

REVIEW

# Current Data on and Clinical Insights into the Treatment of First Episode Nonaffective Psychosis: A Comprehensive Review

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## ABSTRACT

Implementing the most suitable treatment strategies and making appropriate clinical decisions about individuals with a first episode of psychosis (FEP) is a complex and crucial task, with relevant impact in illness outcome. Treatment approaches in the early stages should go beyond choosing the right antipsychotic drug and should also address tractable factors influencing the risk of relapse. Effectiveness and likely metabolic and endocrine disturbances differ among second-generation antipsychotics (SGAs) and should guide the choice of the first-line

treatment. Clinicians should be aware of the high risk of cardiovascular morbidity and mortality in schizophrenia patients, and therefore monitoring weight and metabolic changes across time is mandatory. Behavioral and counseling interventions might be partly effective in reducing weight gain and metabolic disturbances. Ziprasidone and aripiprazole have been described to be least commonly associated with weight gain or metabolic changes. In addition, some of the SGAs (risperidone, amisulpride, and paliperidone) have been associated with a significant increase of plasma prolactin levels. Overall, in cases of FEP, there should be a clear recommendation of using lower doses of the antipsychotic medication. If no or minimal clinical improvement is found after 2 weeks of treatment, such patients may benefit from a change or augmentation of treatment. Clinicians should provide accurate information to patients and relatives about the high risk of relapse if antipsychotics are discontinued, even if patients have been symptom free and functionally recovered on antipsychotic treatment for a lengthy period of time.

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## INTRODUCTION

Schizophrenia is a heterogeneous disorder with a worldwide lifetime prevalence among adults near 1% [1, 2]. The illness typically debuts in late adolescence or young adulthood, can affect personal, educational, social, and vocational skills, and ranks among the 20 leading global causes of disability worldwide [3]. Fortunately, and based on recent evidence, the conceptualization of illness outcome has progressively evolved to a more optimistic and inspiring perception of the illness with an expectation of functional recovery from the first episode [4, 5]. Imaging, clinical, and cognitive longitudinal data do not support the notion of a deteriorating course of the illness [6–10], which consequently raises legitimate expectations of living a normal life with mental illness. Systematic reviews of outcome studies have reported that 40–42% of people with a first episode of psychosis (FEP) have a good outcome [11, 12], although when more stringent criteria of functional recovery are used the rate drops to 13.5% long term [13].

Schizophrenia is unquestionably a potentially disabling and severe mental illness; however, an appropriate multidisciplinary and integrated treatment approach from the first episode can make a fulfilling and productive life and the achievement of full potential possible in spite of the limitations caused by the illness. “Recent-onset psychosis” has been previously proposed as a more accurate term for referring to individuals who have experienced a short duration of illness (e.g., 2–5 years) [14]. By contrast, the term “first episode psychosis” may include all subjects with a first treatment

contact, independently of the duration of the symptoms. It has been stated that there is a critical period of 2–5 years following onset of psychosis during which future trajectories of functional outcome may be set and when interventions are likely to have a maximum beneficial effect [15]. Recovery from a FEP has come into focus as the main goal of any treatment strategy. Many changeable factors such as clinical (medication adherence, treatment response) and psychotherapeutic treatments, psychoeducation about the illness, therapeutic alliance, support and recognition of the needs of the people with a FEP and carers, societal stigma, substance misuse, social and family support, and physical health may affect reaching this functional status [16]. Preventing relapse in the early stages of disease has become a major challenge due to its critical impact on life-long functionality [17]. Non-adherence to antipsychotic treatment and lack of insight into the illness are very frequent in people with a FEP [18]. Poor adherence to treatment is associated with an increased rate of relapse [19, 20]. Lack of insight promotes non-adherence to medication and leads to a poorer course of illness and functioning [21–23]. Either because clinicians are not always fully aware of these notions or because these ideas are not well understood and accepted by people in the early stages of the illness, achieving and maintaining good adherence to the prescribed treatment is a major clinical issue.

Implementing the most suitable treatment strategies and making appropriate clinical decisions about individuals with a FEP is a complex and crucial task, with associated impact on illness outcome. These beneficial effects seem to be more pronounced for those patients who received the proper comprehensive specialty care as early as

possible in the course of the illness [24]. Early detection and specialized intervention programs have been extensively implemented in the last decades for both individuals suffering a FEP and their carers, offering a wide range of pharmacological and psychosocial interventions according to their needs. Treatment approaches in the early stages should go beyond choosing the right antipsychotic drug to reduce acute psychotic symptomatology and should also address tractable factors influencing the risk of relapse, with the greatest challenge of accomplishing the long-term goal of functional recovery (to achieve their best premorbid functional level) in most of the individuals with a FEP. These conceptualizations and interventions should also be shared and assumed by clinicians dealing with FEP cases and working in non-specialized mental health clinical settings.

