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Research report

Pharmacotherapy challenges in patients with first-episode psychosis

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ABSTRACT

The first episode of a psychotic disorder typically occurs in late adolescence or young adulthood, a critical time of development with respect to personality, social role, education, and vocation. The first few years of psychosis appear to be a critical period during which intervention needs to be initiated before the consequences of psychosis become more severe. Early intervention is therefore crucial in maximizing outcomes. Although response rates to antipsychotic medication in first-episode psychosis (FEP) are good, there is a relatively high risk of relapse. The greatest challenges that physicians face in treating FEP and preventing relapse are engaging patients in treatment and preventing non-adherence to therapy. Overall rates of non-adherence to antipsychotic medications for FEP patients are estimated to be at or higher than 50% within the first year of treatment, suggesting that malleable factors linked to non-adherence need to be targeted in interventions provided. Factors influencing adherence can be categorized into four groups: (1) environment-related, (2) patient-related, (3) medication-related, and (4) illness-related. This paper will review the factors associated with adherence and discuss solutions to optimize engagement, adherence to medication, and treatment in order to prevent relapse. Factors like social and family support, therapeutic alliance, attitudes and beliefs toward illness and medication, insight, substance use disorders, medication efficacy, tolerability, and accessibility will be discussed. Solutions, such as early psychosis specialized services integrating psychosocial therapies and careful selection of appropriate antipsychotic medication, will be proposed.

1. Introduction

The first episode of a psychotic disorder typically occurs in late adolescence or young adulthood. More than 40% of cases, however, have their onset in adolescence between the ages 15 and 18 (Ballageer et al., 2005), a critical time of development with respect to personality, social role, education, and vocation (Patel et al., 2007; Redmond et al., 2010). The symptoms of psychosis (e.g., hallucinations, delusions of persecution) can be very traumatic at this stage in life and may lead to increased psychological and physical risks for the person, including increased risk of suicide (Jackson et al., 2004; Mueser et al., 2010; Payne et al., 2006). Further, certain consequences of seeking and receiving treatment (e.g., police involvement, involuntary hospitalization, the use of seclusion or restraints in the hospital, and being forced to take medication against their will) can add to this trauma. Patients often feel afraid, confused, worthless, ashamed, and depressed, increasing their social isolation (Kilkku et al., 2003). Family and caregivers can feel distressed and anxious about the patient's unpredictable and, at times, aggressive behavior, constituting part of the burden associated with caring for a loved one with a mental illness (Addington et al., 2003a; Tennakoon et al., 2000). The maximum impact of psychotic disorders occurs in the first few years following onset through continued vulnerability to repeated episodes in the first few years (Robinson et al., 1999). Studies have shown that 2-year

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outcomes predict long-term outcome (Abdel-Baki et al., 2011; Harrison et al., 2001). The first 2 to 5 years of the illness, therefore, seem to be a critical period during which treatment should be initiated before the consequences of psychosis become more severe (Birchwood et al., 1998). Based on this and strong evidence that delay in treatment of psychosis is associated with a poor outcome (Marshall et al., 2005; Norman and Malla, 2001), a specialized early intervention (SEI) approach to first-episode psychosis (FEP) has been regarded as the best practice in this phase of illness (Marshall and Rathbone, 2011; McGorry et al., 2008). This approach has clear advantages compared to routine care (Crumlish et al., 2009; Harvey et al., 2007; Murphy et al., 2009; Petersen et al., 2005; Yap, 2010) and may be particularly relevant for those patients with onset during adolescence as they seem to encounter even longer delay in the treatment of their psychosis (Ballageer et al., 2005).

Most patients with first-episode psychosis (82%) respond to antipsychotic medication within 2 years (Malla et al., 2006), with more than half of individuals experiencing remission of psychotic symptoms within the first 3 months of initiating treatment, about 75% experiencing remission within the first 6 months, and up to 80% experiencing remission at 1 year (Addington et al., 2003b; Cassidy et al., 2010; Lieberman et al., 2003; Tohen et al., 2000; Whitehorn et al., 2002). Although response rates are good, patients face a high risk of relapse (80%) especially in routine care. This high relapse rate is associated primarily with non-adherence to medication (Robinson et al., 1999) and substance abuse (Malla et al., 2006). Early intervention for psychosis services try to prevent decline in social functioning and development of resistance to treatment by offering a whole range of psychosocial and pharmacologic interventions (International Early Psychosis Association Writing Group, 2005). One of the goals of SEI services is to educate youth and their families in the early stages of disease about the importance of medication adherence, the strongest predictor of relapse (Gearing et al., 2009; Malla et al., 2010).

