment satisfaction [101].

In one study, following unsatisfactory treatment with oral antipsychotics, 182 patients with schizophrenia were switched to a LAI antipsychotic for 6 months [120]. Compared to baseline, over the 6-month observation period significant improvement ($p < 0.05$) was seen in the PANSS score. Moreover, significant improvement ($p < 0.05$) was seen in Global Assessment of Functioning, health-related quality of life and patient satisfaction. The effects of LAI on functional improvements and quality of life were also evaluated in a placebo-

TABLE XIV.
Decision algorithm for choosing a long-acting antipsychotic based on treatment compliance predictors reported in the literature (from Rossi et al., 2012, modified) [124]. *Algoritmo decisionale per scegliere un antipsicotico LAI basandosi sui fattori predittivi di compliance al trattamento riportati in letteratura (da Rossi et al., 2012, mod.)* [124].

Good compliance		Poor compliance
Late	Age at onset	Young
Long	Lenght of illness	Short
Yes	Insight	No
Mild	Positive and negative symptoms	Severe
No	Drug abuse	Yes
Low	Percentage of relapse	High
Low	Frequency of hospitalizations	High
Oral	Ongoing therapy	Oral/depot
No	Previous depot	Yes
↓		↓
Evaluate patient's interest in taking depot treatment considering: • Insight of illness severity • Educational level • Therapeutic alliance • Possibility of sharing the therapeutic decision with the physician		Evaluate patient's interest in switching to atypical depot. Considering: • Severity of illness • Dosages of ongoing therapy • Efficacy profile of the depot

