

Antipsychotic Medication Nonadherence: Risk Factors and Remedies

Abstract: Understanding determinants of antipsychotic medication adherence is critical as nonadherence plays a significant role in psychotic relapse and each relapse contributes to accrued social toxicity and disability. “Insight” or lack thereof and a negative medication attitude are critical variables that have repeatedly been shown to be risk factors for nonadherence. We examine how those risk factors can lead to nonadherence and describe evidence-based interventions to improve nonadherence. We also discuss newer approaches adapted from other branches of medicine that have shown some promise in increasing adherence to antipsychotics, specifically directly-observed-therapy (DOT) and providing financial incentives. Adherence-improving interventions need to be deployed in a stepped-up manner of increasing intensity and tailored to the specific etiologies of nonadherence.

ANTIPSYCHOTIC NONADHERENCE

Suboptimal adherence to antipsychotic medications plays a major role in determining the frequent relapse and rehospitalization that is characteristic of schizophrenia. Antipsychotic medications are effective in the treatment of acute episodes of psychosis (1) and in the prevention of relapse (2), reducing the risk of relapse in both first-episode (3) and chronic schizophrenia (4) patients. Although estimates of nonadherence vary widely depending on the sample, stage of illness, methodology used to assess adherence, and duration of follow-up, a recent review article estimated that 41% of schizophrenia patients are nonadherent (5). It is important to note that insufficient adherence to medications is a pervasive problem in all of medicine (6). For example, adequate 2-year adherence to statins for the secondary

prevention of further cardiac events was only 40% in a cohort of elderly patients following an acute coronary syndrome (7), suggesting widespread difficulties adhering to maintenance medication in the general population and not just psychiatric patient populations. However, while patients with schizophrenia share some risk factors for nonadherence with medical patients (e.g. poor memory) they also pose specific challenges (e.g. lack of insight into illness).

Understanding determinants of antipsychotic medication adherence in schizophrenia patients is critical as each psychotic relapse can contribute to accrued social toxicity and disability; or as Lieberman and Fenton put it, “untreated psychosis damages lives” (8). In addition to the undisputed social toxicity, some have argued that untreated psychosis may have neurotoxic effects (9), although there is currently limited evidence to support this theory and confounding variables make this difficult to study (10). In this clinical review article, we will examine negative drug attitude and lack of insight as two important clinical risk factors for nonadherence in patients with schizophrenia and review interventions to improve adherence to antipsychotics.

RISK FACTORS FOR NON-ADHERENCE

Many studies have examined risk factors for antipsychotic nonadherence in patients with schizophrenia. In a major literature review of 39 articles, Lacro

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Dr. Freudenreich reports *Consultant:* Beacon Health Strategies, Transcept; *Research Grant:* Pfizer, *Honorarium:* Reed Medical Education

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Dr. Cather reports no competing interests.

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and colleagues (5) identified the following consistent predictors of nonadherence: poor insight, negative attitude or subjective response toward medication, previous nonadherence, substance abuse, shorter illness duration, inadequate discharge planning or aftercare environment, and poorer therapeutic alliance. A recent cohort study in Ireland examined nonadherence prospectively in 171 first-episode psychosis patients and identified almost a quarter of patients (24%) as nonadherent at the 4 year follow up (11). In this study of individuals early in the course of treatment, nonadherence was associated with substance misuse, lack of insight, and negative attitudes toward medications.

NEGATIVE DRUG ATTITUDE

Drug attitude correlates with adherence and refers to the patient's overall appraisal of the risks and benefits associated with a particular medication (12). It can easily be measured with the Drug Attitude Inventory (13), originally a 30-item true/false scale (now often used in an abbreviated 10-item version) assessing subjective negative and positive effects of medication and beliefs about the meaning of taking medication. Antipsychotic side effects, such as extrapyramidal side effects, sedation, weight gain and sexual side effects make an important contribution to a negative drug attitude and increase the risk for nonadherence. Freudenreich and colleagues (14) did not find differences in drug attitude between patients taking first-generation agents and those taking second-generation agents, suggesting that the patient's appraisal of side effect burden may be more important in determining drug attitude than the type of side effect. Moreover, Leucht and Davis' (15) recent reappraisal of the problematic and arbitrary distinction between first- and second-generation antipsychotics cautions clinicians to simply make side effect assumptions based on the first- and second-generation distinction. Instead, clinicians need to comprehensively assess and monitor side effect profiles of antipsychotic medications regardless of class assignment.