2. Non-adherence to medication

Patients' non-adherence to medication poses the greatest challenge in the treatment of FEP. For first-episode patients, overall rates of non-adherence to antipsychotic medications are estimated at over 50% within the first year (Coldham et al., 2002; Mojtabai et al., 2002; Rabinovitch et al., 2009), increasing dramatically within the first 3 to 6 months (Kampman et al., 2002; Novak-Grubic and Tavcar, 2002; Verdoux et al., 2000). Rates of treatment discontinuation, the ultimate form of non-adherence, are estimated at 20 to 57% (Gaebel et al., 2002; Kamali et al., 2006; Linden et al., 2001; Novak-Grubic and Tavcar, 2002). Poor adherence is associated with an increased risk and rate of relapse (Coldham et al., 2002; Perkins et al., 2008), increased number of voluntary and involuntary admissions (Verdoux et al., 2000), greater levels of residual positive symptoms (Coldham et al., 2002), poor quality of life (Coldham et al., 2002), poor social relations, poor activities of daily living (Malla et al., 2002) and increased costs to society (Hill et al., 2010; Novick et al., 2010). Moreover, non-adherence is associated with other factors such as continued substance abuse, depression, treatment response failure, higher baseline cognitive performance, reaching remission status, adverse side effects, less family support, poor therapeutic alliance, and lower insight (Coldham et al., 2002; Perkins et al., 2008; Robinson et al., 2002). These results suggest that efforts should be made to target relevant risk factors in patients with schizophrenia to improve medication adherence.

Kane (2007) maintains that clinicians should have 4 goals in the treatment of patients with psychosis. These goals are (1) bringing about symptomatic response, (2) preventing relapse, (3) achieving remission, and (4) attaining functional recovery and rehabilitation in a social role. Through careful management of treatment strategies and assessment of patients' progress, clinicians can optimize treatment to reach these goals. This can be more difficult in adolescent patients whose symptoms may be more severe than those observed in adults, whose diagnosis is often less clear and whose personality development has been interrupted or retarded by illness process (Masi and Liboni, 2011; Rabinovitch et al., 2009; Werry et al., 1994).

To achieve these treatment goals, clinicians need to address at least the more malleable factors influencing non-adherence such as social and family support, therapeutic alliance, attitude toward medication, substance misuse, medication efficacy, tolerability, and accessibility. They can be categorized into four groups: (1) external or environment-related factors (which include factors related to family, friends, and treating team), (2) patient-related factors, (3) medication-related factors, and (4) illness-related factors (Fenton et al., 1997; Velligan et al., 2009).

2.1. Environment-related risk factors for non-adherence

2.1.1. Social and family support

Social and family support in achieving adherence to medications very early in the course of treatment of FEP may decrease the risk of relapse, improve adherence, and reduce re-hospitalization (Coldham et al., 2002; Pharoah et al., 2010). Rabinovitch et al. (2009) reported that the level of social and family support, as rated by case managers, was a significant predictor of adherence at 6 months ($OR = 3.552$, $p = 0.03$).

The patient's family's beliefs about mental health, treatment, and especially about mental illness influence the patient's attitude toward his illness and treatment (Franz et al., 2010; Lester et al., 2011). Our clinical experience shows that some patients and their family members feel they should allow “natural healing” to take place and are reluctant to try medication. A patient's or his/her family's attitude toward treatment may also be influenced by a history of mental illness in the family or by personal experiences with family members who are mentally ill (Lopez, 1991; Riana et al., 2008). Fear of stigma and concerns about the impact of mental illness on the patient's self-esteem and identity are sources of worry for family members (Iyer et al., 2011). Some patients and their families cannot accept the diagnosis of mental illness or hide the illness because they are afraid of the patient being stigmatized (McCann et al., 2011). This may lead to a patient being unwilling to take their medication, because they fear that family and friends might be aware of their mental illness, resulting in non-adherence.

2.1.2. Therapeutic alliance

A positive therapeutic alliance is known to be associated with better adherence to antipsychotic medication (Day et al., 2005; Lacro et al., 2002; Tunis et al., 2007; Weiss et al., 2002). Frank and Gunderson (1990) demonstrated that the development of therapeutic alliance with young adults in the early treatment phase for schizophrenia was difficult and required considerable time (only 14.2% had a good alliance after 1 month and 29.8% at 6 months). It did not improve during the next 6 months, indicating that if therapists do not secure a good alliance within the first 6 months, the odds of their subsequently doing so were low. Moreover, the results of their study demonstrated that after 2 years, patients were significantly more likely to remain in psychotherapy, comply with their prescribed medication regimens, and achieve better outcomes when they formed good alliances with their therapists compared with patients who formed poor alliances in the first 6 months of treatment.

Misdrahi et al. (2009) developed a 4-Point Ordinal Alliance Scale (4PAS) as a tool for clinicians to easily assess therapeutic alliance and to help identify patients at risk for poor adherence. Analysis of patients' responses on the 4PAS identified two factors related to therapeutic alliance as being strongly linked with patients' adherence. The first with the strongest association referred to the general positive perception of the relationship between patient and clinician and reflected empathy experienced by the patient. The second factor referred to the patient's positive perception that his/her disease was being satisfactorily managed by the physician.

Youth-friendly, easily accessible clinics are likely to strengthen the patient's positive perception of treatment and help in building a good therapeutic alliance (Singh and Merino, 2008). Above all, if the patient and physician can share beliefs about illness, need for treatment and a treatment strategy, a good therapeutic alliance is very likely. Often the first contact with health care services influences the patient's attitude toward and acceptance of treatment. Pathways to care in FEP are complex and diverse, with the largest proportion of patients having first contact with a physician, and emergency services being the referral source for the greatest proportion of patients (Anderson et al., 2010; Singh and Grange, 2006). Unfortunately, in the actual health care systems, patients have to make many contacts with health professionals before they get appropriate care for an FEP, many months after their first contact (Anderson et al., 2010; Norman et al., 2004). Early identification of FEP, which can be optimized by education of general practitioners, assertive outreach, low-threshold detection teams and general information campaigns, can help to avoid traumatizing first contact with the health care system and reduce the duration of untreated psychosis (Larsen et al., 2009; McGorry, 1992). Continuity of care by the same team and ideally the same persons in the different mental health treatment settings (e.g., hospital ward, ambulatory services, emergency) also improves therapeutic alliance in this phase of treatment when trust is still poor. These results demonstrate the importance of a clinician's empathy toward the patient, a good therapeutic alliance between the clinician and the patient, and family involvement and a youth-friendly treatment environment to achieve positive treatment outcomes. All of these factors are malleable and should be given particular attention.

