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Review

# Interventions to improve adherence to antipsychotic medication in patients with schizophrenia–A review of the past decade

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ABSTRACT

*Objective:* Nonadherence to antipsychotic medication is highly prevalent in patients with schizophrenia and has a deleterious impact on the course of the illness. This review seeks to determine the interventions that were examined in the past decade to improve adherence rates.
*Method:* The literature between 2000 and 2009 was searched for randomized controlled trials which compared a psychosocial intervention with another intervention or with treatment as usual in patients with schizophrenia.
*Results:* Fifteen studies were identified, with a large heterogeneity in design, adherence measures and outcome variables. Interventions that offered more sessions during a longer period of time, and especially those with a continuous focus on adherence, seem most likely to be successful, as well as pragmatic interventions that focus on attention and memory problems. The positive effects of adapted forms of Motivational Interviewing found in earlier studies, such as compliance therapy, have not been confirmed.
*Conclusion:* Nonadherence remains a challenging problem in schizophrenia. The heterogeneity of factors related to nonadherence calls for individually tailored approaches to promote adherence. More evidence is required to determine the effects of specific interventions.


## 1. Introduction

Antipsychotic medication is held to be the cornerstone in the treatment of patients with schizophrenia. Antipsychotics are effective in reducing psychotic symptoms, in preventing psychotic relapses in maintenance therapy and in improving psychosocial functioning [33]. Although some patients turn out to be treatment-resistant to all antipsychotic medication, an effective antipsychotic can be found among the available medications for the majority of patients [15]. The overall efficacy of antipsychotic medication in comparative trials seems evident. However, the grim reality we face is that the actual effectiveness of antipsychotics, for example when we look at relapse rates in naturalistic studies, is much lower than would be concluded from medication trials [62]. This efficacy-effectiveness gap may be largely due to adherence problems with antipsychotic treatment [22].

Nonadherence is highly prevalent in patients with schizophrenia. Reviews of the literature report very divergent rates of nonadherence, ranging from 20% up to 89% [113]. The overall rate of nonadherence to antipsychotics is estimated roughly at 50% [55]. The median rate of nonadherence during the first two years following a psychotic episode is 55% [30], and in first episode patients this leads to a five times higher chance of readmission within a year [86].

This rate may even be an underestimation, as it does not account for patients who refuse medication from the start or drop out of follow-up studies [115].

The consequences of nonadherence can be devastating, for patients and their families in terms of personal suffering, hospitalization, reduced quality of life as well as for society in general due to loss of income and direct costs of healthcare [109]. When looking at the problem of nonadherence, the divergent rates reported in studies may partly reflect methodological obstacles. One such obstacle concerns the difficulty to reliably measure whether a patient is taking medication or not. In many studies, self-report measures are used. In general, adherence self-reports have proved to be unreliable, as they are likely to be inaccurate and tend to overestimate actual levels of adherence [17,105]. Pill counts are considered more reliable indicators of adherence, but still offer no proof that the medication is actually taken. The measuring of serum levels is a more direct method, but this often forms an obstacle for patients who are reluctant to cooperate with blood samples. Moreover, nonadherence is not an 'all or nothing' phenomenon. Partial adherence or changing adherence over time

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frequently occurs. At first glance partial adherence seems to be a more limited problem compared to complete nonadherence. Research, however, shows that even partial nonadherence is associated with an increase in hospitalization rates and hence with poorer outcomes, proportional to increasing days of nonadherence [64,110].

This review aims at providing a comprehensive overview of the available data on interventions designed to improve adherence to medication in schizophrenia. Following an overview of the possible causes of nonadherence, we will first give a summary of the research findings published before 2000, based on two previous reviews [26,115]. Subsequently we will review the studies on interventions for improving adherence to antipsychotic medication in patients with schizophrenia published between 2000 and 2009.

## 2. Factors influencing (non-) adherence

Why do patients stop taking their antipsychotic medication, when there is clear evidence that in all likelihood doing so will lead to an unfavorable outcome? On the other hand, one might ask why patients do take their medication, as it appears to be difficult for anyone (including health care professionals themselves) to adhere to a treatment, such as complying fully with the completion of an antibiotic therapy, once the acute symptoms of an infection have disappeared. The Health Belief model [5,78] proposes that a person is willing to comply with a treatment when one realizes that one's health is at risk and one is ready to act on that threat, and when the perceived benefits of a proposed treatment outweigh the costs of that treatment. For patients with schizophrenia, there are several factors that may play an important part in this intriguing process.