A number of previous publications have reviewed early intervention models or specific issues (i.e., side effects of antipsychotics or long-acting injectable antipsychotics) in the treatment of people with a FEP. However, there is a lack of updated reviews of the pharmacological treatment of people with a FEP, including use of novel antipsychotics that help clinicians to choose and manage these medications. This article aims to provide clinicians with practical recommendations on how best to manage people with a FEP. The selection of an antipsychotic in the first stage of the illness could be a highly relevant decision, with a direct impact on adherence to medication and acceptance of the illness, and therefore influence the course and the outcome of the illness. Advantages and disadvantages of currently widely used drugs to treat schizophrenia are outlined and discussed.

## METHODS

To obtain a fuller picture of the current best treatment of people with a first episode of non-affective psychosis a literature search (1966 up to December 2015), using the MEDLINE database, was conducted for English-language published reviews, meta-analyses, and clinical trials of first generation antipsychotics (FGAs), second generation antipsychotics (SGA), and newly approved antipsychotics. The following keywords were used: first episode psychosis, recent-onset psychosis, schizophrenia, non-affective psychosis, antipsychotics, neuroleptics, effectiveness, and side effects. The review is based upon studies carried out with adults as well as children and adolescents. We attempted to identify additional studies through searches of the reference lists of identified studies and reviews. Relevant data obtained from articles based on chronic schizophrenia samples were clearly identified and separately reported to avoid any misleading literature on first episode subjects.

This article is based on previously conducted studies and does not encompass new studies of human or animal subjects performed by any of the authors.

## AIMING FOR EFFICACY AND EFFECTIVENESS

Balancing risks and benefits of antipsychotic agents and, subsequently, increasing the likelihood of adherence to treatment is the real challenge in the treatment of FEP individuals [25]. Table 1 summarizes the advantages and disadvantages of the antipsychotic agents discussed in this review. The initial better tolerability of SGAs based on the diminished emergence of extrapyramidal

**Table 1** Characteristics and profiles of antipsychotics used in the treatment of people with a first-episode psychosis (FEP)

Antipsychotic	Minimum effective doses in FEP (mg/day)	Oral/long acting	Advantages	Disadvantages
Haloperidol and other FGAs	2 (haloperidol)	Several agents have long-acting injection forms	Overall efficacy in psychotic symptoms Best level of evidence	High risk of EPS, cognitive and depressive symptoms High risk of hyperprolactinemia Lower effectiveness compared to SGAs QTc prolongation (Haloperidol and other agents)
Olanzapine	5	Long-acting injection form available	High mid- and long-term effectiveness compared to other antipsychotics Low risk of hyperprolactinemia	Very high risk of weight gain Very high risk of lipid and glucose disturbances Risk of sedation
Risperidone	2	Oral and long-acting injection form available	High mid- and long-term effectiveness compared to other antipsychotics	Moderate risk of weight gain and lipid disturbances High risk of hyperprolactinemia Risk of EPS compared to other SGAs
Quetiapine	150	Oral	Efficacy in several symptomatic domains Low risk of hyperprolactinemia	Very high risk of weight gain Very high risk of lipid and glucose disturbances Sedation Probably lower effectiveness compared to other SGAs

**Table 1** continued

Antipsychotic	Minimum effective doses in FEP (mg/day)	Oral/long acting	Advantages	Disadvantages
Ziprasidone	80	Oral	Lowest risk of weight gain and neutral effect on glucose and lipids Low risk of hyperprolactinemia	Probably lower effectiveness compared to other SGAs QT prolongation
Amisulpride	400	Oral	Efficacy and effectiveness	High risk of hyperprolactinemia Limited evidence in first episode psychosis
Aripiprazol	10	Oral and long-acting injection form available	Low risk of weight gain and lipid and glucose disturbances Lowest risk of hyperprolactinemia Low risk of sedation	Risk of akathisia
Paliperidone	3	Oral and long-acting injection form available	Low risk of sedation	Moderate risk of weight gain and lipid disturbances High risk of hyperprolactinemia Risk of EPS compared to other SGAs Limited evidence in first episode psychosis
Clozapine	–	Oral	Greatest efficacy and effectiveness Efficacy in people with a FEP that do not respond to first-line antipsychotic treatment	Risk of weight gain and lipid disturbances. Agranulocytosis and cardiac risk Only for resistant patients
Other SGA agents	No data available from FEP samples			

*FGA* first generation antipsychotic, *SGA* second generation antipsychotic, *EPS* extrapyramidal symptoms

symptoms and tardive dyskinesia has led to the recommendation of SGAs as the first choice for the treatment of a first episode of schizophrenia

in almost all international guidelines for early psychosis [26, 27]. Presently it is widely accepted that there is not an obvious

difference between FGAs and SGAs in terms of efficacy in decreasing the severity of positive symptoms in schizophrenia [26]. However, SGAs have shown higher treatment effectiveness (lower rates of treatment discontinuation) compared to FGAs (findings primarily driven by haloperidol) in people with a FEP [28–31]. This higher discontinuation rate seems to be related not only to extrapyramidal symptoms but also to some other disadvantages of FGAs, as they may produce more secondary negative and cognitive symptoms [32]. Additionally, these negative effects do not seem to be homogeneous among different medications within the SGA group [33, 34].