2.2. Patient-related risk factors for non-adherence

2.2.1. Patient attitude toward medication

Patients experiencing their first episode of psychosis may perceive the risks and benefits of treatment differently from their physicians or from patients who have experienced repeated non-adherence to medication, subsequent relapses, and multiple psychotic episodes (Gearing et al., 2009; Robinson et al., 2002). Partial clinical improvement may be disappointing to young patients who hope for improvement of social and vocational functioning (work or studies) and complete elimination of symptoms (Misdrahi et al., 2009). Moreover, adolescents may be less tolerant of the physical adverse effects of antipsychotics (e.g., sexual dysfunction, sedation), leading to treatment discontinuation (Nasrallah et al., 2005). Adolescents are also at risk for discontinuing their treatment because they are afraid of the stigma of mental illness, have a generally oppositional attitude toward adults (e.g., parents, physicians), are likely to be more impulsive, and impatient if the treatment is complicated or does not improve their symptoms quickly enough (Gearing et al., 2009; Nasrallah et al., 2005).

The Health Belief Model Framework for Antipsychotic Adherence takes into consideration factors other than health beliefs that may influence patients' adherence (e.g., socioeconomic status, cultural factors, and previous experiences). According to this model, two factors play a critical role in the acceptance of medication (Lacro et al., 2002). First, the patient must recognize the need for treatment (i.e., must perceive his/her vulnerability to illness and the severity of illness), and secondly, the patient must believe that the benefits of treatment outweigh the perceived risks. This model may be particularly relevant for the initiation of drug therapy for first-episode psychosis where a patient's negative attitude toward medication is associated with non-adherence to treatment (Baloush-Kleinman et al., 2011). Mutsatsa et al. (2003) determined that a negative attitude toward medication is more strongly linked to non-adherence than the impact of side effects of the same medication. Consistent with the health belief model, the severity of the illness strongly influences the FEP patients' perception of the benefit of medication, and young people who have recovered from their FEP associate medication use with feeling much better (Charach et al., 2008).

Perkins et al. (2006) examined the relationship between antipsychotic medication non-adherence and patients' beliefs about the need for treatment, the benefits of treatment, and the negative aspects of treatment in FEP patients. Patients who did not believe in the need or the benefit of treatment were most likely to be non-adherent to medication. Baloush-Kleinman et al. (2011) determined that the patients' awareness of the need of medication, social consequences, perceived trust in physician and severity of negative symptoms predicted a positive attitude toward medication which in turn predicted adherence. These findings were supported by a 4-year follow-up study in FEP patients (Hill et al., 2010). These results suggest that psychological interventions should target patients' beliefs about the need for treatment

and the benefits of medication to improve long-term patients' adherence to antipsychotic medication. Currently, there is no clear evidence to suggest that psychological interventions targeting compliance benefit patients with FEP. Some studies report that therapy can improve compliance with drug treatment in psychotic inpatients and enhance overall functioning, with gains persisting for at least 6 months (Kemp et al., 1996, 1998), while other studies demonstrate no significant effects from compliance therapy (Byerly et al., 2005; Ilott, 2005; McIntosh et al., 2006; O'Donnell et al., 2003).

2.2.2. Insight

Insight is a multifactorial and multidimensional concept comprising "awareness of having a mental disorder, awareness of the need of treatment, understanding the social consequences of the disorder, awareness of specific signs and symptoms of the disorder, and attribution of symptoms to the disorder" (McEvoy et al., 2006; Parellada et al., 2011). Insight may change over time and is frequently deficient among patients with psychosis (McEvoy et al., 2006; Wiffen et al., 2010). In FEP patients, reduced insight is associated with medication non-adherence (Lepage et al., 2010) and is the best predictor of non-adherence in patients who do not abuse alcohol or other drugs (Kamali et al., 2006). Lepage et al. (2010) demonstrated a significant association between insight and medication adherence, and that improved insight after 6 months of treatment was more strongly associated with adherence than at onset of treatment. Poorer level of insight also predicts non-adherence to cognitive–behavioral therapy in adolescents and young adults with first-episode psychosis (Álvarez-Jiménez et al., 2009). Therefore, investigators have attempted to identify factors that contribute to insight deficiency (Nosé et al., 2003). Less insight was associated with higher Positive and Negative Syndrome Scale (PANSS) scores, younger age, less treatment adherence, and poor cognitive functioning (Lepage et al., 2008; McEvoy et al., 2006).

