Chapter 1

Antipsychotic treatment and adherence in schizophrenia

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Introduction
This chapter falls into two main sections. In the first section we provide an overview of schizophrenia and antipsychotic treatment. This includes the course of schizophrenia, the relationship between duration of untreated psychosis and relapse and disease progression, the role of antipsychotics in relapse prevention, and current treatment guidance for antipsychotic treatment in schizophrenia. Unfortunately the goals of antipsychotic treatment are frequently undermined by poor medication adherence. The second section of the chapter provides a comprehensive review of adherence with antipsychotic medication in schizophrenia. Many of the issues will apply to other disorders where long-term maintenance antipsychotic treatment is required such as bipolar disorder. We start by considering how adherence is defined and measured before considering its predictors, an area that is best understood by considering a health belief model. This is followed by a review of the extent and consequences of poor adherence in schizophrenia. We then consider interventions that can be employed to improve antipsychotic adherence, including psychosocial interventions, changes to the oral medication regimen, and a switch to a long-acting injection. The strategy or strategies that are adopted will depend on the individual patient and should be based on full discussion between the patient and doctor. The chapter ends with a brief summary of key points.

The course of schizophrenia
The course of schizophrenia can be divided into premorbid, prodromal, first-episode, and chronic phases. Patients in the premorbid phase often have subtle deficits in cognitive, motor, and social functioning (Fuller et al. 2002; Niemi et al. 2003; Zammit et al. 2004). The schizophrenia prodrome is most often defined retrospectively as a pre-psychotic state that represents a deviation from the usual behaviour of an individual (Yung & McGorry 1996). Patients in the prodromal phase have a gradual onset of symptoms (misperceptions, over-valued beliefs, ideas of reference) prior to the onset of psychotic symptoms. There is often a decline in cognitive, social, and vocational functioning during the prodromal phase (Ang & Tan 2004; Fuller et al. 2002; Zammit et al. 2004).
The psychotic symptoms that characterize the first episode of schizophrenia can have an acute or insidious onset (Harrison et al. 2001). The onset of psychotic symptoms occurs between 15 and 30 years of age for 75% of the patients with schizophrenia (an der Heiden & Hafner 2000). Women have a slightly older age of onset relative to men (Hafner et al. 1998; Jablensky & Cole 1997). Positive symptoms such as systematized delusions and hallucinations are most common during the earlier stage of the illness (Lieberman 1999). There is often a time-limited deterioration with the decline in level of functioning most apparent during the first three years of the illness (McGlashan & Fenton 1993). As the symptoms of schizophrenia emerge during the first episode, cognitive impairment leads to further deficits in social and vocational impairments (Green et al. 2000).

After this initial phase of deterioration, patients with schizophrenia have a chronic, plateau phase. The disease course during the chronic phase of schizophrenia is highly heterogeneous from complete recovery to chronic, disabling symptoms. Approximately one-third of the patients with schizophrenia have relatively good outcome characterized by mild symptoms and mild functional impairment. The remaining two-thirds of the patients have moderate to severe symptoms and severe functional impairment (Bottlender et al. 2002; Harrison et al. 2001; Kua et al. 2003; Mason et al. 1995; Svedberg et al. 2001; Wiersma et al 1998). About 10% of the patients with schizophrenia in the chronic phase have persistent, unremitting psychotic symptoms throughout the course of the illness (Thara et al 1994; Wiersma et al. 1998).

**Duration of untreated psychosis, relapse, and disease progression**

The original conceptualization that untreated psychosis is ‘toxic’ to the brain was based on clinical studies showing worsening outcomes with antipsychotic treatment delays or discontinuations (Wyatt 1991). These clinical studies generated the hypothesis that psychosis reduces neuronal connectivity (Norman & Malla 2001; Wyatt 1991). This topic has generated considerable debate. One of the original proponents of this hypothesis later acknowledged that this idea was ‘speculative’ (Wyatt 1997). Despite this ongoing debate, duration of untreated psychosis and psychotic relapses do appear to be associated with increased disability and treatment resistance (Bottlender et al. 2002).

