

# Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies

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**Abstract:** Nonadherence with medication occurs in all chronic medical disorders. It is a particular challenge in schizophrenia due to the illness's association with social isolation, stigma, and comorbid substance misuse, plus the effect of symptom domains on adherence, including positive and negative symptoms, lack of insight, depression, and cognitive impairment. Nonadherence lies on a spectrum, is often covert, and is underestimated by clinicians, but affects more than one third of patients with schizophrenia per annum. It increases the risk of relapse, rehospitalization, and self-harm, increases inpatient costs, and lowers quality of life. It results from multiple patient, clinician, illness, medication, and service factors, but a useful distinction is between intentional and unintentional nonadherence. There is no gold standard approach to the measurement of adherence as all methods have pros and cons. Interventions to improve adherence include psychoeducation and other psychosocial interventions, antipsychotic long-acting injections, electronic reminders, service-based interventions, and financial incentives. These overlap, all have some evidence of effectiveness, and the intervention adopted should be tailored to the individual. Psychosocial interventions that utilize combined approaches seem more effective than unidimensional approaches. There is increasing interest in electronic reminders and monitoring systems to enhance adherence, eg, Short Message Service text messaging and real-time medication monitoring linked to smart pill containers or an electronic ingestible event marker. Financial incentives to enhance antipsychotic adherence raise ethical issues, and their place in practice remains unclear. Simple pragmatic strategies to improve medication adherence include shared decision-making, regular assessment of adherence, simplification of the medication regimen, ensuring that treatment is effective and that side effects are managed, and promoting a positive therapeutic alliance and good communication between the clinician and patient. These elements remain essential for all patients, not least for the small minority where vulnerability and risk issue dictate that compulsory treatment is necessary to ensure adherence.

**Keywords:** adherence, nonadherence, antipsychotics, schizophrenia, long-acting injections, relapse, risk factors

## Introduction

The challenge of patients not following medical advice is not new. In the 4th century BC, Hippocrates observed that some patients did not take their prescribed treatments.<sup>1</sup> In the 19th century, Robert Koch, the father of modern bacteriology, was critical of patients with tuberculosis who did not adhere to strategies to reduce infection. In 1955, soon after the introduction of antibiotics, it was observed that approximately one third of patients did not complete a 1-week course of oral penicillin for acute pharyngitis or otitis media.<sup>2</sup> A recent national guideline concluded that between a third and one half of medicines that are prescribed for long-term conditions are not taken by

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patients as recommended by the prescriber.<sup>3</sup> Poor adherence is not limited to medication-taking and encompasses other treatment recommendations or “healthy behaviors”, such as exercise and diet. This is recognized by the World Health Organization, which defines therapeutic adherence as “the extent to which a person’s behavior corresponds with agreed recommendations from a health care provider”.<sup>4</sup>

Medication adherence can be defined as the extent to which a patient’s medication-taking matches that agreed with the prescriber. A range of alternative terms have been used, including treatment compliance and fidelity, but adherence is currently favored partly due to its neutrality. In contrast, compliance implies an unequal power balance between the prescriber and patient. Medication adherence lies on a spectrum ranging from individuals who take no medication, despite agreeing with the prescribing clinician to do so, to those who take each dose precisely on time. In between these two extremes are patients who show varying degrees of adherence, taking some medication some of the time but not consistently as prescribed. This is termed partial adherence, and includes those who consistently miss doses on a regular basis and those who go through cycles of varying levels of adherence over time, eg, taking 100% of medication during a relapse but gradually reducing their intake when in remission. Problems with adherence can include taking excess medication, but this is less common, and this review is concerned with those who take less medication than prescribed. Adherence is usually dichotomized for research purposes and is often defined as missing at least 20% of the medication in question. This cutoff has validity in predicting subsequent hospitalization across several chronic conditions,<sup>5</sup> although for individual patients the degree of nonadherence that affects health outcomes will vary and depend on multiple factors including the condition, its severity, the risk of recurrence, the relative effectiveness of the medication, and its dose and frequency of administration. In this paper, the term “nonadherence” is used to refer to total nonadherence and clinically relevant degrees of partial adherence.