2.2.3. Cannabis and substance abuse

Substance abuse is a robust risk factor for patients' non-adherence to treatment (Kamali et al., 2006; Lacro et al., 2002; Nosé et al., 2003; Perkins et al., 2008), with cannabis and alcohol use featuring prominently in first-episode patient populations worldwide (Tucker, 2009). Given that both psychosis and substance abuse show onset in adolescence or early adulthood, the rate of substance abuse among populations experiencing their first episode of psychosis is higher than in the general population (Tucker, 2009). Compared with adults experiencing their first episode of psychosis, the adolescents used more cannabis at baseline and at 2-year follow-up and experienced an increased number of relapses (Pencer et al., 2005). Patients with persistent substance misuse experience more severe depression, more positive symptoms, poorer functional outcome, and greater rates of relapse than patients who stop and patients who had never misused substances (Turkington et al., 2009).

2.2.4. Patient's developmental stage and living conditions

The patient's stage of development influences her/his adherence to treatment in ways that may always be predictable. Young adolescents may initially require supervision in remembering to take their medication. Because of the need for adolescents to assert a degree of separation and individuation, physicians and family need to find a balance between supervising the patient and allowing the patient to develop his/her independence and autonomy in disease management without putting them at risk of relapse. Some patients might not take their disease seriously and therefore might not follow their treatment carefully.

Our experience tells us that the patients' vocational status and living conditions can influence adherence to treatment as well. Patients who work may become less adherent to their medication because their work schedule (e.g., rotating shifts) may interfere with taking their medication on a regular basis or because of fear of experiencing sedation while working. Patients who make very quick progress and are able to return to work soon after the episode of psychosis may perceive having been "cured" and no longer in need for medication. Homeless patients or those with housing instability face some of the greatest challenges to adherence because they have no organized schedules or daily routine to insure treatment adherence and no support to help them (as opposed to patients living with their families). For patients who face these various challenges in taking their oral medication as prescribed, long-acting injectable medications may become a possible option.

The above brief review suggests that identifiable subgroups of patients with FEP are at high risk of non-adherence to treatment and that, in light of no single effective intervention to improve adherence to medication, promoting insight early in the course of psychosis, especially in patients with cognitive deficits, and offering integrated, early, specialized intervention targeting substance-use-disorders comorbidity could improve adherence and outcome.

2.3. Medication-related risk factors for non-adherence

2.3.1. Efficacy of medication

Patient adherence to medication is linked to efficacy (Coldham et al., 2002). Patients are less likely to adhere to their treatment if they feel they are not benefiting from the medication. Moreover, their evaluation of the efficacy of treatment may be based on different criteria than those of their physician or their family (e.g., different symptoms or problems). It is therefore important for the physician to have an open discussion with the patient on the importance and urgency for improvement so as to target the treatment in an appropriate way. Even if the response rate to antipsychotic medication is high in FEP (Malla et al., 2006), the choice of medication and its lack of efficacy may result in some patients becoming non-adherent to their treatment. In the European First-Episode Schizophrenia Trial (EUFEST), the effectiveness of low doses of haloperidol versus regular doses of amisulpride, quetiapine, olanzapine, and ziprasidone on treatment discontinuation during 12 months of follow-up in FEP patients was assessed (Kahn et al., 2008). The study demonstrated that patients receiving haloperidol were more likely to discontinue their treatment due to insufficient efficacy compared with patients receiving the second-generation antipsychotics (SGAs). In the Comparison of

Atypicals for First Episode (CAFE) study, McEvoy et al. (2006) measured patient adherence to olanzapine, quetiapine, or risperidone over a 52-week period and demonstrated that the overall discontinuation rate was 70% by the end of the study. While the patient's decision to stop treatment despite strong advice to continue medication from their treating team was the most frequent reason (41.5%), lack of efficacy (10.8%) as well as intolerable side effects (10%) were given as other reasons for discontinuation. Interventions such as motivational interviewing and psychoeducation and a better therapeutic alliance could possibly increase the proportion of patients following treatment recommendations.

2.3.2. Adverse effects

Pharmacotherapy with antipsychotic medications that block the dopamine D2 receptor (dopamine antagonist or partial agonist) is the core treatment for psychosis in children and adolescents as well as in adults (Fraguas et al., 2010; Kumra et al., 2008). Blocking dopamine receptors changes the neurochemical milieu from one that incites aberrant salience to one where established aberrant salience is more likely to extinguish and new aberrant salience is less likely to form (Kapur et al., 2006). To optimize the use of antipsychotics, clinicians begin treatment at lower doses and increase gradually until 60 to 70% D2 blockade has been achieved (McEvoy et al., 2010). Doses of antipsychotics resulting in greater than 70% blockade do not hasten or improve therapeutic response. Rather, they induce adverse effects (e.g., hyperprolactinemia and extrapyramidal side-effects (EPS) increase significantly as D2 occupancy exceeds 72% and 78% respectively), which are often linked to high patient non-adherence and high relapse rates (Kapur et al., 2000; McEvoy et al., 2010).

The most common adverse effects leading to non-adherence include EPS, prolactin elevation, sexual dysfunction, cardiovascular effects, weight gain, metabolic effects, sedation, and hematological toxicity (Masi and Liboni, 2011). In Buis' (1992) study evaluating subjective discomfort of side effects related to antipsychotic medication, patients ranked sedation, weight gain, diminished sexual function, and akathisia among the top 10 side effects causing the most inconvenience. These were ranked worse than bradykinesia, tremor, rigidity, or dystonia.