In first-episode patients, treatment effectiveness has been shown to be a powerful predictor of adherence (16). Using data from the European First Episode Schizophrenia Trial (EUFEST), Gaebl and colleagues (12) found that drug attitude was a valid and the strongest predictor of later drug discontinuation. Sexual side effects and a high psychopathology score (consistent with lack of effectiveness) also predicted nonadherence in this population.

LACK OF INSIGHT

Although the concept of "insight" has played an important role in the classification and treatment of many psychiatric disorders, it is perhaps most central to psychotic disorders. In fact, "lack of insight" was identified in a seminal World Health Organization study as a pathognomonic, core symptom of schizophrenia (17). Retained insight is among the diagnostic criteria for the recently proposed illness category of "Attenuated Psychosis Syndrome" (18) (see DSM-5 website (19) for proposed criteria). Aubrey Lewis (20) defined insight as "a correct attitude to a morbid change in oneself." Since his early definition, insight has been expanded into a multidimensional construct, comprising at least 3 agreed-upon dimensions (21): awareness of symptoms (i.e. capacity to relabel inner experiences as pathological symptoms); recognition of mental illness (i.e. attributing symptoms to a psychiatric illness), and acceptance of need for treatment. The latter dimension is generally meant to imply that patients accept *psychiatry's remedies* in the form of medications. Subsequent authors (e.g. Kirmayer and colleagues (22)) have refined this definition, by including the socio-cultural dimension in recognition that a patient's insight is not determined in a vacuum but instead by a clinician who measures a patient's agreement with the clinician's professional view. Insight can thus be understood as the end-result of an intersubjective construction of meaning. Tranulis and colleagues (23) proposed the term "narrative insight" to describe this construction of meaning about illness. Narrative insight is developed not only through abstract reasoning and introspection, but also through concrete interpersonal interactions and actual experiences of illness and treatment.

Better illness insight in schizophrenia matters with regards to medications as it is a robust predictor of better adherence (24). Conversely, many studies have shown that lack of insight is associated with treatment discontinuation and poorer outcomes (25). Moreover, a systematic literature review concluded that patients with poor insight are very likely to be deemed incompetent (26) which might have significant medical-legal implications. A subgroup of patients with poor insight seems to have a stable, anosognosia-like neurocognitive deficit (27). Incompetent patients with poor insight who actively refuse medications require court-mandated assisted treatment approaches in order to receive treatment. In many cases, however, there is partial insight (28) which is sufficient to enable clinicians and patients to collaborate productively with regards to psychiatric treatment needs and choice.

The remedies for nonadherence discussed in the next section are most appropriate for patients with at

least partial insight and for those patients in whom nonadherence is inadvertent (e.g. forgetting to take medications due to memory problems). However, the adherence-improving measures described below can be applied to all patients who are willing to go along with treatment, regardless of degree of insight, as insight is a helpful but not necessary ingredient in adherence.

REMEDIES FOR NONADHERENCE

In order for nonadherence to be remedied, it must first be recognized. An underappreciated aspect of nonadherence is how commonly it goes undetected by clinicians, patients, and families. Both clinicians and patients overestimate adherence and consequently do not necessarily appreciate that adherence is a problem (29, 30). In one prospective trial of 52 schizophrenia outpatients, adherence rates calculated by pill count were strongly correlated with electronic monitoring but only weakly with either clinician estimate or patient self-report (31). Medication drug levels did not correlate with any measure of adherence. Interestingly, clinical state correlated with adherence estimates by both clinicians and patients, suggesting that clinicians and patients use clinical state as a proxy of adherence. Additionally, nonadherence is not a dichotomous either-or variable but exists on a continuum, such that partial adherence is also possible. However, even partial adherence matters with regards to rehospitalization rates and symptom exacerbation. Weiden and colleagues (32) have used California Medicaid pharmacy refill and medical claims data to show that partial adherence predicts rehospitalization risk in a dose-dependent manner.

Subotnik and colleagues (33) found in a prospectively assessed cohort of outpatients with early course schizophrenia that even a mild degree of nonadherence robustly predicted psychotic symptom exacerbation.