Initiation of antipsychotic therapy for patients in the first episode of psychosis is often delayed. The delay in treatment is poorly understood but may be related to lack of recognition of the mental illness by the patient and significant others. Duration of untreated psychosis is defined as the time from the earliest manifestation of psychotic symptoms to initiation of treatment (Norman & Malla 2001). The average time from psychosis to initiation of treatment in most communities is greater than one year (Larsen et al. 2001). Duration of untreated psychosis has been extensively studied in the schizophrenia literature with retrospective and longitudinal designs (Norman & Malla 2001). Longitudinal studies assess patients for duration of untreated psychosis at their first presentation and then follow them up for possible outcomes. These studies have a more accurate estimation of the duration of untreated psychosis and allow for
better control of possible confounds. A systematic review of 26 longitudinal studies found an association with long duration of untreated psychosis and worse outcomes with symptoms and quality of life in patients with schizophrenia (Marshall et al. 2005). Furthermore, the patients with the longer duration of untreated psychosis were less likely to achieve remission. Early treatment is crucial as studies of treatment–response in early psychosis suggest that the duration of psychosis prior to treatment is a predictor of response to medication (Szymanski et al. 1996; Wiersma et al. 1998). A few studies have documented that first-episode patients have a rate of response to typical antipsychotic drugs at least as good (70%) and perhaps better than in chronic patients (Sheitman et al. 1997). This analysis supports the importance of early intervention for first-episode patients.

Many patients will have a psychotic relapse after their first episode. In a five-year longitudinal study of 104 first-episode patients, the cumulative first relapse rate was 82%, and a second relapse rate was 78% (Robinson et al. 1999). Relapse often leads to a psychiatric readmission and decline in functioning. Recurrent episodes are also associated with symptom chronicity and increased disability (Wiersma et al. 1998). Relapses are also associated with development of treatment resistance in schizophrenia. Treatment-resistant, poor-outcome patients can have progressive functional deterioration and evidence of structural brain changes throughout the disease course (Mitelman & Buchsbaum 2007). Relapse prevention with maintenance antipsychotic treatment is essential to the successful long-term treatment of schizophrenia.

**Antipsychotics and relapse prevention**

Environmental factors such as community demands, available resources, and treatment significantly alter the disease course of schizophrenia (Lieberman et al. 2001). The effectiveness of antipsychotics drugs in reducing the risk of relapse is incontrovertible and consists of drug discontinuation studies and studies that compare continuous maintenance treatment with intermittent treatment. Multiple studies show that discontinuation of antipsychotic treatment is associated with increased risk of psychotic relapse (e.g. Almerie et al. 2007; Gilbert et al. 1995; Leucht et al. 2003). Gilbert et al. (1995) reviewed 66 discontinuation studies published between 1958 and 1993. The follow-up period ranged from two months to two years (mean 6.3 months). The mean rate of relapse in the patients on maintenance therapy was 16% in comparison with 53% in those withdrawn from medication. Relapse was most likely to occur within the first three months of antipsychotic discontinuation. Almerie et al. (2007) conducted a meta-analysis of clinical trials that compared withdrawal of chlorpromazine with continued treatment for patients with schizophrenia. Chlorpromazine withdrawal significantly increased the risk of relapse across all three periods assessed i.e. in the short term, medium term and long term. Leucht et al. (2003) conducted a systematic review and meta-analysis of randomized, controlled trials that assessed the efficacy of second-generation antipsychotic (SGA) drugs in relapse prevention in schizophrenia. An analysis of six placebo comparison studies, involving a total of 983 patients, showed a significantly lower relapse rate for SGAs versus placebo. It is interesting to note that a further analysis of studies that compared SGAs to first-generation antipsychotics (FGAs)
showed that the relapse rate was significantly, although modestly, lower with SGAs (Leucht et al. 2003). It was unclear whether this reflected improved adherence or superior efficacy.

Discontinuation of antipsychotic treatment is associated with not only an increased risk of relapse but also poorer social adjustment, increased disability, and treatment resistance (e.g. Gilbert et al. 1995; Hogarty et al. 1976). The early discontinuation studies showed a relationship between a period of antipsychotic discontinuation and poor social adjustment after patients had resumed antipsychotic treatment (Curson et al. 1985; Johnson et al. 1983).

Studies of continuous treatment versus intermittent or targeted dosing also support the role of antipsychotics in the maintenance phase of schizophrenia (Davis et al. 1994; Kane 1996). Intermittent dosing strategies can be subdivided into fixed intermittent dosing, early warning sign interventions, and crisis interventions. Early warning sign interventions initiate antipsychotic treatment as the patient starts to show signs of a relapse (Herz et al. 1991). Crisis interventions initiate antipsychotic treatment after the patient has developed psychotic symptoms (Gaebel et al. 2002). These studies have repeatedly shown that intermittent therapies are less effective than maintenance treatment in preventing relapse (Gaebel 1994; Gaebel et al. 2002; Kane 1996; Schooler et al. 1997). The results of five such studies are shown in Figure 1.1. Intermittent therapies have also been associated with an increased risk of tardive dyskinesia (McCreadie et al. 1980). In a study of several lifetime medication variables, including cumulative amount of antipsychotics and of anticholinergics, only the number of antipsychotic interruptions was significantly related to tardive dyskinesia (van Harten et al. 1998).