The response rate to an initial antipsychotic trial is robust and thereafter the likelihood of response decreases notably [35]. It is erroneous to think that all SGAs are equally efficacious and effective [35]. Differences among SGAs in terms of effectiveness have turned out to be a topic of increasing clinical interest, although head-to-head comparisons between the different SGAs are scarce in real-world clinical practice. Crespo-Facorro and colleagues [34, 36, 37] observed that individuals on quetiapine were more likely to discontinue treatment after a first episode due to insufficient efficacy compared to those people treated with aripiprazole and ziprasidone. A higher risk of treatment discontinuation has been associated with quetiapine treatment during the early phases of treatment [18]. Kahn et al. [31] described no difference between quetiapine and ziprasidone in the rate of treatment discontinuation for any cause, although discontinuation because of insufficient efficacy was to some extent higher with quetiapine (40%) compared with ziprasidone (26%) recipients at 1 year. Inadequate and transient dopamine D2 receptor occupancy with quetiapine may lead to insufficient antipsychotic efficacy [38, 39].

Additionally, ziprasidone has been reported to be slightly less effective than other antipsychotics in the treatment of people with a first episode of psychosis [40]. In a sponsored investigation, there were no significant differences between olanzapine, risperidone, and quetiapine in clinical efficacy or rate of treatment discontinuation after 1 year [41]. Most of the medium-term randomized studies have shown similar rates of clinical response and all-cause treatment discontinuation in people with a FEP treated with other SGAs (risperidone, olanzapine, ziprasidone, aripiprazole, amisulpride) [28, 31]. Robinson et al. [33] showed a similar efficacy and effectiveness between aripiprazole and risperidone for the acute treatment of first-episode schizophrenia. Olanzapine might lead to longer treatment maintenance than haloperidol or ziprasidone in treatment-naïve people with a FEP [40]. Accordingly, Glick et al. have reported in a meta-analysis of medium and long-term effectiveness that olanzapine and risperidone appear to be the most effective antipsychotics in the treatment of schizophrenia and FEP [42].

In accordance with these findings, studies based on samples of people with chronic schizophrenia also pointed out that quetiapine and ziprasidone could be somewhat less effective than some other widely used SGAs. Quetiapine has been shown to be less effective than risperidone (24% dropouts due to inefficacy in the quetiapine group vs. 19% in the risperidone group, RR: 1.26) or olanzapine (70% dropouts due to any reason and 25% due to inefficacy in quetiapine vs. 57% and 14%, respectively, in the olanzapine group, RRs 1.22 and 1.8) [43]. When compared to olanzapine, subjects on ziprasidone had a RR of 1.26 of stopping medication due to any reason and of 1.57 of due to medication inefficacy [44]. Efficacy and

effectiveness in chronic schizophrenia does not seem to be significantly different among the rest of the SGAs [45, 46].

Differences in effectiveness among SGAs could help clinicians to avoid choosing the lesser efficacious antipsychotics as first line treatment.

## CARDIOMETABOLIC SIDE EFFECTS: SILENT LONG-TERM DAMAGE

In deciding among therapeutic options, clinicians need to be aware of the differential efficacy and safety of each agent. The choice by clinicians of which antipsychotic drug to use for first-line treatment of the illness is widely based on the profile of side effects that may put treatment alliance (at short-term) and physical health (at medium- and long-term) at risk. Drug-naïve subjects are at a higher risk of suffering antipsychotic side effects [47, 48]. Appearance of disturbing side effects and concerns over the long-term damage associated with antipsychotics are among the key factors that make individuals discontinue treatment once their acute symptoms have subsided after a first episode of psychosis [29, 49]. The risk of metabolic and endocrine disturbances differs among SGA drugs.

Clinicians should be aware of the high risk of premature mortality and lower life expectancy in people with schizophrenia, the increase in cardiovascular morbidity and mortality in FEP being a critical factor for this risk status [50]. Therefore, prevention of the development of cardiovascular risk factors (metabolic syndrome and obesity, lifestyle, physical inactivity, and unhealthy diet) from the first manifestation of the illness is crucial in an integrative treatment of psychosis [51]. Cardiovascular risk (weight or metabolic indices), however, seems to be similar

in untreated FEP individuals and healthy controls and noticeably increases after first-time antipsychotic treatment [52]. Antipsychotic medication, in particular SGAs, are related to marked weight gain and frequent metabolic side effects, largely in young people during early phases of the illness [53–55].

Weight gain may indirectly give rise to the development of other components of metabolic syndrome, and therefore be associated with distress, lower functional outcome and non-compliance with medication in individuals with chronic schizophrenia [56–58], and thus should ideally be prevented from the first manifestation of the illness. Even so, psychiatrists and patients should keep in mind that cardiometabolic disturbances might emerge without significant weight gain [59, 60].

Monitoring likely weight and metabolic changes across time is mandatory in FEP individuals who have just initiated antipsychotic treatment.