The relative contributions of nonadherence risk factors will be different for different patients and intervention selection depends on the reason for nonadherence. Velligan and colleagues (34) proposed a 3-tier approach to address adherence based on a public health model of intervention (i.e. universal, selective, and indicated prevention). Under this model, it is suggested all patients receive universal prevention in the form of psychoeducation and general systems-based interventions. Selective intervention, a higher level of care (e.g. implementing pill organizers, enlisting families in medication supervision), is indicated for patients who are judged to be at high risk for nonadherence. The risk assessment takes into account prior adherence and treatment attitude. Of note, behavioral tailoring, linking medication taking behavior to a routine daily behavior (e.g. brushing one's teeth) has been demonstrated to improve adherence to antipsychotic medication among individuals with schizophrenia (35). Patients who are known to not take their medications should receive appropriate indicated prevention (e.g. directly observed therapy (DOT) as described below). Table 1 summarizes some remedies for nonadherence discussed in the following section.

IMPROVING THE THERAPEUTIC ALLIANCE

Especially in the early phases of treatment, it has been shown that perceived clinic or physician support

Table 1. Remedies for Nonadherence to Antipsychotic Medications in Schizophrenia Patients

Risk Factor ^a	Intervention ^b
<u>For intended nonadherence</u>	
Poor therapeutic alliance	Optimize overall care experience Minimize perceived coercion
Negative drug attitude	Persist in trying to achieve good efficacy Increase "subjective well-being under neuroleptics"
Poor insight ^c	Consider long-acting injectable (LAI) antipsychotic Consider directly observed therapy (DOT) Incentivize taking antipsychotics (e.g. financial) Use motivational principles (e.g. Compliance Therapy)
<u>For unintended nonadherence</u>	
Cognitive difficulties	Consider Cognitive Adaptation Training (CAT) Consider long-acting injectable (LAI) antipsychotic Consider directly observed therapy (DOT)

^a Risk factors are not mutually exclusive

^b The interventions are not specific for just one risk factor. For example, DOT would also be appropriate for patients with a poor therapeutic alliance or negative drug attitude.

^c In some patients insight per se might not be amenable to change

is a powerful predictor of adherence (36). Indeed, when patients do not have direct experience with medications, trust might be the most important predictor of adherence. Trust was identified as one of the key predictors of adherence in first episode psychosis samples (37) and described retrospectively as a crucial initial factor in accepting treatment (38). In a sample of 228 patients with schizophrenia or schizoaffective disorder admitted with an acute exacerbation of psychosis, negative treatment attitudes were predicted by a less positive relationship with the prescriber, perceived coercion during admission, and low insight (36). Interventions should thus focus on improving the overall treatment experience as well as experience with specific medications, regardless of the patient's explanatory framework. The most critical question is not whether a patient agrees with the clinician's diagnosis but rather whether the patient sees the role of psychiatric treatment as at least potentially beneficial. Although it remains unclear if perceived coercion negatively affects short-term outcomes (39) it seems reasonable to suggest that clinicians and health care systems try to reduce the amount of perceived coercion to avoid alienating patients.

IMPROVING ATTITUDE TOWARD TREATMENT

Beck and colleagues (40) have pointed out that targeting treatment-related attitudes has a better chance of improving adherence than interventions intended to increase global illness insight. Letting patients work out the benefits and risks from taking medications to facilitate more positive drug attitudes is a strategy consistent with a shared-decision making approach (41). Another way to increase positive medication attitude is to improve subjective well-being while taking antipsychotic medication (also referred to as "subjective well-being under neuroleptic treatment" or SWN for short)—for example by reducing dose to target itinerant side effects or by adding medications to decrease negative mood states such as anxiety or depression (42). Showing flexibility in dosing and switching medications are frequently necessary maneuvers to improve SWN. Unfortunately, psychiatric medications are often only partially effective and invariably have side effects. Patients learn that increased efficacy (e.g. taking a medication regularly) can lead to increased side effects (43).

IMPROVING INSIGHT

The general interventions discussed above and the specific intervention strategies that will be described below can at least partially circumvent the issue of insight as insight is neither necessary nor

sufficient with regards to treatment adherence. It remains to be seen to what extent insight can be improved in at least some patients with schizophrenia and if improved insight then increases antipsychotic adherence. A randomized, multisite trial that attempts to increase insight in schizophrenia is currently conducted in the Netherlands, comparing an insight-increasing social-cognitive treatment with cognitive remediation as the control group (25).