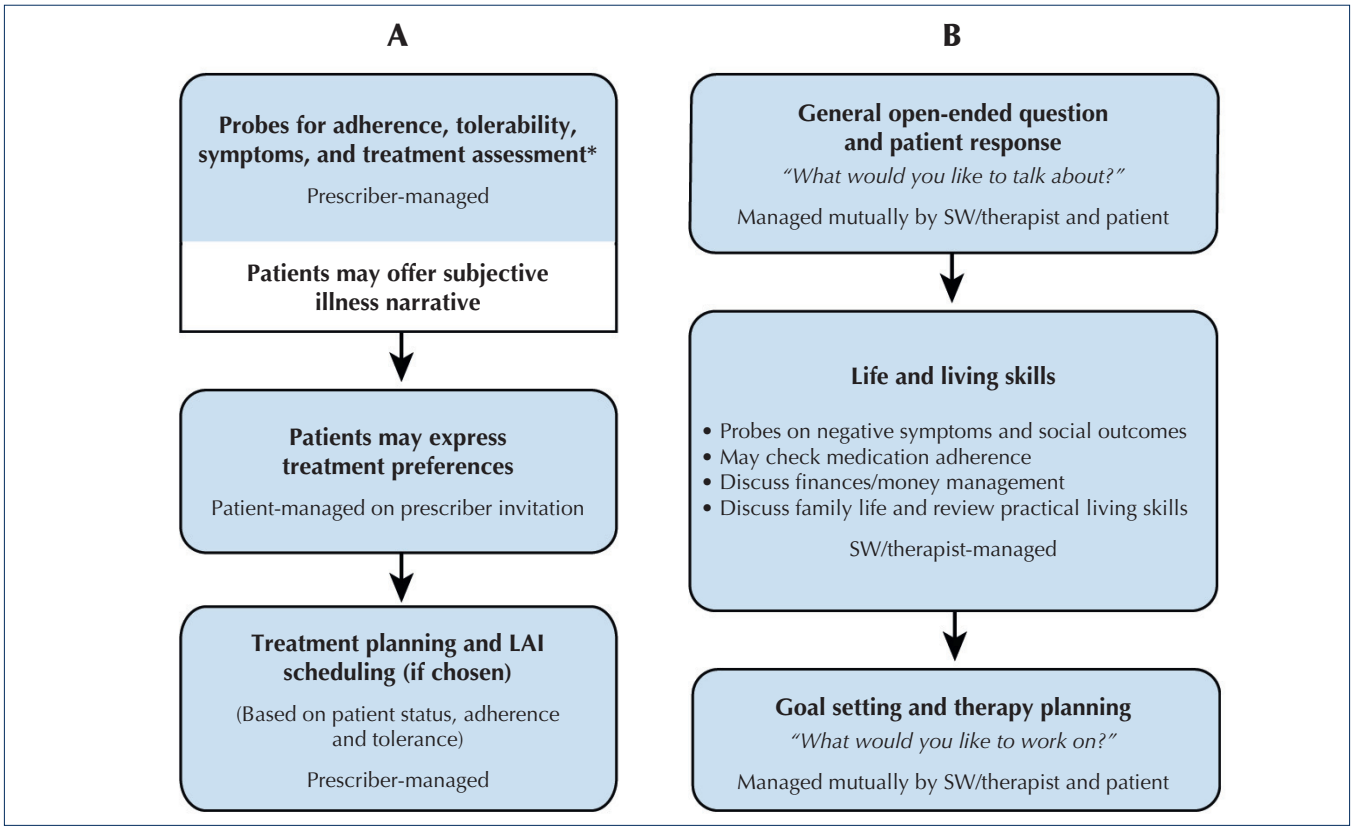


FIGURE 5.
Observed conversation flow between: A) patients and prescribers (n = 69); B) patients and social workers or therapists (from Potkin et al., 2013, modified) [128]. *Flusso di conversazione osservato tra: A) pazienti e prescrittori; B) pazienti e terapisti sociali (da Potkin et al., 2013, mod.)* [128].

controlled, randomised, double-blind, 8-week study on 404 outpatients with schizophrenia [121]. Significant ($p < 0.01$) improvement was seen with a LAI formulation compared to placebo in the quality of life and in the Short Form Health Survey. Macfadden et al. [122] assessed the efficacy of a LAI formulation on the quality of life and functioning in an observational, prospective 24-month study on 532 patients with schizophrenia. After initiation of therapy with a LAI, patients reported improvement at 3 months that continued throughout the 24-month follow-up period. Improvements were seen in Global Assessment of Functioning, Strauss-Carpenter Levels of Functioning, Personal and Social Performance and overall health. The Switch To Risperidone Microspheres trial [123] was carried out in patients with schizophrenia who were switched from an oral antipsychotic or first-generation LAI to a second-generation LAI for lack of efficacy, adverse effects, or poor adherence. After 6 months, improvements vs baseline were seen with the second-generation LAI for symptoms, global functioning, quality of life, treatment satisfaction and rate of hospitalisation.

Current uses and guidelines for LAI antipsychotics

Current guidelines [53 74 83 92 93] generally recommend LAI antipsychotics for maintenance therapy, among the other options for maintenance therapy, and/or when better adherence is needed. According to the guidelines, LAI can even be considered in the acute phase of schizophrenia if there is repeated lack of adherence or poor adherence [92 124], while the data on the use of new LAI formulations in patients with a first episode are considered to be too limited to allow any specific recommendations (Table XIV). However, many experts feel that the guidelines are too conservative and that the position of LAIs in treatment of schizophrenia should be reconsidered [96]. With the increase in information on the efficacy and tolerability of atypical LAI antipsychotics, international guidelines should be updated regarding the different phases of disease in which LAIs can be recommended and on the patients who could benefit from their administration.
Other data that has emerged from studies carried out in several Western countries, including Italy, concerns the

