Understanding and Addressing Adherence Issues in Schizophrenia: From Theory to Practice

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If an easy answer to the problem of medication nonadherence in schizophrenia existed, it would have already been found. Despite the magnitude of the problem, in the past decade, significant advances have been made in understanding the nature of the adherence problem in schizophrenia. Just as there is no single adherence intervention but a range of interventions that can be matched to the specific challenges of the individual patient, there is not a single theory that explains adherence and nonadherence. Rather, there are a range of theories and concepts, with their own strengths and limitations. The goal of this article is to help provide a crosswalk from some of the emerging theories and concepts to practical clinical management approaches. To enhance understanding of this complex issue and help practitioners implement practical therapeutic interventions that encourage adherence, the following 5 theories regarding medication adherence are presented and suggestions made for applying them in clinical practice: (1) Adherence is not a clinical outcome and only matters as it interferes with outcome. (2) In schizophrenia, adherence problems are often entangled with efficacy limitations of antipsychotics. (3) Adherence can be viewed as a behavior (taking/not taking) or an attitude (prefers taking/prefers stopping). (4) When considering adherence *attitudes*, patient belief is *always* reality. (5) Adherence *behavior* changes and fluctuates over time and should be considered as part of the illness in the context of the long-term trajectory of desired clinical outcomes such as recovery.

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In treating schizophrenia, nonadherence to medication is one of the reasons that remission, the optimal outcome of treatment, is not achieved. If managing medication nonadherence were easy, clinicians would already know the best strategies, but understanding nonadherence and improving adherence are complicated. It is known that the way to approach the problem is to match an intervention to the specific adherence barriers and concerns confronting the individual patient, but there are many challenges in doing so. In many ways, part of the progress has been in understanding what does not work. For example, the availability of newer second-generation antipsychotics that are often much less distressing for patients does not automatically translate into better adherence compared with the older medications. Just as no single intervention approach for nonadherence works for all patients, no single concept or theory explains the entire problem, and a more flexible approach to adherence should be embraced.

Despite these challenges, significant advances have been made in the theoretical understanding of the causes and risk factors for medication nonadherence, as well as the companion understanding of why patients actually take their medication. The author of this article is confident that these advances in conceptualizing adherence and nonadherence can and will translate into better clinical outcomes for patients with schizophrenia.

The first step to achieve such an admittedly ambitious goal is to explain some of these concepts, including their strengths and limitations. The second step is to provide clinical situations in which some of these concepts and theories can be applied with the goal of helping patients achieve better outcomes. This article will present 5 concepts or theories about antipsychotic medication adherence in schizophrenia, along with practical therapeutic interventions that can be used in clinical situations. This review is not meant to be comprehensive and does not present all current theories in the same amount of detail; research methodology and assessment issues are not emphasized. The clinical focus here is on adherence to ongoing, long-term antipsychotic medication rather than adherence during the acute psychotic episode.

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FACTORS CONTRIBUTING TO ADHERENCE AND NONADHERENCE

The literature[1–4] suggests many reasons why patients stop taking medication and describes numerous factors that contribute to nonadherence, such as the presence of persistent positive, negative, or cognitive symptoms; distress from side effects; change in relationships with people who support or supervise medication-taking; length of time the patient is stable; and the presence or absence of comorbid substance abuse. These factors can be arranged into various domains and specific problems categorized into patient, disease, medication, side effect, and environmental categories. These categories are helpful in providing an overview of the almost overwhelming number of factors that have the potential to waylay a treatment plan. The downside of failing to integrate these factors into a theoretical understanding of adherence and nonadherence is that clinicians may wonder where to begin when developing a treatment strategy for individual patients. A clearer understanding of concepts of adherence and nonadherence may help clinicians prioritize and individualize treatment interventions. Rather than go over the same territory as some of these excellent reviews,[1–4] this article will focus on some of the concepts with the goal of identifying approaches that will help the clinician uncover the most relevant issues for individual patients.

FIVE THEORIES REGARDING MEDICATION ADHERENCE

Theoretical models of adherence already exist,[4] but a flexible approach to adherence theory may result in a better understanding of the ways in which adherence can be defined and lead to an enhanced range of potential therapeutic interventions. Although they are not definitive, the 5 theories outlined here are relevant in day-to-day clinical practice and can be applied when prescribing antipsychotics for patients with schizophrenia (Table 1). Suggestions for putting each theory into clinical practice are included.