Although nonadherence is a problem throughout medicine, there are several factors that make it especially challenging in schizophrenia. These include lack of illness awareness (a term encompassing insight, but also attitudes and beliefs about the nature of the illness), the direct impact of symptoms (including depression, cognitive impairment, and positive and negative symptoms), social isolation, comorbid substance misuse, stigma, and the increasing fragmentation of mental health services in many countries. Not surprisingly, these multiple disadvantages for people with schizophrenia

mean the prevalence of nonadherence in psychosis is at least as high if not higher than in many chronic medical disorders.<sup>6</sup> In this review, we concentrate on nonadherence with antipsychotic medication. We consider the prevalence of nonadherence, its costs, and the factors that contribute. Next we review the assessment of nonadherence in research studies and clinical practice. We review a range of interventions to improve adherence, including basic strategies that should accompany prescribing, specific psychosocial interventions, antipsychotic long-acting injections (LAIs), electronic reminders, service interventions, and financial incentives. In reality, there is overlap between some of these approaches. We conclude by highlighting some key areas for future research. Strategies to improve adherence assume that in clinical practice the benefits of antipsychotic medication are often undermined by nonadherence. In view of this, we start with a brief review of the evidence base for the use of antipsychotic medication in the management of schizophrenia.

## Antipsychotic medication and schizophrenia

The course and outcome of schizophrenia show considerable variability between individuals.<sup>7</sup> A small proportion of individuals experience a single psychotic episode, make a full recovery, and remain well without medication. However, for most of those affected, schizophrenia is a chronic condition, although this should not obscure the fact that the long-term prognosis is favorable or at least stable for a high proportion. In a 5-year follow-up of patients who experienced a first episode of psychosis, the cumulative first relapse rate was 82% and the second relapse rate was 78%.<sup>8</sup> A systematic review of longitudinal studies in first-episode psychosis, with a mean follow-up of 35 months, reported a good outcome for 42% and a poor outcome for 27% of individuals.<sup>9</sup>

The efficacy of antipsychotic medication in the acute and maintenance treatment of schizophrenia is clear from large meta-analyses of placebo-controlled trials. A meta-analysis of 38 randomized controlled trials (RCTs) that compared second-generation antipsychotics with placebo in acute treatment of schizophrenia showed a moderate effect size of approximately 0.5, with a number needed to treat of six for response.<sup>10</sup> Another meta-analysis of 65 trials, in which patients stabilized on antipsychotic medication were randomized to continue medication or switch to placebo, showed that antipsychotics significantly reduced the rate of relapse at 1 year compared with placebo, with a number needed to treat to benefit of three (Figure 1).<sup>11</sup> Those treated with

antipsychotic drugs were also less likely to be admitted to hospital or to drop out for inefficacy or for any reason.<sup>11</sup>

Antipsychotics are not a panacea. Their benefit in acute treatment is largely in terms of the treatment of positive symptoms while other symptom domains, particularly negative symptoms, show less improvement. Some patients do not respond to antipsychotic medication including clozapine; the proportion of such patients is higher in tertiary services<sup>12</sup> but treatment resistance occurs, albeit less frequently, in first-episode patients.<sup>13</sup> Maintenance antipsychotic treatment does not eliminate the risk of relapse, but does reduce it. Antipsychotics can have a wide range of side effects.<sup>14</sup> In the maintenance meta-analysis by Leucht et al, weight gain, sedation, and movement disorders were more common in those treated with antipsychotic medication than in those treated with placebo (Figure 1).<sup>11</sup> Antipsychotic-induced weight gain,<sup>15</sup> metabolic disturbance,<sup>16</sup> and hyperprolactinemia<sup>17</sup> are particularly important due to their potential impact on future physical health. Antipsychotics can also impair cognition.<sup>18</sup> Many of these adverse effects are dose-related.<sup>14</sup>

There is growing interest in the possibility that carefully selected patients with schizophrenia may be able to be treated both acutely and long-term with psychological interventions as an alternative to medication.<sup>19</sup> At present, the data are limited and such an approach cannot be advocated as routine

practice. Most guidelines for the treatment of schizophrenia recommend that pharmacological relapse prevention strategies are considered for every patient diagnosed with schizophrenia, with treatment being continued for between 1 and 2 years after a first episode.<sup>20</sup> In clinical practice, the duration of maintenance treatment needs to be determined on an individual patient basis by weighing up its advantages and disadvantages. Many patients require indefinite antipsychotic treatment, although this should be at the lowest effective dose and combined with psychosocial approaches and regular follow-up that includes monitoring for side effects, with intervention as appropriate.