2.3.2.1. Sedation. Sedation is a common adverse effect of both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), with children and adolescents seemingly more affected by somnolence, hypersomnia, and sedation than adults (Correll et al., 2006; Toren et al., 2004). Because sedation ranks highly in subjective discomfort, it may lead to patients becoming non-adherent to treatment (Perkins, 2002). Clinicians may regard sedation as helpful during an acute episode (for patients presenting insomnia and agitation) but it may no longer be needed and thus become more of a liability and should be closely monitored.

2.3.2.2. Weight gain and metabolic syndrome. Children and adolescents are highly vulnerable to weight gain and metabolic adverse effects, such as dyslipidemia, hypertension, and impaired glucose tolerance, induced by treatment with antipsychotics (Fraguas et al., 2008; Schimmelmann et al., 2007; Vitiello et al., 2009). Because of an association of these effects with adverse health outcomes, a set of criteria were developed for children and adolescents treated with antipsychotics to identify those at risk (Correll and Carlson, 2006; Correll et al., 2006). A relative weight gain of 5% during the first 3 months of treatment can be considered as a possible cut-off as it is associated with a 55% increase in the risk of metabolic syndrome. In addition to medical morbidity, clinicians need to be aware of non-adherence issues associated with weight gain/obesity leading to self-consciousness about bodily appearance, lower self esteem, social withdrawal or exclusion (Kane, 2011; Masi and Liboni, 2011; Perkins, 2002; Weiden et al., 2004). Therefore, prescribing antipsychotics should be based on a careful risk–benefit evaluation to preserve metabolic health while treating psychosis (Correll et al., 2006).

2.3.2.3. Hyperprolactinemia and sexual dysfunction. Hyperprolactinemia is a common adverse effect of antipsychotics and can be of clinical significance in children and adolescents (Masi and Liboni, 2011). Because estrogen stimulates prolactin synthesis and enhances prolactin responses to antipsychotics, post-pubertal girls may be more sensitive to endocrinological adverse effects. All FGAs and some SGAs can induce hyperprolactinemia; however, some SGAs (e.g., clozapine, quetiapine and aripiprazole) carry a low risk for doing so (Alfaro et al., 2002; Findling et al., 2008; Saito et al., 2004). The main effects of hyperprolactinemia include amenorrhea and other menstrual cycle disorders, gynacomastia, galactorrhea, and sexual dysfunction (e.g., decreased libido, anorgasmia, erectile difficulties and ejaculatory problems) (Masi and Liboni, 2011). Hyperprolectinemia may also cause delay of pubertal maturation, stimulation of adrenal androgen secretion, and osteoporosis caused by hypogonadism (Correll and Carlson, 2006). These adverse effects can be particularly distressing since sexual exploration, orientation, and identity take place in adolescence (Short and Rosenthal, 2008). Because the distress and discomfort caused by endocrinological adverse effects are strongly associated with poor adherence (Perkins, 2002), sexual dysfunction should be assessed regularly. Physicians should consider solutions such as reducing the medication dosage, and switching to prolactin-sparing antipsychotics (e.g., quetiapine or aripiprazole) from more offending agents (e.g., risperidone and paliperidone being the worst). If these two solutions are not possible, the use of adjunctive medication (e.g., oral contraceptives for menstrual irregularities, sildenafil or tadalafil for male sexual dysfunction) could be considered although evidence for this approach is sparse and no studies have evaluated such solutions in FEP cohorts or adolescents (Correll, 2008; Costa et al., 2006; Golden and Carlson, 2008; Haddad and Wieck, 2004).

2.3.2.4. Extrapyramidal side effects. EPS such as akathisia and parkinsonism occur more frequently in children and adolescents than in adults and even more so in drug naive patients (Masi and Liboni, 2011). Although some degree of EPS can occur during treatment with SGAs, it is seen most often during treatment with FGAs. Parkinsonian side effects significantly increase the risk of treatment discontinuation in

first-episode patients during the first year of illness, emphasizing the need for careful adjustment of medication to avoid this adverse effect (Robinson et al., 2002). Relatively mild parkinsonism can be quite disturbing for young people who feel they lose psychomotor abilities (i.e., flexibility, coordination) which can impact on their sports performance, on their ability to play musical instruments, or alter their appearance through restricted affect and movement. Cognitive parkinsonism mimics psychomotor retardation (i.e., alogia, cognitive dulling or slowness), which is often a reason for ceasing medication in young adolescents for whom studying is of primary importance (Kim and Byun, 2009). Neuroleptic-induced dysphoria, which includes unpleasant subjective changes in arousal, mood, thinking, and motivation, occurs early during treatment and typically manifests as a drug aversiveness. Neuroleptic-induced dysphoria is more likely to occur with high potency FGA but can possibly be associated with any antipsychotic medication. It is still unclear if it is a variant of extrapyramidal reaction, but it has been associated with adverse clinical consequences such as treatment non-adherence, substance abuse, poor clinical outcome, increased suicidality and compromised quality of life (Awad and Voruganti, 2004, 2005; Marder, 2005). Akathisia is a subjective or objective restlessness with a need for movement which often goes unrecognized or is sometimes mislabeled (Masi and Liboni, 2011). It is sometimes misrecognised as worsening of agitation, which can cause clinicians to mistakenly increase the antipsychotic dosage, resulting in further worsening of akathisia. Akathisia can be very distressing and is often associated with non-adherence. Decreasing the antipsychotic dosage can sometimes improve restlessness. Adjunctive medications include low-dose such as benzodiazepine or propranolol. Clozapine can be given in severe and resistant cases. Dystonia is more likely to occur in emergency situations when young, often antipsychotic-naive patients receive high doses of injectable short-term FGA because they are agitated or aggressive. Dystonia can be quite traumatizing; therefore, lower doses of antipsychotic combined with benzodiazepines or diphenhydramine are a more appropriate pharmacological strategy offering sedating effects and preventing the occurrence of dystonic reaction.