Table 1. Five Theories Regarding Medication Adherence in Patients With Schizophrenia

Theory	Description
Theory 1:	Adherence is not a clinical outcome and only matters as it interferes with outcome
Theory 2:	Adherence problems are often entangled with efficacy limitations of antipsychotic medications
Theory 3:	Adherence can be viewed as a *behavior* (taking/not taking medication) or as an *attitude* (prefers taking/prefers stopping medication)
Theory 4:	When considering adherence attitudes, patient belief is always reality
Theory 5:	Adherence behavior changes and fluctuates over time and should be considered part of the illness

Theory 1: Adherence Is Not a Clinical Outcome and Only Matters as It Interferes With Outcome

Symptom control, functioning, remission, and recovery are all examples of clinical outcomes. Medication adherence does not fit this category of clinical outcome. Instead, medication adherence is a means to an end, and it only matters for treatments that are effective. On the basis of extensive literature (for example, see Robinson et al.,[5] Weiden and Olfson,[6] and Weiden et al.[7]), adherence to antipsychotic medication is clearly a major factor in helping control symptoms and allowing patients to maintain stability and remain in the community. Medication adherence is also a necessary platform for other psychosocial interventions that address quality of life, social and occupational functioning, and the likelihood of remaining on a recovery trajectory. Or, from the opposite perspective, nonadherence greatly increases the chances of poorer outcomes such as uncontrolled symptoms, relapse, and suicide.

The clinical implications of this concept go beyond semantics. From the patient's perspective, adherence is a tool to achieve life goals. From the clinician's perspective, nonadherence should be considered within the context of being a barrier to other mutually shared or desired outcomes. From this perspective, nonadherence is only a problem when it has an adverse effect on outcome. Unfortunately, when adherence is by itself elevated to a clinical outcome (as it often is, or communicated to the patient as such), the stage is set for serious communication problems. The doctor may be perceived as being more concerned about obedience on the patient's part than about the achievement of other clinical goals.

Excessive focus on adherence as the primary outcome may also lead to underappreciation of other limitations of the current treatment plan, which can lead to other misconceptions about adherence to antipsychotic medication. Patients may mistakenly think that antipsychotics are curative and, therefore, will not appreciate the incomplete but significant improvements that occur when they are adherent as being meaningful. Patients may then interpret their residual symptoms to mean the medication does not work. Conversely, if symptoms abate while patients are taking antipsychotic medication, they may conclude that the dose can then be lowered or the medication discontinued. Further, because patients may continue to feel well after they stop taking the medication, they may believe they have recovered and are stable. Patients may not understand that when medication is discontinued, the protective benefits against relapse are lost more gradually than the adverse effects. Adverse effects can seem to patients to impede recovery, so they lose sight of the necessity of taking antipsychotic medication to remain stable, not realizing that antipsychotic medication is the starting point for all pathways to recovery. Familiarity with the concept of adherence not as a clinical outcome but as an indirect means to

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other clinical outcomes can help clinicians understand patient beliefs and behaviors relating to the illness and its treatment.

Clinicians can also forget that antipsychotic medications are not curative, that they have limitations, and that they are not always as effective as clinicians would wish. Clinicians may focus too much on the benefits of medication without realizing how far the patient feels he or she still has to go. Even with perfect adherence, taking antipsychotics does not always lead to full remission, and patients may be disappointed and frustrated by having persistent symptoms.

In clinical practice. Both clinicians and patients need to be realistic about their expectations of medication. It is essential that the clinician convey to the patient that medication does not guarantee remission, that staying on medication treatment is an important step in maintaining stability and reducing the risk of relapse, and that relapse would delay remission and recovery.

Theory 2: Adherence Problems Are Often Entangled With Efficacy Limitations

In medical illness, the standard model of relapse is that patients stop their medication, their symptoms worsen, and they then relapse. However, in psychiatric patients, symptom exacerbation may precede nonadherence to medication. Nonadherence may be assumed to be the cause of a poor treatment outcome when lack of efficacy of the medication is the real cause. For example, a patient may experience symptom exacerbation because medication is not sufficiently effective, and psychotic symptoms may then interfere with his or her ability to take the medication. The patient may become too paranoid or too disorganized to adhere to the prescription. Lack of insight and abrupt changes in cooperation are often symptoms of psychiatric relapse, unlike symptoms of relapse in other medical conditions. Patients who were perfectly compliant when stable can become noncompliant during psychotic relapse, even when noncompliance is not the root cause of the relapse. In such cases, an efficacy problem can look like an adherence problem. Misattributing poor outcomes to nonadherence to medication can hinder finding a more effective pharmacologic treatment regimen and harm the therapeutic alliance between the patient and the clinician.