### Prevalence of antipsychotic nonadherence

Nonadherence with medication is a problem in all chronic medical conditions including, for example, the use of insulin in diabetes,<sup>21</sup> antihypertensives in hypertension,<sup>22</sup> brimonidine in glaucoma,<sup>23</sup> antiretroviral therapy in those with human immunodeficiency virus,<sup>24</sup> and statins in those with hyperlipidemia.<sup>25</sup> A review of medication adherence in psychiatric and physical disorders, spanning papers published between 1975 and 1996, reported the mean amount of prescribed medication taken to be 58% for patients prescribed antipsychotics, 65% for those prescribed antidepressants, and 76% for those prescribed medication for physical disorders.<sup>6</sup>

Patient Related Outcome Measures downloaded from https://www.dovepress.com/ by 162.129.250.13 on 03-Apr-2017 For personal use only.

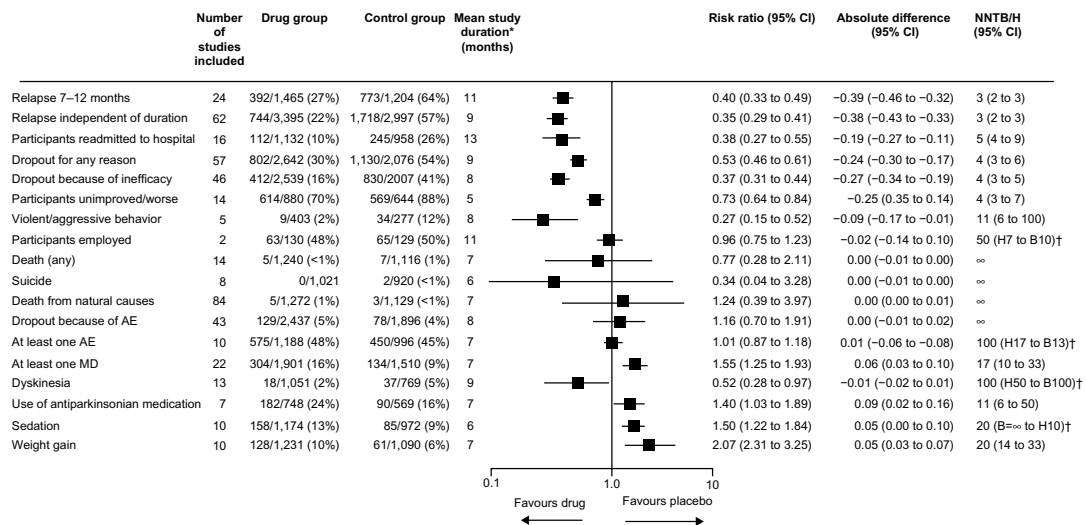


Figure 1 Efficacy of maintenance antipsychotic medication versus placebo in schizophrenia (65 trials, n=6,493).

Notes: Data are n/N (%) unless otherwise stated. The random effects model by DerSimonian and Laird<sup>144</sup> was used throughout, with weights calculated by the Mantel-Haenszel method. \*Weighted by sample size of individual trials. †Because of space limitations, we did not use the display suggested by Altman.<sup>145</sup> Reprinted from The Lancet, 379, Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis, 2063–2071, Copyright © 2012, with permission from Elsevier.<sup>11</sup>

Abbreviations: AE, adverse event; MD, movement disorder; n, number of participants with an event; N, number of studies; CI, confidence interval; NNTB/NNTH, number needed to treat to benefit/harm; H, harm; B, benefit.