### Weight Gain

The first months of antipsychotic treatment represent the critical period for changes in weight [61, 62]. Longitudinal studies in drug-naïve subjects have shown that the percentage of obese (body mass index (BMI) >30) subjects increased from 5% to 32% and the percentage of overweight rose up to 65% at 3 years after the initiation of treatment with olanzapine, risperidone, or haloperidol [62]. Marked differences in likely weight gain exist among the different SGAs. Of clinical relevance is the fact that several reviews and studies have shown that olanzapine and clozapine are associated with a greater risk of weight gain and higher percentage of extreme weight gain (>7%) and aripiprazole and ziprasidone have a low risk of weight gain [52, 60, 63]. In a recent

study in drug-naïve individuals with a FEP, aripiprazole and quetiapine showed a significant increase in weight compared to ziprasidone [54]. Studies on drug-naïve subjects are in agreement with this statement, in particular during the first months of treatment [45, 64, 65]. The EUFEST study revealed that ziprasidone has a lesser effect on weight gain than quetiapine and olanzapine [31, 66]. Low doses of risperidone and aripiprazole show a similar pattern of weight gain during early phases of treatment in people with a FEP [33, 54].

Accordingly, aripiprazole and ziprasidone have shown lower liability for inducing weight gain and metabolic adverse reactions than olanzapine and risperidone in long-term schizophrenia populations [64, 67–69]. Furthermore, several studies have shown that switching from treatments with a high risk of weight gain to ziprasidone [70, 71] or to aripiprazole [72] is an effective strategy to reduce weight and improve metabolic outcomes in people with stable chronic schizophrenia or schizoaffective disorder. Finally, short-term, double-blind clinical trials comparing ziprasidone with placebo parameters [73, 74] or aripiprazole with placebo [75] in people with chronic schizophrenia or schizoaffective disorder have not found significant differences in their effects on metabolic variables.

The severity of weight increase, and therefore fatty change, is correlated with hepatic and cardiovascular toxicity. Thus, obesity is a risk factor for nonalcoholic fatty liver disease (NAFLD), which is the most common cause of liver disease in Western countries [76]. Overall, it has been described that 50% of people with a BMI >30 may suffer NAFLD. In a recent study, it has been demonstrated that over 25% of individuals with a FEP will develop liver

steatosis after 3 years of treatment (Morlan et al. 2015 submitted, personal communication). Because of the link between cardiometabolic risk, NAFLD, and antipsychotic medication, early detection in clinical practice of NAFLD development, based on non-invasive techniques, could be worthy of consideration, as these subjects should be considered for liver disease treatment and for monitoring and potential treatment of underlying cardiovascular risk factors [77]. It has been observed that individuals treated with olanzapine who gained a substantial amount of weight manifested significantly lower heart rate variability (a marker of high cardiovascular risk) [78].

In addition to physical disturbances, weight stigmatization and discrimination lead to important psychological stress that increases the risk for depression, low self-esteem, and body dissatisfaction in people with schizophrenia [79]. In the long term, weight gain may lead to poorer social and functional outcomes [80] and weight loss is linked to an improvement in social functioning [81] in people with schizophrenia.

Behavioral and counseling interventions including smoking cessation, dietary measures, and exercise might be partly effective in reducing weight gain and metabolic disturbances in early stages of treatment [82–84]. Nonetheless, the benefits of these lifestyle interventions do not seem to persist across time [85]. The preferential use of or switching to medications with a lower risk of weight and/or metabolic abnormalities is recommended [86].

### Glucose Metabolism

The risk of glucose intolerance and diabetes associated with antipsychotic treatments seems



to be increased in younger subjects [87]. After 3 years of antipsychotic treatment, insulin plasma levels and the HOMA index tend to increase in FEP individuals [62]. Olanzapine, clozapine, and quetiapine have been associated with more prevalent hyperglycemia independently of body mass in both drug-naïve [88] and chronic schizophrenia individuals [89, 90]. Higher levels of insulin and insulin resistance were associated with olanzapine treatment in patients with FEP or schizophrenia and in healthy normal-weight men [31, 91, 92]. Quetiapine treatment has also been shown to increase the risk of triglycerides to HDL-C ratio (a marker of insulin resistance) in FEP [50]. A critical factor to bear in mind by clinicians is the fact that type 2 diabetes might have an onset a median of 4 years after first antipsychotic treatment, although subjects on olanzapine had a shorter time to diabetes onset [88]. It has also been reported that olanzapine discontinuers did not have an increased risk of diabetes [88]. Higher antipsychotic dosages and male sex seem to be related to an increased risk for diabetes. Due to the close association between metabolic effects and the greater risk of diabetes, pre-diabetes or type 2 diabetes should be prevented or postponed by choosing as a first choice an antipsychotic with a lower cardiometabolic burden.

### Lipid Metabolism

After 3 years of antipsychotic treatment, a high proportion of FEP individuals may have been exposed to high plasma total triglyceride concentrations (up to 23%), low levels of HDL-C (23%), and a high total cholesterol/HDL-C ratio (29%) [62]. Olanzapine and quetiapine have shown the greatest effect on lipid status, whereas aripiprazole and ziprasidone have produced the lowest effects

on lipid levels in both FEP and chronic schizophrenia populations [32, 93]. Our group has described that after 12 weeks of treatment ziprasidone has a neutral effect on fasting plasma lipids and glucose [54]. Importantly, increases in dyslipidemia and triglycerides have been shown to be meaningfully associated with olanzapine treatment independent of weight gain in both FEP and chronic schizophrenia [94, 95]. In a recent study, Robinson and colleagues (2015) observed that cholesterol and LDL-C levels, but not triglycerides and HDL-C, were significantly less affected in individuals on aripiprazole compared to risperidone-treated FEP patients [33].