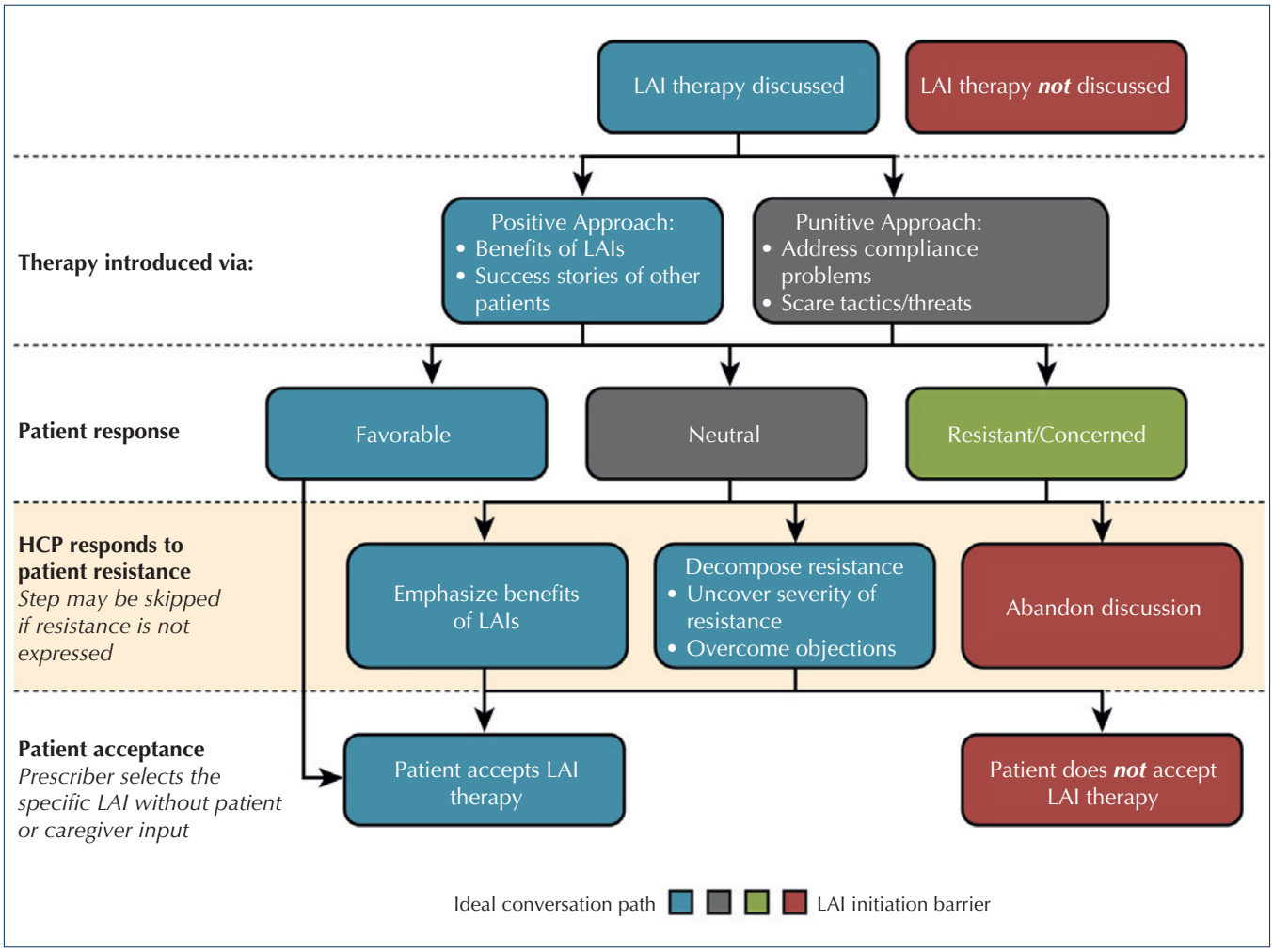


FIGURE 6.
Observed conversation decision tree for prescriber interactions with patients regarding initiation of long-acting injectable antipsychotics (from Potkin et al., 2013, modified) [128]. *Albero decisionale delle conversazioni osservate nelle interazioni con i pazienti riguardo all'inizio di una terapia con antipsicotici LAI (da Potkin et al., 2013, mod.)* [128].