![Figure 1.1](image.png)

**Fig. 1.1** Rates of relapse in patients with schizophrenia after one year of continuous or intermittent maintenance therapy in five studies. Most patients had had more than one prior psychotic episode. Reproduced from Kane (1996) Copyright © [1996] Massachusetts Medical Society. All rights reserved.
A recent study in the Netherlands (the MESIFOS study) assessed targeted treatment versus maintenance antipsychotic treatment in remitted first-episode psychosis (Wunderink et al. 2007). After six months of remission patients were randomized to gradually stop medication, with a view to restarting it should they show signs of relapse (targeted treatment), or to received maintenance treatment. During the 18-month follow-up period, twice as many relapses occurred in the discontinuation group compared to the maintenance group (43% vs. 21%, \( p = .011 \)). The findings confirm earlier intermittent treatment studies in patients with established schizophrenia, namely that antipsychotic medication reduces the risk of relapse but is more effective when administered continuously in comparison to medication administered intermittently.

**Antipsychotic treatment guidelines**

Various treatment guidelines for schizophrenia are available including those of the American Psychiatric Association (Lehman et al. 2004), the National Institute of Clinical Excellence (2009a), the Canadian Psychiatric Association (2005), and the Royal Australian and New Zealand College of Psychiatrists (2005). These guidelines are more similar than different, and, in the interest of brevity, this section is limited to a review of the American Psychiatric Association guidelines regarding antipsychotic treatment for patients at different stages of the illness (Lehman et al. 2004).

The American Psychiatric Association treatment guidelines for the first-episode of psychosis emphasise diagnostic clarification (Lehman et al. 2004). A thorough and systematic effort at differential diagnosis is mandatory, not only for the identification of potentially reversible neurological and medical causes of psychosis but also because idiopathic forms of psychosis have important prognostic implications. First-episode patients are more sensitive to the therapeutic effects and side-effects of antipsychotic medications. It is therefore particularly important to consider the different side-effect profiles of antipsychotics when selecting a drug for the treatment of first-episode psychosis (Haddad & Sharma 2007).

More than 75% of the first-episode patients will achieve cross-sectional symptom remission within the first year of initiation of treatment (Lieberman et al. 1996). There is debate about how long antipsychotic medication should be continued in first-episode patients. However, first-episode patients who have at least one year of symptom remission while taking antipsychotic medications may be candidates for medication discontinuation. Clinicians working with remitted first-episode patients should engage them in a discussion of the risks and benefits associated with risks and benefits of long-term (indefinite) maintenance therapy (Tauscher-Wisniewski & Ziursky 2002) versus a gradual tapering and discontinuation of antipsychotic treatment and risk of relapse. If the patient elects medication discontinuation, the antipsychotic dosage should be gradually reduced at the rate of 10% per month. The treatment plan should also include additional precautions such as regular follow-ups with a physician even after medication discontinuation. Family members should be educated regarding the importance of identifying early warning signs of relapse (such as changes in sleep, anxiety, depression, ideas of reference) to maximize the likelihood of preventing a full psychotic relapse (Bustillo et al. 1995).
Psychotic relapses in multi-episode patients occur from medication non-adherence, substance use, psychosocial stressors, and the natural course of schizophrenia (Lehman et al. 2004). The patient’s history of symptom response and side-effects guides the selection of antipsychotic medication during a relapse (Leucht et al. 1999; National Institute for Clinical Excellence 2009a). The time to onset of antipsychotic action has been debated but meta-analytic studies have shown that response to antipsychotic medication typically occurs shortly after initiation of therapy (Agid et al. 2003). If the patient is not improving, the clinician may consider increasing the dose gradually to the maximum licensed dose, assuming this is tolerated, and continuing this for a finite period such as two to four weeks. If dose adjustment does not improve clinical response, a different antipsychotic should be considered.

Treatment resistance has been defined in various ways. One of the most rigorous definitions is persistent illness and continuing psychotic symptoms despite adequate trials of three antipsychotics and a prospective failure of a high-dose haloperidol trial (Kane et al. 1988). Numerous controlled trials have demonstrated clozapine’s superiority over other antipsychotics in treatment-resistant populations (Conley et al. 1998; Kane et al. 1988; Kumra et al. 1996; Pickar et al. 1992). The American Psychiatric Association guidelines recommend a consideration of clozapine for ‘patients who have shown a poor response to other antipsychotic medications’ (Lehman et al. 2004).