The authors concluded that nonadherence may be a greater issue in psychiatry than in general medicine, but that the difference could reflect differences in the methodology used to assess adherence. Studies using electronic monitoring show that the extent of antipsychotic nonadherence is underestimated by psychiatrists.<sup>26</sup>

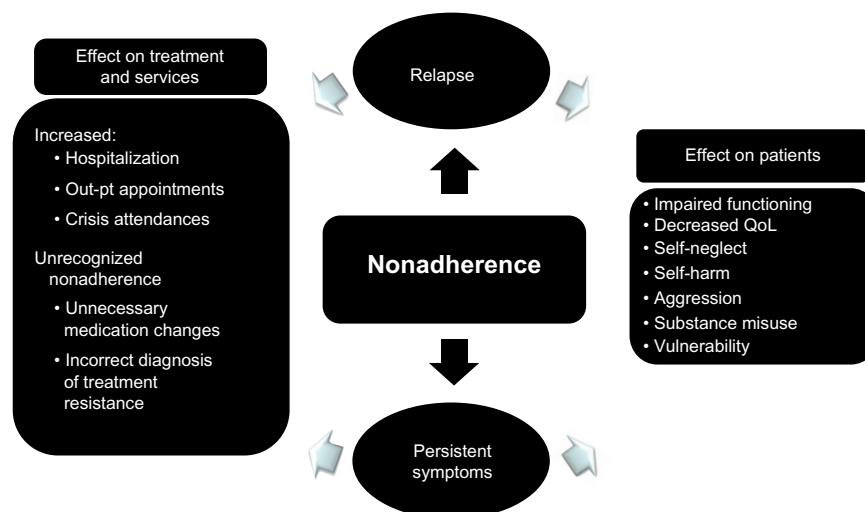
The rate of nonadherence with antipsychotics in schizophrenia varies between studies, reflecting differences in the populations studied and the methodology used in terms of the definition and measurement of adherence and the period of time over which it is assessed (see Assessment of nonadherence section). However, there is a clear consensus that nonadherence is a major problem. A systematic review of 39 studies reported a mean rate of medication nonadherence in schizophrenia of 41%.<sup>27</sup> When the analysis was restricted to the five methodologically most rigorous studies, which included defining adherence as taking medication at least 75% of the time, the nonadherence rate increased to 50%.

Valenstein et al assessed approximately 34,000 Veterans Affairs patients with schizophrenia.<sup>28</sup> Medication possession ratios (MPRs, ie, percentage of days with an antipsychotic prescription) were calculated for 4 consecutive years, with good adherence defined as an MPR  $\geq 0.8$  during a year. Patients were divided into those who had consistently poor adherence (MPR  $< 0.8$  in all years) and consistency good adherence (MPR  $\geq 0.8$  in all years). The cross-sectional prevalence of poor adherence was stable

over time, with about 36% being poorly adherent each year. Adherence was not a stable trait, and when assessed over 4 years, 18% of subjects had consistently poor adherence, 39% had consistently good adherence, and 43% were inconsistently adherent. Thus, in total, 61% of patients had at least 1 year during which they showed poor adherence. Those with consistently poor adherence were more likely to be younger, nonwhite, have comorbid substance misuse, and to have been admitted to a psychiatric hospital. This study, like many, would underestimate nonadherence because it assumes that collecting medication from a pharmacy equates to taking it.

## Costs of nonadherence

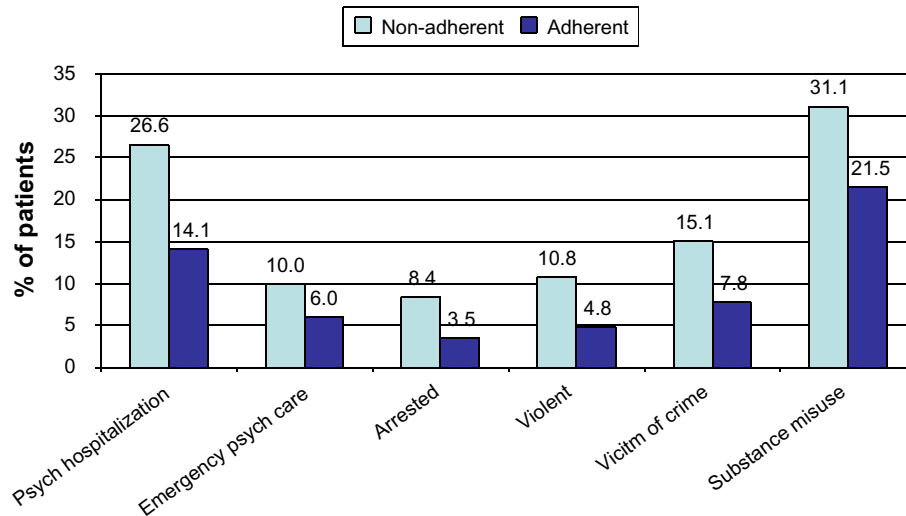
Nonadherence with antipsychotic medication can lead to relapse for patients in remission and persistent symptoms for those with existing symptoms, and both scenarios can cause multiple patient and service costs (Figure 2). The costs of nonadherence were demonstrated in a 3-year, prospective, observational study of schizophrenia in the USA in which a composite measure of patient-reported adherence and MPR was used to determine adherence.<sup>29</sup> Outcome data were gathered at regular points throughout the study by reviewing medical records and conducting structured interviews with the participants. Nonadherence was associated with a significantly higher rate of psychiatric hospitalization, use of emergency psychiatric services, arrest, violence, victimization, and substance use (Figure 3) plus poorer mental functioning,