relatively low use of LAIs even in patients who could clearly benefit from them. This can be explained by a number of misunderstandings and prejudices among prescribers, patients and caregivers for LAI formulations, which are considered older drugs, that are forced upon patients, reserved for those with poor adherence, and associated with adverse events and reduced involvement of healthcare personnel in the care of psychiatric patients [125]. Some psychiatrists consider LAIs as a 'last resource' of treatment, which should be used only when all other pharmacotherapies have failed, and reserved for patients who have presented with multiple episodes.
The high cost of LAI antipsychotics is another relevant barrier to increased prescribing of these formulations [106]. However, recent pharmacoeconomic studies have shown that atypical LAI antipsychotics can represent a favourable therapeutic strategy even from an economical standpoint.

Practical recommendations on the use of atypical LAI antipsychotics

There is broad consensus among specialists that the optimal use of new LAI formulations requires substantial changes in the general attitudes towards treatment with depot antipsychotics [82 96]. LAI antipsychotics should be utilised for any patient undergoing long-term treatment, and not only for those with problems in adherence [83 96 126]. Effective maintenance therapy can be considered as a starting point that leads to successful multimodal treatment programmes and rehabilitation. Since it is believed that oral antipsychotics should be initiated in patients with a new

diagnosis of schizophrenia [83], even if data on the efficacy of LAI antipsychotics are still limited, it can be expected that these formulations will also be favourable compared with oral antipsychotics in this setting. In patients with acute exacerbations of schizophrenia, in which the guidelines recommend treatment with oral antipsychotics, when the exacerbation is due to repeated non-adherence to poor adherence, the use of a LAI antipsychotic is advised [82]. Switching from an oral to LAI formulation requires precise strategies to maintain or improve therapeutic efficacy and minimise rebound cholinergic or histaminergic effects [127].

In conclusion, the recent development of LAI formulations of atypical antipsychotics has increased the number of treatment options for individualised treatment of schizophrenia, which is a fundamental aspect of management of patients with mental illness. Early intervention and continuity of treatment are key factors is achieving long-term remission, which prevents disruptive progression of disease and reduces the costs of the disease. The availability of new LAI formulations, with better tolerability in terms of EPS than typical depot antipsychotics, allows for the possibility to extend treatment with long-acting drugs, traditionally reserved for non-adherent patients with multiple episodes, to young patients in the initial phase of schizophrenia, who have a relevant risk of relapse if treatment is discontinued and the consequences of which would be devastating. Radical change in attitudes is needed among both physicians and patients to realise that long-acting antipsychotics can offer a new treatment paradigm: no longer ''last resort' drugs, but rather a potential first step towards continuity of treatment and clinical remission.

Two recent studies have confirmed this consideration. In the first, Potkin et al. [128] assessed the points of view of the patient and prescriber towards LAI antipsychotics by examining the conservations between patients and psychiatrists: the study revealed that the lack of information and dialog was often the basis for questionable choices, which excluded the possibility to consider the use of LAI antipsychotics even in cases for which they are clearly indicated (Figs. 5, 6). In the second study [129], negative attitudes and reluctance by many psychiatrists in prescribing LAI antipsychotics, and not patient resistance, was found to be the true cause of underuse of these formulations. In the future, we believe that well-designed long-term studies are needed to confirm the encouraging results obtained with atypical LAI antipsychotics.

Conflict of Interests

Carlo Altamura has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Roche, Lundbeck, Merck, AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Sanofi, Eli Lilly, Pfizer and Otsuka.

Andrea Fagiolini has received grant/research and/or has collaborated as consultant and/or chairman and/or has participated as a speaker on symposia for Angelini, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, Lundbeck, Novartis, Otsuka, Pfizer, Roche.

Silvana Galderisi has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Janssen-Cilag, Roche, Otsuka, Lundbeck, Pierre Fabre e Amgen-Dompé.

Paola Rocca has participated as speaker on symposia for Bristol-Myers Squibb, Janssen-Cilag, Otsuka, Roche.

Alessandro Rossi has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Takeda, Roche, Lundbeck, Janssen-Cilag.

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