For patients with multiple episodes or two episodes of psychosis within five years, lifetime maintenance treatment with antipsychotics is recommended (Lehman et al. 2004). Some data suggest that second-generation antipsychotics may be associated with greater efficacy in relapse prevention (Csernansky & Schuchart 2002; Leucht et al. 2003). The goals of maintenance therapy include preventing a psychotic relapse and maximizing the quality of life and level of functioning (Lehman et al. 2004). Relapse in the context of a previous clear response to antipsychotic treatment should not necessarily be assumed to represent treatment resistance. A psychotic relapse may be attributable to the natural disease course of schizophrenia, co-morbidities such as substance abuse, and problems with adherence.

**Defining adherence**

Adherence is defined as the extent to which a person’s behaviour matches the recommendations from a health care provider (Haynes et al. 1979). More specifically adherence with medication describes the extent to which the patient’s medication intake matches that agreed with the prescriber. Adherence can be applied to health care recommendations other than medication intake. For example, one can consider adherence with dietary advice or adherence with an exercise regime. Adherence and compliance are synonymous but adherence is generally preferred. Adherence is often confused with concordance but the two terms describe different phenomena. Adherence describes a person’s behaviour, whereas concordance usually refers to a consultation process in which the patient and health care professional agree on therapeutic decisions that incorporate their respective views (Haynes et al. 1979).

Despite widespread acceptance of the term, operational definitions and measurement of adherence have considerable variability from study to study (Velligan et al. 2006). Further clouding of this concept are the many shades of adherence. Adherence lies on a
continuum from medication refusal to non-adherent to partially adherent to fully adherent (Velligan et al. 2006). Patients who immediately decline to take medications are 'medication refusers' to distinguish them from 'medication acceptors' (Velligan et al. 2006). Those who initially accept medications and continue to take them as prescribed are fully adherent. Most investigators define fully adherent patients as those who take their medications as prescribed at least 80% of the time.

Most patients with schizophrenia are partially adherent with their medications. This has been defined as adherence with treatment at least 50% to 80% of the time (Velligan et al. 2009). Partial adherence is difficult to assess and may be related to important outcome measures such as symptoms, relapse, and suicide. Patients may deviate from dosage or timing for unintentional or intentional reasons. Unintentional reasons include forgetting to take a dose, misunderstanding on medication directions, and environmental barriers such as lack of transportation (Velligan et al. 2006). The missed doses may be covert and kept away from staff. Unintentional dosage deviations and irregular adherence may further erode insight and therapeutic alliance resulting in the intentional discontinuation of antipsychotic treatment.

**Measuring adherence**

Percentage of medication taken, medication possession ratios, and medication event monitoring are used to measure adherence. In a comprehensive review of 161 studies on adherence, indirect methods such as self-report, provider report, significant other report, or chart review were used the majority of the time (77%) to measure adherence (Velligan et al. 2006). These subjective reports are prone to error. In one study, 55% of the participants reported that they were ‘perfectly adherent’ but blood level data showed that only 23% were adherent (Velligan et al. 2003). Another study compared clinician ratings of adherence with an electronic monitoring device (Byerly et al. 2005). The electronic monitoring device (objective) determined that 48% of the patients were non-adherent, whereas the Clinician Rating Scale (subjective) failed to detect a single, non-adherent patient. Subsequent studies have confirmed that both patients and clinicians overestimated adherence relative to electronic monitoring (Byerly et al. 2007; Velligan et al. 2007). The report from informants or significant others is largely dependent on their time and involvement spent with the patient (Velligan et al. 2006). Chart reviews are largely dependent on the patient’s self-report. The inability of patients and clinicians to accurately gauge adherence is likely to have consequences for patient outcomes and argues for different methods of measuring adherence.

Direct or objective measures such as pill count, blood/urine analysis, electronic monitoring, and refill records are also available to measure adherence. Pharmacy-based measures include the medication possession ratio (Sajatovic et al. 2007). The medication possession ratio measures adherence by dividing the number of days’ supply of medication by the number of days the patient needed to take the medication continuously. Retrospective reviews of pharmacy refill data have shown a direct correlation between estimated adherence and risk of psychiatric hospitalization (Karve et al. 2009; Weiden et al. 2004). Despite these correlations, the medication possession ratio or refill records may be confounded by the patient’s use of samples or old medications that are still available to the patient (Velligan et al. 2006). Medication event
monitoring records the time and date whenever the pill bottle is opened. Medication event monitoring is the most accurate measure of adherence and the ‘gold standard’ for adherence monitoring with other populations of chronic illness. However, studies with medication event monitoring in schizophrenia have high rates of missing data (Velligan et al. 2006). Medication event monitoring studies may be confounded by the cognitive impairment and unstable living situations common with schizophrenia.