From a therapeutic perspective it is most interesting to focus on modifiable factors influencing adherence to antipsychotic medication.

### 2.1. Illness awareness, insight into illness and general beliefs

Several studies and reviews report that patients with a low degree of illness awareness and insight into their illness are more likely to show poor adherence to treatment [1,30,55]. Also, general beliefs and attitudes towards health and taking medication, based on previous experiences, cultural factors and socioeconomic status, are associated with adherence [56]. These factors might contribute to the fact that the younger the age, the earlier the age of onset of schizophrenia and the shorter the duration of illness, the poorer the adherence rates are.

### 2.2. Psychopathology

Psychotic symptoms, especially paranoid and grandiose delusions have been found to be negatively associated with adherence [30], although not all studies on this issue show consistent results [56]. Cognitive impairment as a cause for nonadherence yielded inconsistent results in earlier studies [30], whereas more recent research revealed that basic cognitive deficits like attention and memory deficits are related to a patient's difficulty in managing medications [28,50]. Although negative symptoms intuitively interfere with adequate adherence and are mentioned in the literature in this respect [74], no data are as yet available to support this hypothesis.

### 2.3. Medication related aspects

Efficacy of antipsychotic medication is intricately related to adherence. The antipsychotic effect reduces psychopathology, thereby improving adequate logic reasoning, required for insight into illness. A good response to antipsychotic medication is positively related to adherence, which is clearly demonstrated in numerous studies. However, in the case of nonadherence, it seems hard to determine whether lack of efficacy of medication causes nonadherence, or that nonadherence itself leads to persistence of psychotic symptoms. In other words: is it the cause or the consequence?

Another factor regarding medication and adherence are medication side effects. Clearly, side effects are strongly and negatively correlated to adherence. With the first generation antipsychotics especially extrapyramidal side effects are reported [87,108], but also neuroleptic dysphoria may play a role [23,102]. With the second-generation antipsychotics, sedation and weight gain are associated with nonadherence [76]. In studies comparing first and second-generation antipsychotics, the latter show small advantages in tolerability and relapse rates. However these advantages are not (directly) associated with differences in adherence rates [61]. Therefore it appears that in order to improve adherence, the choice of drug should be dependent on the patient's individual attitude and response towards medication.

A third factor concerns the route of administration and dosing strategies. On the one hand low dosing may result in fewer side effects; however, very low doses may lead to sub-optimal efficacy. Reducing the dosing frequency to once-daily regimens has been demonstrated to improve adherence rates [24,38]. The use of depot medication has shown to be effective in preventing nonadherence in studies with a follow-up of 1–7 years [85]. Also, the one-year relapse rate for patients using depot medication was significantly reduced, compared to the relapse rate of patients receiving oral medication [90]. Depot medication appears particularly suitable to prevent covert nonadherence, as nonadherence is directly noticeable by depot refusal and/or no-show on physician appointments, which enables the treating physician to act on this. Nevertheless, some studies show that even with depot medication, nonadherence rates remain relatively high [13,103]. Although randomized controlled data comparing adherence to depot and oral antipsychotics are scarce due to methodological problems, the available data have led to recommendations in several guidelines for the use of depot medication for patients with known recent medication nonadherence [60].

### 2.4. Therapeutic alliance

It has been demonstrated that a good therapeutic alliance is associated with better adherence rates [32]. Presumably related to this, better adherence rates are also predicted by adequate discharge planning and maintaining contact with outpatients [56,66].

### 2.5. Environmental factors

Social support and in particular the support of family or friends in assisting with medication taking, as well as stability of living conditions, show some positive association with adherence [30,56].

### 2.6. Substance abuse

Substance abuse is highly prevalent in patients with schizophrenia and is strongly associated with nonadherence, leading to a 13-fold increased risk of patients with schizophrenia and substance abuse to be non-adherent, in comparison with patients who do not use substances [51].