## ADDITIONAL RELEVANT ADVERSE EVENTS

### Prolactin-Related Side Effects

Hyperprolactinemia is considered to be a disturbing adverse effect of antipsychotic medication, although recent investigations have described that it might be also a pre-existing or stress-related condition, since it has been described in antipsychotic-naïve people with FEP [96–99] and in subjects with an at-risk mental state [96]. Antipsychotic medications differ in their propensity to induce hyperprolactinemia (for a review see Peuskens et al. [100]). Most FGAs have been associated with a pronounced elevation of prolactin levels in the treatment of FEP [30, 101], but some investigations in FEP have described no significant prolactin changes at long term associated with haloperidol treatment [31, 98]. Some of the SGAs are considered prolactin-sparing antipsychotics and quetiapine, ziprasidone, olanzapine, clozapine, and aripiprazole are less likely to induce sustained hyperprolactinemia

[31, 39, 54, 98, 102], but others have been associated with significant increases in plasma prolactin levels, and thus are considered to be prolactin-elevating antipsychotics – risperidone, amisulpride, and paliperidone [31, 101]. Nonetheless, clinicians should be fully aware that 40% of the subjects on *prolactin-sparing* antipsychotics might exhibit hyperprolactinemia. Plasma prolactin level elevations with antipsychotic drugs are generally dose dependent [100].

Many patients with elevated prolactin levels are asymptomatic, and others may not report symptoms unless specifically questioned [103]. Sustained elevation of prolactin may cause amenorrhea, galactorrhea, hirsutism, gynecomastia, impotence, loss of libido, and infertility in the short term. Long term hypogonadism due to hyperprolactinemia may lead to osteoporosis and hip fracture [100]. The expected utility of switching to or adding aripiprazole to rapidly decrease elevated prolactin levels induced by prolactin-elevating antipsychotics has been described in samples of patients with chronic schizophrenia [104, 105].

Antipsychotic-associated hyperprolactinemia is the most common cause of elevations in prolactin levels in individuals with schizophrenia, but additional appropriate investigations may also be warranted for those individuals with persistently elevated prolactin levels [106]. Clinicians should consider reducing the antipsychotic dosage or switching to an antipsychotic drug with a lower potential to elevate prolactin in cases of hyperprolactinemia.

### Sedation

Sedation is a common and unpleasant adverse effect of both FGAs and SGAs [18], with young

subjects seemingly more affected by somnolence and hypersomnia than older adults [107, 108]. Given that sedation-related side effects may particularly cause discomfort and daytime dysfunction, this effect may lead to patients becoming non-adherent to treatment in patients with schizophrenia [109]. Some clinicians may regard sedation as a helpful effect during an acute episode for addressing symptoms such as insomnia and agitation and may use antipsychotics with sedative effects, antipsychotic combinations or higher doses in order to obtain sedation. However, in a phase-specific treatment, sedation may no longer be needed and should be closely monitored and prevented, including the reduction of antipsychotic doses, avoiding polypharmacy, or switching the antipsychotic [110]. Leutch et al. showed evidence that clozapine and chlorpromazine are associated with higher sedation, and amisulpride and paliperidone certainly produce less sedation in the treatment of individuals with schizophrenia [111].

## OTHER KEYSTONE ASPECTS IN THE TREATMENT OF FIRST-EPIISODE INDIVIDUALS

### What are the Recommended Doses at Early Phases?

Young people suffering from a first episode of psychosis seem to be highly responsive to low doses of antipsychotics and more susceptible to extrapyramidal side effects and to acute weight gain [112, 113]. In the last few decades, chlorpromazine doses in people with schizophrenia and other psychoses have been gradually reduced and this has probably led to less extrapyramidal side effects [114]. A clear

limitation when establishing the lower effective antipsychotic dose in the FEP population is that available dose-equivalency methods for antipsychotics are not applicable to FEP [115]. Additionally, people with a FEP are more likely to respond to lower doses of antipsychotic medications and treatment should be started at the lower half of the recommended dosage range for multiple episodes (300–500 mg chlorpromazine equivalents per day) [116]. There is a clear recommendation for using lower doses of antipsychotic medications in cases of FEP [27, 116, 117]. Previous studies assessing the efficacy of antipsychotics in FEP have evaluated the efficacy of lower doses. The mean modal doses of risperidone have ranged from 2.4 to 4 mg/day [41, 101, 118, 119], and of olanzapine from 9.1 to 12.6 mg/day [31, 41, 120]. Minimum effective doses of 2 mg of haloperidol [121] or lower and 2 mg of risperidone [120] have been previously reported in FEP. As an example, in our cohort, FEP was effectively treated with initial modal doses at 6 weeks of 5 mg of haloperidol (range 3–9 mg/day), 4 mg of risperidone (3–6 mg/day), 15 mg of olanzapine (5–20 mg/day) [49], 15 mg of aripiprazole (5–20 mg/day), 80 mg of ziprasidone (40–160 mg/day), or 300 mg of quetiapine (100–600 mg/day) [36]. In a recent investigation Robinson et al. used mean daily doses of 14.8 mg for aripiprazole and 3.2 mg for risperidone [33]. Even with a “start low, go slow” model, given that people with a FEP require low doses, they may be treated with effective doses from the first week and the antipsychotic rapid titration should allow adjusting doses to avoid side effects.