The medication event monitoring studies may bias results towards higher level of adherence as the opening of the pill bottle does not necessarily mean that medication happened (Velligan et al. 2006). This is illustrated by a study that measured adherence to metered dose inhalers with a Nebulizer Chronologs (the metered dose inhaler equivalent of the medication event monitoring) in patients with chronic obstructive pulmonary disease (Simmons et al. 2000). Thirty per cent of the patients activated their inhalers more than 100 times in a three-hour interval shortly before a clinic follow-up visit. Self-reported inhaler usage, demographic variables, smoking status, pulmonary function tests, and respiratory symptoms were similar for ‘dumpers’ and ‘non-dumpers’. The authors concluded that ‘deception’ among the non-adherent is common in clinical trials and often not revealed by the usual methods of monitoring adherence. Covert non-adherence most likely occurs in the psychiatric clinic as well.

The subjective ratings are still widely used in adherence studies despite the ‘gold standard’ of electronic monitoring. Researchers have improved the accuracy of self-reported medication adherence with the development and evolution of adherence scales such as The Dug Attitude Inventory, the Medication Adherence Rating Scale, and the Brief Evaluation of Medication Influences Scale (Dolder et al. 2004; Fialko et al. 2008; Hogan et al. 1983; Thompson et al. 2000). The Brief Adherence Rating Scale was the most recently developed scale to measure adherence (Box 1.1). This scale was validated with electronic monitoring, the preferred direct measure of medication adherence (Byerly et al. 2008; Osterberg & Blaschke 2005). The Brief Adherence Rating Scale provides a sensitive, reliable, and valid measure of antipsychotic adherence in patients with schizophrenia as compared to electronic monitoring. Furthermore, this scale is simple, quick, and easy to administer making it applicable for clinical settings. Expert consensus guidelines for measurement in adherence studies recommend the use of a subjective ratings and an objective direct measure such as electronic monitoring (Velligan et al. 2006, 2009).

**Predictors of adherence**

Predictors of adherence may be contextualized in the ‘health belief model’ (Bebbington 1995). The health belief model is based on four constructs or core beliefs—perceived susceptibility, severity, barriers, and benefits (Rosenstock 1966). This model emphasizes the collaboration between physician and patient in treatment decisions. The patient will weigh the benefits of antipsychotic treatment such as symptom reduction
Box 1.1 The Brief Adherence Rating Scale. This is a clinician-administered scale. The clinician should read aloud questions 1, 2, and 3 to the patient and translate the patient’s responses to these questions in the right-hand column next to each question. The clinician then records an overall rating of adherence on the visual analogue scale (Byerly et al. 2008).

<table>
<thead>
<tr>
<th>Patient Identification: __________________________</th>
<th>Date: ________________</th>
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**BRIEF ADHERENCE RATING SCALE**

The following information is obtained by the clinician:

1. How many pills of ____________________ (name of antipsychotic) did the doctor tell you to take each day?
2. Over the month since your last visit with me, on how many days did you NOT TAKE your ____________________ (name of antipsychotic)?
   - Few, if any (<7)
   - 7-13
   - 14-20
   - Most (>20)
3. Over the month since your last visit with me, how many days did you TAKE LESS THAN the prescribed number of pills of your ____________________ (name of antipsychotic)?
   - Always/Almost Always (76-100% of the time) = 1
   - Usually (51-75% of the time) = 2
   - Sometimes (26-50% of the time) = 3
   - Never/Almost never (0-25% of the time) = 4

**Note:**
1 = poor adherence  
4 = good adherence

Please place a single vertical line on the dotted line below that you believe best describes, out of the prescribed antipsychotic medication (________________) doses, the proportion of doses taken by the patient in the past month.

- None
- Half
- All

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Response struck on above line (%) = ________________
Rater’s Initials: ________________

with the associated costs of antipsychotic treatment such as side-effects. Benefits of antipsychotic treatment are largely dependent on the patient’s knowledge about their illness and belief the treatment may have on the severity of their symptoms. The health belief model emphasizes the patient’s as opposed to the physician’s understanding of illness and treatment (Perkins 2002).