COMPLIANCE THERAPY

Compliance therapy (CT) is an approach rooted in cognitive-behavioral therapy and motivational interviewing that attempts to help patients weigh risks and benefits from treatment, similar to how patients would approach their treatment for hypertension or diabetes (44). A key component of motivational interviewing as it relates to CT is to assist the patient creating discrepancies between his or her goals and values vis-à-vis his or her current state in the service of enhancing adherence to facilitate increased life satisfaction. While an initial randomized-controlled trial of CT showed improved adherence and a reduced rate of relapse following hospital discharge (45), a subsequent multicenter effectiveness trial failed to replicate the benefit seen in the initial trial (46). It remains to be seen whether subgroups of patients may be more receptive to CT than others.

LONG-ACTING INJECTABLE ANTIPSYCHOTICS (LAIs)

LAI are effective in reducing symptomatic exacerbations and relapse in the maintenance phase of patients with schizophrenia (47). A recent randomized trial in 369 schizophrenia patients who were either hospitalized or at high risk of hospitalization compared clinician-choice oral antipsychotics with long-acting injectable risperidone (48). No difference in hospitalization rates, symptom improvement and quality of life between the treatments was found, suggesting that in those patients willing to consider either oral medications or a LAI (a condition for participation in this trial) there is no benefit from long-acting formulations over oral antipsychotics. More generally, although LAI are often suggested for patients with no insight who do not want to take any medication, challenges remain in developing interventions to enhance motivation to accept LAIs.

COGNITIVE ADAPTATION TRAINING (CAT)

Schizophrenia-associated neurocognitive impairment is an important factor that can contribute to inadvertent poor adherence (35). Velligan and

colleagues (49) designed a multipronged intervention (cognitive adaptation training or CAT) to help patients adhere better to medication. The 9-month intervention consisted of tailored environmental support and compensatory strategies and improved adherence significantly compared with a treatment-as-usual control group. The effect of the intervention persisted beyond the intervention period, suggesting this may be a durable approach to improving adherence. Longer-term follow ups are needed to establish the durability of this approach.

DIRECTLY OBSERVED THERAPY

In general medicine, directly observed therapy (DOT) is used for patients with infectious diseases like human immunodeficiency virus (HIV) or tuberculosis where a high degree of adherence is critical for good outcomes (50, 51). The main intervention in DOT is as the name implies directly observing and thus verifying that the patient actually takes the medication as prescribed. In psychiatric setting, this can easily be instituted in group homes. For patient's living independently, visiting nurses or family members can be enlisted to achieve the same degree of supervision. Farooq and colleagues (52) adapted DOT for schizophrenia outpatients in a resource-poor area. They randomized 110 patients to family-supervised medication administration or treatment as usual (TAU). The intervention resulted in better adherence in the intervention group (complete adherence 67.3%) than in the TAU group (45.5%). In the future, information technology can play a greater role in directly monitoring patients and their adherence. Spaniel and colleagues (53) piloted a cell-phone based telemonitoring system to detect nonadherence and signs of early relapse in 45 patients. This intervention reduced hospitalizations by 60% compared with the same time period prior to participation.

FINANCIAL INCENTIVES

Paying patients to take medications can improve medication adherence (54). In addiction medicine, giving patients vouchers in exchange for "clean" urines is one the most effective interventions (contingency management) (55, 56). Informally, nudging and subtle coercion by clinicians and family members (e.g. withholding money) are little discussed yet often employed tools (38). Providing financial incentives to take antipsychotic medications poses its own set of ethical questions (57, 58). Nevertheless, a pilot study in the Netherlands showed that acceptance of injections in 5 patients increased from 44% to 100%, leading to an almost 10-fold reduction in days spent

in the hospital (59). The incentives approach is currently being studied in the randomized Financial Incentives for Adherence Trial (FIAT) in Great Britain (60).

Achieving good antipsychotic medication adherence is an important treatment goal in the care of patients with schizophrenia as good adherence improves clinical outcomes. Clinicians need to take into account specifically insight and drug attitude when working with this patient population. A wide variety of adherence-improving interventions that differ in intensity and intrusiveness are available for deployment in a stepped-up and tailored manner, depending on the etiology of poor adherence.

NOTE

References that are key to this update are denoted with a [*].

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