2.3.2.5. Cardiovascular effects. Cardiovascular adverse effects occur less frequently in children and adolescents than in adult patients during treatment with FGAs or SGAs (Masi and Liboni, 2011). All antipsychotics may be associated with prolongation of the QTc interval which increases the risk of ventricular arrhythmias (Labellarte et al., 2003). Tachycardia and orthostatic hypotension associated with dizziness are the most disturbing cardiovascular side effects. Therefore, a pre-treatment electrocardiogram (ECG), periodic ECG monitoring, and discontinuation of treatment when QTc is >500 ms are recommended in children and adolescents (Masi and Liboni, 2011; Masi et al., 2003). Although, young people rarely complain about cardiovascular side effects, they should be monitored for these adverse effects, particularly during antipsychotic initiation and during dose augmentation.

2.3.2.6. Hematological adverse effects and blood test monitoring. Decreases in white blood cell counts are caused to varying extents by all antipsychotics, although these decreases are not usually clinically significant (Stübner et al., 2004). Clozapine, however, can cause potentially life-threatening agranulocytosis and neutropenia (Alvir and Lieberman, 1994). Because of the risk for neutropenia and agranulocytosis, patients treated with clozapine are recommended to have their blood drawn every week for the first 6 months and every other week for another 6 months and monthly thereafter (Miller, 2000). This can be quite adverse to young patients who might be afraid of needles or reluctant to come every week to the clinic. However, clozapine remains the most effective antipsychotic treatment following failure of at least two antipsychotic medications at maximum therapeutic doses. Therefore, to improve acceptance of "less attractive medication" when indicated, patient and family psychoeducation and youth friendly clinics (including clinic environment and staff) for blood test or injections of long-acting injectable antipsychotic are of primary importance.

2.3.3. Accessibility

Accessibility to medication is a barrier to patients that can result in treatment non-adherence and subsequently lead to relapse. New medications for the treatment of FEP can be quite expensive costing from $1 to $20 per day. Patients often live alone, are isolated from family and friends, and have low income. They may also be disorganized, suffer from cognitive deficits, and lack the experience required to obtain on their own the medication they need. These patients may require help to obtain the treatment in the beginning. This may include helping the patient obtain samples of medications if he cannot afford treatment, helping the patient activate a private or government insurance plan to get access to the medication he needs, or helping the patient go to the pharmacy to fill his prescription. Patients who have difficulty taking their medication regularly need the help of psychoeducation to support their decision or inform them on what action is required when they skip or forget to take their medication. Financial cost and practical issues to facilitate accessibility to treatment should be taken into account in the treatment proposal.

It is part of the role of treating clinicians to assist patients and their families with efforts at advocacy so as to improve access to low- or no-cost medications that are effective.

2.4. Illness-related risk factors for non-adherence

Non-adherence increases with duration of untreated psychosis (DUP) (Norman and Malla, 2001). Symptoms associated with longer DUP generally take longer to respond to medication and may not respond fully (Lambert et al., 2008; Perkins et al., 2004). It is likely that such poor response may discourage patients from continuing to take medication.

3. Non-adherence and relapse following an FEP

Clinicians face many challenges in the treatment of adolescents with FEP to prevent relapse in the short-term but especially in the long-term. Robinson et al. (1999) demonstrated that most patients experience multiple relapses during the first 5 years of illness. Short-term adherence to treatment is easier to achieve because patients are suffering the traumatic experience of a first-episode psychosis and

feel the need for treatment. However, once they feel better, they often no longer feel the need to continue. Steger et al. (2011) demonstrated that patients are more likely to adhere to medication if their treatment produces a sustained remission of positive symptoms, while many patients who experience rapid negative symptom remission reduce or discontinue medication, despite its benefits. Perhaps they are less likely to view themselves as "ill." This is especially true for adolescent patients who have a sense of relative invulnerability.

Relapse prevention is an important goal following initial resolution or significant improvement of psychotic symptoms. Apart from being distressing for the patient and the patient's family, a relapse threatens to interrupt psychosocial recovery, increases the risk of treatment resistance, hastens social and functioning decline, and is associated with increased costs of treatment (Gleeson et al., 2010). Unfortunately, the majority of first-episode psychosis patients will experience relapse. At 5 years of follow-up, 82% of subjects had experienced one relapse, 78% of subjects had a second relapse after recovering from their first relapse, and 86% of subjects had a third relapse after recovering from their second relapse (Robinson et al., 1999).