Perceived benefits of treatment are largely dependent on the patient’s illness awareness and insight. Insight has been one of the most common predictors of adherence problems (Lacro et al. 2002; Perkins 2002). Insight is not necessarily found in all patients who are adherent with antipsychotics (Garavan et al. 1998). Perceived benefits of treatment also include the therapeutic relationship. The quality of the therapeutic relationship is related to medication adherence (Fenton et al. 1997; Frank & Gunderson 1990). In a cross-sectional and longitudinal adherence study with 162 patients, working alliance was most consistently related to medication adherence (Weiss et al. 2002). Patient satisfaction in the physician–patient relationship may lead to a greater willingness to follow the physician’s advice independent of the level of insight of the patient.

Costs of treatment include the patient’s perception of medication side-effects. Extrapyramidal side-effects include akinesia, akathesia, dystonia, and dyskinesia. Extrapyramidal side-effects are frequently cited as a reason for medication discontinuation (McCann et al. 2008). Akinesia and akathesia are closely related to patient distress and a negative subjective response to antipsychotic medication (Buchanan 1992; Gervin et al. 1999). The negative subjective response or ‘neuroleptic dysphoria’ is closely related to non-adherence (Gervin et al. 1999). Other side-effects of antipsychotics include sedation, weight gain, sexual dysfunction, and various symptoms that reflect raised prolactin including galactorrhoea and menstrual irregularities (Haddad & Sharma 2007). When patients perceive adverse effects as problematic or unacceptable they may lead to poor adherence (Fleischhacker et al. 1994). On the contrary patients will often continue to take medication despite unpleasant side-effects if they perceive the benefits of medication as outweighing the disadvantages caused by side-effects. A good example of this is clozapine, which is often associated with high adherence and continuation rates despite a range of adverse effects including weight gain, sedation, and hypersalivation (Gasznier & Makkos 2004). It is likely that this is partly owing to patients who were treatment resistant appreciating that they have gained symptomatic improvement since starting clozapine.

Other patient-related factors may contribute to poor adherence. Severity of psychopathology and a failure to respond to treatment are associated with adherence problems (Fenton et al. 1997; Perkins et al. 2008). Paranoia can be detrimental to the development of a successful working alliance. Co-morbid substance abuse is strongly associated with adherence problems (Olfson et al. 2000). Cognitive impairment, especially executive dysfunction, might also be associated with adherence problems (Perkins 2002). These factors are often present in the same patients and may synergistically complicate adherence.

The introduction of second-generation oral antipsychotics in the early 1990s led to speculation that the reduced risk of extrapyramidal side-effects would lead to less improved adherence in schizophrenia (Young et al. 1999). The results were unfortunately equivocal and did not live up to the initial expectations for second-generation
antipsychotics (Diaz et al. 2004; Dolder et al. 2002; Gianfrancesco et al. 2006; Menzin et al. 2003). Aside from clozapine, second-generation oral antipsychotics do not have improved rates of adherence compared to first-generation oral antipsychotics. Interventions to improve adherence need to be considered irrespective of which antipsychotic is prescribed (Dolder et al. 2002).

**Extent of poor adherence in schizophrenia**

Poor adherence is common in schizophrenia. In a longitudinal study of 162 patients, the risk of becoming non-adherent was constant throughout the 22 months of this study (Weiss et al. 2002). The average time of treatment adherence was only 13.3 months. Another longitudinal study followed patients for a period of four years and calculated medication possession ratios to measure adherence (Valenstein et al. 2006). In each year 36%-37% of patient were poorly adherent whereas 61% of the patients had problems with adherence at some time in the four-year period. An often quoted review estimated a medication adherence rate in schizophrenia in 58% (Cramer & Rosenheck 1998). This is similar to another review that gave a median adherence rate of about 50% (Oehl et al. 2000). As mentioned previously, adherence is dynamic with up to 67% of patients being non-adherent for a month or more for some period during a 12-month period (Williams et al. 1999). Overall, about 80% of patients with schizophrenia will be non-adherent at some stage of their illness (Corrigan et al. 1990).

Problems with adherence are not unique to schizophrenia. Virtually all chronic illnesses, such as asthma and rheumatoid arthritis, have significant percentages of patients with partial or poor adherence to treatment (Kyngas 1999; Viller et al. 1999). The National Institute for Clinical Excellence (2009b) has established a set of guidelines for initiating a patient-centred approach that encourages ‘informed adherence’. Patients with schizophrenia may have more pronounced problems with adherence compared to patients with other chronic diseases. This may be related to the illness itself. Schizophrenia often involves thought disorder and cognitive impairment, and there is a high prevalence of co-morbid substance abuse, which affects the symptom severity and directly adherence. Finally, the ‘missed dose’ in schizophrenia is often silent and will not lead to a psychotic relapse until months later.