**Figure 2** Consequences of nonadherence to antipsychotic medication.

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**Abbreviation:** QoL, Quality of life.



**Figure 3** Association between antipsychotic nonadherence and outcome in a 3-year prospective observational US study.

**Notes:** Adherence based on patient-reported adherence and medication possession ratio (% days with prescription for any antipsychotic). Data adapted from Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatry*. 2006;67(3):453–460.<sup>29</sup> Copyright © 2006, Physician's Postgraduate Press, Inc.

**Abbreviation:** Psych, psychiatric.

poorer life satisfaction, and more alcohol-related problems. Nonadherence in the first year predicted significantly poorer outcomes in the following 2 years. A 3-year, prospective, observational, European study of outpatients with schizophrenia found that nonadherence was significantly associated with an increased risk of relapse, hospitalization, and suicide attempts.<sup>30</sup> An association between antipsychotic nonadherence and an increased rate of self-harm<sup>31</sup> and suicide<sup>32</sup> has been reported in other studies. A recent analysis from the CUTLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) clinical trial in the UK showed that improved antipsychotic adherence led to improved quality of life.<sup>33</sup>

Relatively short periods of nonadherence have been linked to poorer outcomes. Two US studies, both using pharmacy refills to measure adherence, found that missing medication for 10 days was associated with an increased risk of psychiatric hospitalization.<sup>34,35</sup> In one study, the risk of hospitalization was correlated with the degree of nonadherence, with a gap of 1–10 days in antipsychotic medication being associated with an odds ratio for admission of 1.98, a gap of 11–30 days with an odds ratio of 2.81, and a gap of more than 30 days with an odds ratio of 3.96.<sup>35</sup> It is important to highlight that the degree of nonadherence leading to poorer clinical outcomes will vary greatly between individuals and be influenced by multiple factors. Patients with a low risk of relapse may remain well despite marked degrees of nonadherence. This may explain

why some intervention studies of nonadherence report improved medication adherence but without improvement in clinical outcomes.

Relapse after a first episode of psychosis can be particularly damaging, as those affected are likely to be relatively young and at a critical period in their life. The only factor predictive of relapse in a 3-year follow-up of first-episode patients was medication nonadherence.<sup>36</sup> In a separate 5-year, follow-up study, discontinuation of medication after a first psychotic episode increased the risk of relapse by five-fold.<sup>8</sup> Successive relapses in schizophrenia are associated with a decrease in treatment response<sup>37</sup> and possibly a worsening of the disease process<sup>38</sup> and brain shrinkage.<sup>39</sup> Irrespective of organic mechanisms, successive relapse is likely to lead to accrual of disability, because each relapse can damage an individual's confidence, social networks, and employment opportunities.

The impact of antipsychotic nonadherence on economic costs in people with schizophrenia is complex and varies across services.<sup>40</sup> QUATRO (Quality of Life following Adherence Therapy for People Disabled by Schizophrenia and their Carers), a multicenter European RCT, found that community-based day service costs and societal costs were lower among nonadherent patients with schizophrenia and that nonadherence was not significantly associated with total health and social care costs.<sup>40</sup> In contrast, two systematic reviews, one of seven studies conducted in the USA<sup>41</sup>



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