Risk of relapse is particularly associated with poor medication adherence, underlying the importance for clinicians to overcome the challenges of patients' non-adherence to treatment (Coldham et al., 2002; Perkins et al., 2008). Sustenance of remission of both positive and negative symptoms following treatment of FEP is associated with improved functioning in work and social spheres (Cassidy et al., 2010).

Non-adherence is frequent in early psychosis partly because young patients want to manage without medication once they have improved significantly. Wunderink et al. (2007) demonstrated in a randomized controlled trial that "guided discontinuation" of antipsychotic medication, when compared to continuous treatment after 6 months of remission from FEP, does not augment the risk of severe relapses or readmission, since medication is quickly resumed when symptoms reoccur. Even if very few succeed to remain off antipsychotic medication (<20%), such an open collaboration with the young patient, if desired by the latter, might in the long term improve therapeutic alliance, adherence and retention in treatment. In the same spirit, discussing and monitoring with the patient and his family the "relapse signature" (early warning signs of a psychotic relapse) (Herz et al., 2000) and preparing in advance a psychiatric treatment directive plan (Srebnik and Lafond, 1999) in case of symptom recurrence can be very useful (Gleeson et al., 2010). This is especially true in patients with low medication adherence. It helps the patient and his family recognize the early signs of relapse and develop appropriate strategies to avoid severe relapse often involving hospitalization or coercive interventions (Swanson et al., 2008).

4. Adherence, incomplete remission, and treatment resistance

For 10% to 50% of FEP patients, treatment can be completely unsuccessful (i.e., treatment resistance) or partially unsuccessful (i.e., incomplete remission) (Huber et al., 2008; Lambert et al., 2008). In a study exploring clinical recovery in FEP patients, Wunderink et al. (2009) determined that 41% of patients achieved neither symptomatic nor functional remission (treatment resistance), 40% of patients achieved either symptomatic or functional remission (incomplete remission), and 19% of patients achieved both symptomatic and functional remission (recovery). The factors which contribute to incomplete remission or treatment resistance (absence of remission) are complex and can be divided into three categories: illness-related factors, patient-related factors, or treatment-related factors (Huber et al., 2008). Illness-related factors include biological factors (e.g., structural brain abnormalities, neurological soft signs, neurochemical abnormalities, disorders of neuronal development, and family history), symptomatic factors (e.g., severity of symptoms, marked cognitive impairment, and poor early course of illness), and other illness factors (e.g., poor premorbid adjustment, early-onset, co-morbidity, mental retardation, and long duration of untreated psychosis). Patient-related factors include environmental factors (e.g., lack of social network and migration background), psychological factors (e.g., lack of insight, negative attitude toward treatment, situational stress, and reluctance to accept treatment), and other factors (e.g., male gender, non-adherence to medication, and disengagement with treatment). Treatment-related factors include non-pharmacological predictors (e.g., long duration of untreated prodrome and/or psychosis, insufficient quality of treatment and rehabilitation, and poor therapeutic alliance) and pharmacological predictors (e.g., delay in treatment initiation, incorrect choice of psychotropic treatment, EPS, and drug bioavailability problems). This extensive list emphasizes the multifactorial nature of poor response to treatment. It is therefore essential to consider all of these variables when assessing, confirming and managing treatment resistance and incomplete remission (Lambert et al., 2008). The key management strategies in preventing incomplete remission and treatment resistance in first-episode patients are to reduce the duration of untreated psychosis, reduce the risk of relapse by assuring adequate treatment (including medication), provide high quality of care, detect treatment resistance early, and adapt treatment quickly.

5. Physiological characteristics during adolescence and their relevance for treatment of psychosis

Physiological differences between adults and adolescents can make it difficult for physicians to treat adolescents with FEP. Most antipsychotics used to treat adolescents are used "off label" (Mehler-Wex et al., 2009). This practice comes with an immediate risk of under- or overdosing the patient and a delayed risk of long-term side effects. The factors that need to be considered in the selection of a dose are drug absorption and drug metabolism in the adolescent patient (van den Anker, 2010). Drug absorption is generally slower in adolescents and therefore the time to achieve peak plasma levels is longer. Drug bioavailability in adolescent patients may be markedly different from that in adults because there are developmental differences in the activity of intestinal enzymes and efflux transporters involved with drug metabolism. However, drug-naive patients may be more sensitive to certain adverse effects (Kwon et al., 2009). These physiological differences between adolescents and

adults emphasize the importance of the extra caution that clinicians need to exercise in individual evaluation, choice and dosage of antipsychotic, and timely adjustment of treatment. The well-known rule "start low, go slow" certainly applies here. However, clinicians have to bear in mind that for some patients when medication is well tolerated and only brings partial response, the doses might need to be increased to higher doses than usually prescribed in adult population of the same weight.