**Clinical consequences of non-adherence**

Studies have repeatedly shown that non-adherence with antipsychotic medication has a range of negative consequences in schizophrenia (e.g. Law et al. 2008; Novick et al. 2010; Olfson et al. 2000). The association between adherence and clinical outcomes was recently investigated in a secondary analysis of data for nearly 7000 patients from the European Schizophrenia Health Outcomes (SOHO) study, a three-year, prospective, observational study of patients with schizophrenia (Novick et al. 2010). Non-adherence with antipsychotic medication, as rated by the assessing clinician, was significantly associated with an increased risk of future relapse, hospitalization, and suicide attempts. In another study, Olfson et al. (2000) found that non-adherence was associated with symptom exacerbation, emergency room visits, readmission, and homelessness within three months of medication discontinuation. Even a short period
without medication has been associated with an increased risk of admission. An observational cohort study of patients with schizophrenia used pharmacy claims to define days without available medication. Individuals in the first 10 days following a missed prescription refill had a significantly increased risk for psychiatric hospitalization compared with those with available medication (Law et al. 2008).

The consequences of poor adherence can last beyond the psychotic relapse. Patients who have psychotic relapses also have a longer time to remission of symptoms (Lieberman et al. 1996). After the first relapse, patients take an average of 47 days to remission. After the third relapse, patients take an average of 130 days to get to remission. Non-adherence is also associated with increased costs related to both psychiatric and medical in-patient hospital days (Gilmer et al. 2004).

Missed dosages, or patients unilaterally reducing the dose of their antipsychotic, may have a greater impact with the current practice of treating patients with the lowest effective antipsychotic dosage during maintenance phases of treatment. In the past there was a tendency to use higher antipsychotic doses and some even advocated that patients in the acute phase were routinely dosed to the ‘extrapyramidal symptom threshold’ (the dose at which extrapyramidal symptoms begin to appear with minimal rigidity; McEvoy et al. 1991).

**Economic consequences of non-adherence**

Relapse is a major contributor to the costs of schizophrenia. In the past relapse usually led to in-patient care. The introduction of assertive outreach teams and crisis home treatment teams in many countries means that today many people with schizophrenia who relapse are managed in the community. Irrespective of this, relapse still leads to increased input from mental health services and as such is expensive. A UK study calculated costs and outcomes by relapse status over a six-month period in a random sample of patients with schizophrenia (Almond et al. 2004). The costs for those who relapsed were more than four times higher than for the non-relapse group.

Several studies have estimated the economic impact of non-adherence in schizophrenia (Knapp et al. 2004; Sun et al. 2007). Knapp et al. (2004) assessed the impact of various factors, including medication non-adherence, on the treatment costs for patients with schizophrenia in the United Kingdom. Non-adherent patients were estimated to be more than one-and-a-half times more likely than adherent patients to use in-patient services. Non-adherence predicted an excess annual cost per patient of approximately £2500 for in-patient services and more than £5000 for total services. Sun et al. (2007) conducted a systematic review of the economic impact of non-adherence in the treatment of schizophrenia. Inclusion criteria were that the studies were in English language, were published between 1995 and 2007, assessed patients with schizophrenia treated in the United States, and assessed the impact of antipsychotic non-adherence in terms of direct health care costs or in-patient days. Seven studies were identified. Despite different measures of adherence, all the studies found that antipsychotic non-adherence was associated with an increased risk of relapse, increased hospitalization rate, or higher hospitalization costs. When hospital costs were extrapolated to the national level it was estimated that the annual rehospitalization cost
owing to antipsychotic non-adherence in the United States in 2005 was between $1392 million and $1826 million.

It follows that improving medication adherence in schizophrenia has the potential to reduce relapse rates and direct treatment costs. In the longer term it is possible that improved adherence may also reduce indirect costs. The published literature contains no high quality economic evaluations of antipsychotic long-acting injections (LAIs) and so the cost-effectiveness of LAIs compared to oral antipsychotic treatment remains unknown (Knapp et al. 2002). However several methodologically simpler studies at least suggest that LAIs have the potential to reduce cost. Modelling studies indicate that treatment with an FGA-LAI (Glazer & Ereshefsky 1996; Hale & Wood 1996) and RLAI (Haycox 2005) is cost-effective compared to oral antipsychotic treatment, at least in certain situations, owing to the potential to reduce relapse and in-patient bed usage. Mirror-image and observational studies for both FGA-LAIs (Haddad et al. 2009) and RLAI (Olivares 2009a, b; Olivares et al. 2008; Taylor et al. 2008) have reported reduced in-patient days, or a longer time to readmission, during LAI treatment compared to previous oral treatment suggesting an economic advantage for the LAI. The main weakness of these studies is that financial costs are either not estimated or if they are then only selected costs are assessed. In addition mirror-image studies have various methodological weaknesses, reviewed by Haddad et al. (2009), which include regression to the mean and the effect of confounders that significantly weaken this evidence.