Although doses may be reasonably increased within the therapeutic range if a clinical response is not obtained, an increase in the

antipsychotic dose is less likely to be successful in FEP, so using high antipsychotic doses is discouraged [35].

It has been suggested that the long-term use of antipsychotics may lead to a dopaminergic supersensitivity state, caused by an upregulation of the dopamine receptors [122] that would predispose patients with psychosis who receive longer and higher doses to relapse. However, studies that have tried to test this theory have failed to prove it, as they did not find differences according to medication type withdrawn or tapered [123].

#### **How Long Should Clinicians Wait Before Switching an Initiated Antipsychotic Drug in Cases of Lack of Efficacy?**

According to international treatment guidelines, there is uncertainty about the recommended time clinicians should wait before switching medication, suggesting an initial trial of “appropriate doses” of antipsychotics from 2 to 6 weeks according to current guidelines [124, 125]. The risk-benefit assessment clearly favors switching antipsychotics when a given medication is clearly ineffective. Nevertheless, clinicians, before making the decision to switch, should ensure that treatment with the pre-switch antipsychotic was optimized in terms of adherence and dose [126]. In a recent meta-analysis, Samara et al. reported that people with schizophrenia who did not even minimally improve at week 2 of treatment with sufficiently high doses are unlikely to respond later and therefore may benefit from a change or augmentation of treatment. Ninety percent of subjects who do not show a minimal response (20% reduction in the PANSS/BPRS score) at the 2-week assessment will not show

clinical improvement at week 6 [127]. Although the application of these results seems to be more appropriate for people who are not in their first episode of schizophrenia, they emphasize the need for a rapid titration model in order to achieve an adequate dose during the first days of treatment. Additionally, clinicians dealing with FEP individuals should be fully aware of the necessity of switching or implementing augmentation treatment strategies early in the course of the antipsychotic treatment to avoid unnecessary long-term exposure to an antipsychotic that is very unlikely to be helpful. Lack of clinical efficacy is among the reasons that might prompt people with an FEP to treatment discontinuation [19]. Strategies for switching have been previously poorly studied in an attempt to make an accurate recommendation, but the future results of two ongoing trials, SWITCH and OPTiMiSE, should help decision making and provide a basis for clinical guidelines. In a previous finding, Agid et al. [128] described only a 20% responsiveness among subjects who did not respond to the first-line antipsychotic drug, whereas the efficacy rate of clozapine in these nonresponsive subjects was 75%; therefore early after a lack of response, a second antipsychotic trial and then the use of clozapine may be indicated when other issues such as adherence or co-morbidity have been addressed [27, 125].

Likely problems in switching antipsychotics in the treatment of schizophrenia such as the risk of discontinuation reactions and the re-emergence of psychotic symptoms have been traditionally described [129, 130]. Thus, overall patients should be monitored carefully throughout the switch procedure for any discontinuation effects or new side effects

[131, 132]. More frequent contacts might be needed during the switching process in order to reassure the patient and to monitor for side effects and discontinuation problems [133, 134].

As with individuals with several episodes, using antipsychotic polypharmacy is discouraged due to a lack of proven efficacy and a higher risk of side effects [125, 135]. Importantly, co-morbid symptoms such as depression, anxiety, suicide risk, and substance misuse must be correctly diagnosed and treated in order to avoid early refractoriness, lack of remission, and relapse [27, 125]. Subjects who not respond to the first antipsychotic trial after a few weeks have a low response rate thereafter. Addressing co-morbidity must include not only choosing the appropriate antipsychotic medication but also offering adequate psychosocial interventions such as cognitive behavior therapy (CBT) or treating associated problems such as substance abuse [136, 137]. CBT has been reported as a useful treatment for schizophrenia in several reviews [138–141], particularly in the treatment of persistent positive symptoms as part of a combined therapy. This has led to the inclusion of CBT into services and recommendations of treatment guidelines for people suffering psychotic disorders, including a FEP [27, 125]. Moreover, CBT seems to be helpful in improving other symptoms such as negative symptoms, functioning, mood, and social anxiety [142–145]. However, Jauhar et al. described in a meta-analysis of CBT effectiveness for symptoms of schizophrenia that pooled effect sizes were in the “small” range for all the classes of symptoms considered (pooled effect size of  $-0.33$  for overall symptoms;  $-0.25$  for positive symptoms;

negative sign favors CBT) [146]. Previous recent meta-analyses by Wykes et al. had described higher levels of effectiveness that were in any case modest (i.e., pooled effect size of  $-0.37$  for positive symptoms, pooled effect size of  $-0.44$  for negative symptoms) [147]. With regard to substance misuse, integrated CBT and motivational interviewing have been used with the aim of reducing the use of substances and reduce subsequent relapses in a FEP; however, results of these interventions are not clearly consistent [137, 148–150]. Although there are some ongoing trials evaluating the specific efficacy of CBT and motivational interviewing in reducing the use of some substances such as cannabis [151], it is possible that the benefits of these psychosocial interventions are best reflected in their effects on symptomatic outcomes rather than in a reduction of substance use or relapse prevention, and therefore the appropriate strategy may be to address associated problems rather than the substance use per se [137]. CBT for psychosis (CBTp) cannot be considered as a global brand because not all approaches are the same. It is now highly recommended that choosing the most appropriate CBTp should take into account patient-defined goals and critical targets and the types of individuals who can benefit from therapy [152].