6. Choice of medication

In deciding which medication to prescribe to the patient, physicians must carefully weigh the risk-to-benefit ratio of each drug and select the one that is less likely to result in undesirable adverse effects in that particular patient. Since no available antipsychotic medication (except clozapine in resistant psychosis) has clearly proven to be superior to others in terms of efficacy, safety issues should determine the choice of antipsychotic (Asenjo Lobos et al., 2010; Gasquet et al., 2009; Jones et al., 2006; Lieberman et al., 2003; Rummel-Kluge et al., 2010a). The clinician must evaluate for each patient profile which medication is least likely to be harmful. EPS associated with the use of FGAs have marked the first four decades of use of antipsychotic medication, and nowadays FGAs are usually less prescribed because of their potentially harmful adverse effects in young patients. Low dose SGAs are suggested as first line treatment for FEP (International Early Psychosis Association Writing Group, 2005), although the side effect profiles vary between the different medications with weight gain and metabolic disturbances being the most frequent and harmful side effects in the long term. Therefore, medications less likely to induce weight gain and metabolic disturbances may be considered as a more reasonable option. However, currently there are no data available regarding outcomes associated with such a choice of first medication for young patients with little or no previous exposure to antipsychotic medication. Aripiprazole, amisulpride, and ziprasidone followed by quetiapine, risperidone, and paliperidone have proven to be less offending than olanzapine and clozapine (Allison and Casey, 2001; Chabroux et al., 2009; Leucht et al., 2009; Marder et al., 2004; Newcomer, 2007; Rummel-Kluge et al., 2010b). In fact, the Schizophrenia Patient Outcomes Research Team (PORT) recommends that antipsychotic medications other than clozapine and olanzapine be used as first-line treatment for patients experiencing their first episode of psychosis because, despite their efficacy, these drugs possess the potential for metabolic harm (Kreyenbuhl et al., 2010).

Physicians must approach treatment strategies with patience and caution. They must find a balance between augmenting doses too quickly (which can result in adverse effects) and adjusting doses too slowly (which can result in patients losing confidence in the efficacy of their medication and stopping treatment). Psychoeducation in a collaborative therapeutic relationship plays an important role in preparing patients on what responses they can expect, on how symptoms will improve, on side-effect management and on how doses of medication may be adjusted.

Avoiding polypharmacy (which increases the risk of side effects and pharmacokinetic interactions) and reducing the number of doses per day and the number of tablets also make it easier for patients to accept and remember taking their pills. As cognitive difficulties, linked with psychosis, may be one of the sources of non-adherence in some patients, adherence can be optimized by using DISPILL™, Dosett ®, electronic pill dispensers or reminders, to help them remember to take their medication (Stip et al., 2011).

However, if a patient has a partial or no response or is at risk of non-adherence, long-acting injectables (LAIs) should be considered (Stip et al., 2011). LAIs offer advantages to the patient and the patient's family including not having to remember to take medication every day, not having to deal with ambivalence about medication every day, no daily reminder that the patient is ill, better relapse and hospitalization prevention, and fewer family arguments, tensions, and conflicts around medication. LAIs insure that the medication is taken at the prescribed dose and that an eventual non-response to treatment is not due to non-adherence but more likely due to treatment resistance. For more severe cases, when LAI treatment has failed, treatment with clozapine is clearly indicated (Masi and Liboni, 2011).

7. Solutions to improving adherence

Solutions to improve adherence also include frequent appointments with the physician or nurse at the onset of treatment to monitor side effects and efficacy and to adjust treatment quickly, thereby avoiding long hospital admissions. Offering patients intensive FEP programs as an alternative to classical long hospital admissions for an FEP may also motivate patients to adhere to their treatment programs. Such FEP programs usually provide youth with a friendly clinical environment, appointment flexibility allowing patients to continue leading "normal" lives (e.g., going to school or work), and group therapies with peers going through a similar experience. Having the same team provide psychosocial help as well as pharmacotherapy can improve adherence to treatment. Patients are often more likely to accept psychosocial assistance first, and when they feel their situation improves, they may be more willing to continue pharmacotherapy because they trust their treatment team can help them efficiently.

Another solution to improving adherence is to include the family in treatment in the form of family meetings with the patient and utilizing family psychoeducation or other forms of family intervention such as multiple family intervention (McFarlane et al., 1995; Onwumere et al., 2011). In the adult population, there is strong evidence that interventions involving the family reduce the risk of relapse. These interventions, therefore, can have a greater impact with adolescents who usually live with their parents and whose parents usually play an important role in their lives. Other patients respond to motivational therapy for adherence to treatment. Still others respond well to psychoeducation and psychosocial therapies targeting substance use comorbidity and beliefs about illness and the need for treatment.

Perhaps one of the most important supports a physician can offer to a patient is to encourage him/her during the medication trial period, and develop a plan with the patient if the patient fails to improve or presents with side effects. If the patient absolutely wants to try stopping the medication once he/she is in remission, the physician can collaborate

with the patient to taper down the medications slowly, instead of stopping it abruptly, to prevent severe relapses. The patient, in collaboration with his physician, can also prepare a psychiatric treatment directive plan in case of symptom recurrence following treatment discontinuation.

8. Conclusion

The treatment of FEP in adolescents presents many challenges to clinicians. Lack of scientific research into the best and safest psychopharmacological treatment strategies in the adolescent FEP population needs to be addressed since clinicians cannot rely on any current evidence to select appropriate treatments for their patients. Two of the greatest challenges in our health care systems for young people presenting with FEP are rapid access to treatment and engagement to treatment. Currently, mental health care organizations do not meet this population's specific needs which differ from those of patients having suffered many previous episodes. This may lead to patients' disengagement from treatment and non-adherence to medication (especially in the long term) which represent risk factors for relapse. Utilization of psychosocial treatment strategies and specialized FEP services can optimize engagement and long-term outcomes, and give young patients the opportunity to live productive lives.

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