### Interventions to improve medication adherence

Interventions to improve adherence to antipsychotic medication include psychosocial interventions, programmatic treatments, and pharmacological strategies. These interventions should not be seen as competing and in practice will often be combined. For example irrespective of whether a patient or a clinician decides to use an LAI or an oral antipsychotic, adherence is likely to be better if the medication is accompanied by psychoeducation and is supervised by an appropriate clinical team/service.

Psychosocial interventions include psychoeducation, compliance therapy, and cognitive adaptation therapy. Psychoeducation incorporates strategies to teach patients and families about schizophrenia, medication benefits and side-effects, and relapse prevention. Psychoeducation and family intervention programmes reduce psychotic relapse and improve medication adherence (Mari & Streiner 1994; Pekkala & Merinder 2002; Pitschel-Walz et al. 2001). Compliance therapy is a cognitive behavioural therapy intervention that incorporates motivational interviewing and psychoeducation to improve treatment adherence. This intervention has also improved adherence to treatment (Kemp et al. 1996, 1998). Cognitive adaptation training targets the cognitive deficits in schizophrenia with environmental supports to improve medication adherence. In a nine-month study, patients continued to have improved adherence months after completing the training (Velligan et al. 2008). Psychosocial strategies may have problems regarding the persistence of their effects if regular ‘top-ups’ are not supplied, and not all authors agree that the benefits on improved adherence are clear (Nose et al. 2003; Zygmunt et al. 2002).
An example of programmatic interventions that have improved adherence is the assertive community treatment. Assertive community treatment is a team-based, intensive case management intended to reduce hospitalizations and improve the level of functioning in patients with schizophrenia. This form of intensive case management has also improved medication adherence (Bush et al. 1990; Marshall et al. 2000).

Pharmacological interventions to improve adherence include close monitoring for medication side-effects, simplification of medication regimens, considering agents with longer plasma half-lives, and switching to antipsychotic LAIs also known as ‘depots’. The LAIs were developed to mitigate the widespread problem of non-adherence and partial adherence. Available antipsychotic LAIs include first-generation antipsychotics and second-generation antipsychotics. Several new, second-generation long-acting antipsychotics are in the later stages of development and are likely to be licensed in the coming years. Expert consensus guidelines for the treatment of schizophrenia including those of the American Psychiatric Association (Lehman et al. 2004), the National Institute of Clinical Excellence (2009a), the Canadian Psychiatric Association (2005), and the Royal Australian and New Zealand College of Psychiatrists (2005) recommend offering a long-acting injectable antipsychotic to patients in whom avoiding non-adherence is a priority. The decision to use an LAI should be made on an individual patient basis. Where possible, the patient should be fully involved in the decision-making process, even when community-treatment orders or other medico-legal constraints pertain.

**Summary and conclusions**

Schizophrenia follows a highly variable course but for most patients it is a chronic relapsing condition. The benefit of antipsychotic medication in preventing relapse is shown by both discontinuation studies and intermittent versus continuous maintenance studies. Despite this, poor adherence to antipsychotic medication is common in schizophrenia, as it is, with ‘maintenance medication’ in many chronic medical disorders such as hypertension and chronic obstructive airways disease. Adherence exists on a spectrum with most patients showing intermittent adherence. Non-adherence can be unintentional or intentional. Antipsychotic non-adherence leads to an increased risk of relapse, hospitalization, and self-harm. Relapse also worsens the longer-term prognosis of patients with schizophrenia; both relapse and duration of untreated psychosis are associated with increased disability and treatment resistance. Poor adherence is best understood in the context of a health belief model. Disease-related symptoms such as cognitive impairment and poor reality testing may limit a patient’s ability to perceive the benefits of antipsychotic therapy; however side-effects may also promote non-adherence. The clinician can use a range of interventions to improve adherence including psychosocial interventions, programmatic treatments, and pharmacological strategies including an LAI. Often a combination of these approaches will be appropriate. The approach that is adopted will depend on the individual patient and should be made jointly by the patient and clinician.
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