### **How Long Should Patients be Maintained on Antipsychotic Medication After Recovering from a First Episode?**

In clinical practice, due to the lack of insight into the prophylactic effects of drugs, emergence of disturbing side effects, and concerns over the long-term harm associated with antipsychotics, it is unlikely that patients will accept an indefinite treatment after a single episode of psychosis [20]. However, stopping

antipsychotic medication has been repeatedly demonstrated as the biggest predictor of relapse after a first episode [153–155]. Wunderink et al. [156], exploring people that remitted after a FEP, observed that relapse rates were two times higher in individuals who gradually tapered or discontinued medication and only 20% of subjects could be successfully discontinued. Strikingly, those patients with an earlier reduction or discontinuation treatment strategy appear to have long-term functional gains compared with individuals who maintained treatment [157, 158]. In a recent investigation, Mayoral-van Son et al. [20] described a high risk of symptom recurrence after antipsychotic treatment discontinuation in individuals who had accomplished a functional recovery after a single psychotic episode. Moreover, those relapsed individuals had a greater severity of symptoms and lower functional status after 3 years. The profile of individuals who would benefit from treatment discontinuation, and the optimal duration of prophylactic antipsychotic medication remain unclear. The lowest effective-dose regimen is highly recommended [20, 154] and a trial off antipsychotic medication is not to be recommended [159]. Clinicians should provide accurate information to people with a FEP (and relatives) about the fact that even if they have been symptom free and functionally recovered on antipsychotic treatment, the risk of relapse is still likely to be high if antipsychotics are discontinued [160]. Despite these clear statements, numerous individuals may still be disposed to discontinue medication after recovering from their single episode of psychosis and, therefore, a planned medication withdrawal strategy with a systematic follow-up should be established in first-episode programs to prevent unrestrained treatment discontinuation.

### What Else Can Clinicians do to Increase Treatment Adherence during Early Phases of the Illness?

Independent of the initial high response rate after a FEP, during follow-up of the illness, the relapse rates are high, being up to 83% 5 years after the FEP [153]. Persistent substance use disorder, carer criticism, poorer premorbid adjustment, and, particularly, medication nonadherence (a fourfold risk) may significantly increase the risk for relapse in FEP [161]. In a previous report analyzing a subsample of 140 first episode individuals, we observed a similar relapse rate of 65% at 3 years after the first break of the illness, being adherence to antipsychotic treatment the only significant predictor for relapse [155]. Therefore, in order to prevent relapse, the best way would be to improve adherence and to reduce other avoidable risk factors such as substance use or carer criticism. A basic strategy that may help clinicians improve their patients' adherence includes improving prescriber-patient communication. The clinician should listen to the patient, understand his or her perspective, beliefs and concerns about the illness and treatment, and should provide information regarding potential effectiveness, side effects, and formulations in order to get the patient involved in decisions about their medications [162]. The use of psychosocial treatments, including psychoeducational interventions, CBT, and individual and family interventions, may specifically improve adherence and must be offered in combination with antipsychotic treatment in order to prevent relapses in patients with a FEP [163]. Finally, after the evaluation of adherence and associated risks and the provision of adequate medication, psychoeducation and long-acting injectable (LAI) antipsychotics should be

offered in order to improve outcome in selected subjects [164, 165]. The use of LAI antipsychotics has been traditionally restricted to people who are noncompliant and who have a history of multiple relapses, and FEP is rarely treated with depot medications [166]. Early introduction of LAI therapy in FEP has been associated with a short-term adherence benefit [167]. However, subsequent follow-up of the same cohort did not reveal differences between patients treated with LAI therapy and patients with oral antipsychotics in time to initial non-adherence at 104 weeks [168]. Although more well designed, randomized, controlled clinical trials using SGA LAIs exploring effectiveness and likely long-term side effects are warranted, LAIs should be given due consideration in early phases treatment of based on their benefits with regard to adherence [169]. In a recent review of the literature on the use of LAIs in first-episode and early schizophrenia, Taylor and Ng concluded that LAIs are useful in reducing symptom severity and the risk of relapse, particularly if they voluntarily accept LAI therapy [170]. Ironically, clinicians are often reluctant to offer LAIs in early phases and tend to overestimate potential objections by patients [171].

After obtaining a clinical response, accomplishing symptomatic and functional remission is one of the major objectives of treating individuals with a FEP, with a final objective of functional recovery. In 2005, the Remission in Schizophrenia Working Group published the most widely accepted criteria to define remission in schizophrenia [172]. This concept includes the remission of positive psychotic, disorganized, and negative symptoms to a severity of mild or less, but also a minimum duration time for this remission of 6 months, and has been used in

FEP. Rates of remission vary widely in different studies and most of them do not provide duration criteria [173]. As an example, after a 1-year follow-up, only 31% of the initial subjects enrolled in the PAFIP program achieved remission [174], in particular due to persistence of negative symptoms or to relapse in the last 6 months, which seem to be related to duration of untreated psychosis and premorbid functioning. Remission is closely related to functional recovery, although symptomatic remission rates tend to exceed functional recovery rates [173]. The best ways to achieve remission after improving initial symptoms seem to be preventing relapses and also detecting and treating secondary negative symptoms as early as possible. Additionally, vocational interventions have been recognized to be beneficial to achieve better functional outcomes [175].

### **What Can we do to Help and Support Families and Caregivers of Individuals Dealing with a First Episode?**

One of the main objectives of FEP programs and early intervention services is to engage with both people with psychosis and their family and to facilitate support. However, until recently, most of the effort has gone into studying, recognizing, and reducing expressed emotion (EE) and its components – critical comments (CC) and emotional over-involvement (EOI) – due to its potential prediction of relapse and symptom exacerbation in schizophrenia. Given that a large majority of people during their FEP live at home with their families, these informal caregivers are affected by a stress-appraisal-coping framework [176]. This would mean that the extent to which the stressors are related to the relative's or

caregiver's negative health is related to his/her appraisal (or subjective evaluation) of the stressor and his/her ability to cope with them. Apart from family interventions, basically aimed at preventing or reducing relapses, psychoeducation and support groups have been developed to improve the experience of caring for people with mental illness, and particularly may be recommended to families and caregivers of people with FEP and severe mental disorders [177]. The role of FEP programs and early intervention services is to detect the needs of the families and caregivers and give sustained appropriate communication and support, in order to improve their experience of caring and reduce associated stress.

### **New Second Generation Antipsychotics: Future Options for First-episode Treatment**

Although the antidopaminergic mechanism (need for D2R blockade) is still essential in the development of new antipsychotics, the investigation of new atypical antipsychotics has focused on either compounds with a broader spectrum of clinical benefits through dual dopaminergic and serotonergic properties – “*serotonin-dopamine activity modulators*”– (e.g., partial agonism of D2R with enhanced affinity for specific serotonin receptor analog of aripiprazole) or exploiting less examined mechanisms (e.g., cholinergic, histaminergic, GABAergic, modulation of glutamate); for a review see Zajdel et al. [178]. Brexpiprazole, with structure, properties and uses that are most similar to those of aripiprazole, has recently exhibited good tolerability, with a lower incidence of akathisia than aripiprazole [179]. Initial animal studies with cariprazine, a potent D3/D2 receptor partial agonist with favored binding to D3

receptors, seem to point out it could be a better treatment option for patients with persistent and predominant negative symptoms [180]. The long half-life of cariprazine's principal active metabolites and the steady-state levels of cariprazine and metabolites within 4 weeks are pharmacological characteristics that may minimize the impact of missing doses on plasma levels [181]. Significant improvement in hostility has been also observed in cariprazine- versus placebo-treated patients [182]. Iloperidone shares a high affinity for both D2 and 5HT2A receptors, with a unique receptor-binding profile that includes a very strong affinity for the noradrenergic alpha 1 (NEa1) receptor [183]. It is a well-tolerated antipsychotic with a very low propensity to cause either akathisia or antipsychotic-induced extrapyramidal symptoms [184]. Lurasidone exerts a potent antagonism toward the dopamine D2, and the 5-hydroxytryptamine (5-HT, serotonin) receptors: 5-HT2A and 5-HT7 [185]. Apparently lurasidone is less efficacious than clozapine, risperidone, paliperidone, olanzapine, and amisulpride, with a lower risk of sedation and body mass increase [111, 186]. However, subjects treated with lurasidone exhibited higher rates of akathisia, parkinsonism, and hyperprolactinemia compared to several other atypical antipsychotics. To the best of our knowledge none of the above new SGAs have been studied in first-episode cohorts to date.

## CONCLUSION

Treating individuals with a FEP is a complex and crucial task, with important impact on illness outcome. The selection of antipsychotic at the first episode of the illness is an important decision, with a direct impact on adherence to

medication and acceptance of the illness, and therefore influencing the course and the outcome of the illness. It is erroneous to think that all SGAs are equal in terms of effectiveness and risk of side effects. Clinicians need to be aware of the potential efficacy and safety of each antipsychotic in order to choose the most appropriate drug for the needs of individual patients. Monitoring likely weight and metabolic changes across time is mandatory in individuals who have just initiated antipsychotic treatment. Intervention strategies in early stages should certainly go beyond choosing the proper antipsychotic and should also tackle tractable factors influencing adherence to treatment and risk of relapse, with the aim of accomplishing the long-term goal of functional recovery. Clinicians should provide accurate information to patients with a FEP and their relatives about the risk of relapse if antipsychotics are discontinued, and assess the needs of the families and caregivers in giving support in order to improve their experience of caring and reduce associated stress.

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