Perfect adherence to antipsychotic medication does not guarantee stability. Even patients taking a depot neuroleptic can relapse,[6,8] despite the fact that their compliance is guaranteed by the nature of the medication. The blame for a poor outcome may sometimes lie with the medication and not the patient. In other cases, continuous and uninterrupted medication is very helpful in maintaining stability and preventing relapse. Even small gaps in taking medication as directed can increase the risk of hospitalization; one study[7] found that the risk of hospitalization among patients with schizophrenia was significantly increased by a gap in medication use of 1 to 10 days in a 1-year period (odds ratio [OR] = 1.98; 95% confidence interval [CI] = 1.27 to 3.25). If patients stop their medication due to negative symptoms or cognition symptoms, then they will be at higher risk of relapse. In such cases, the initial gap may have been triggered by incomplete efficacy and therefore initiated a vicious efficacy/adherence cycle.

Table 2. Adherence Attitudes and Behavior Are Related but Not the Same[a]

	Attitude	
Behavior	Positive	Negative
Positive	Likes medication and takes medication	Does not like medication but takes medication
Negative	Likes medication but does not take medication	Does not like medication and does not take medication

[a]Based on Weiden et al.[10] and Weiden and Rao.[11]

In clinical practice. Clinicians need to carefully evaluate patients for the reasons for nonresponse or breakthrough symptoms and should not automatically attribute an unexpectedly poor outcome to nonadherence to medication without other evidence to confirm that assumption. Clinicians should attempt to establish a temporal order of events and precipitants to identify the primary cause of poor outcomes and to treat the primary cause rather than a secondary complication. The primary cause might be that the medication is failing to control symptoms, that an untreated medical illness is affecting psychiatric symptoms, or that concurrent substance abuse is triggering nonadherent behavior.[6,9]

Theory 3: Adherence Can Be Viewed as a Behavior or as an Attitude

Adherence to medication can be defined as a *behavior*—whether the patient takes the medication or does not take it—or can be defined as an *attitude*—whether the patient wants to take the medication or does not want to take it. Although these terms are related, they are different and need to be assessed separately. Overlooking the difference between behavior and attitude is common, and definitions of adherence tend to focus on behavior more than attitude. As shown in Table 2, there may be overlap, but often patient attitudes are not the same as their behavior.

Since behavior and attitude are different concepts, they raise distinct assessment and management issues. A patient who wants to take medication but either cannot afford it or is disorganized and cannot get to the pharmacy to pick it up is an example of a positive attitude toward taking medication but negative adherence behavior in that the medication is not taken, and a serum blood level would be zero. A patient who does not want to take medication but whose family is administering the medication in the

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Table 3. Beliefs of Patients With Schizophrenia That Direct Adherence to Medication

	Direction of Adherence Influence	
Perceived Benefit of Medication	Toward Adherence	Toward Nonadherence
Symptom relief	Acknowledges some relief	Does not report any day-to-day relief
Prevention of relapse	Fears relapse Recognizes that medication prevents future relapse	Does not fear relapse Believes that medication is unrelated to relapse
Achievement of life goals	Reports that medication would help achieve life goals	Feels that medication interferes with life goals
Maintenance or improvement of current functional status	Acknowledges presence of some problems Believes that medication is still necessary	Does not acknowledge any problems needing treatment Reports that problem is no longer active or in need of treatment

patient's food or drink is an example of someone with a negative attitude to taking medication but with a positive adherence behavior in that the blood would show adequate antipsychotic serum levels. A study using only adherence behavior would consider the first case as nonadherent and the second as adherent. Consideration of adherence attitudes would result in the very opposite conclusion.

Clinicians will likely encounter many patients whose attitudes to taking medication differ from their behavior. Clinicians with patients who have attitudinal concerns about medicines and do not want to take medication should find ways to persuade, convince, or educate the patient to take medication. In such situations, changing the patient's attitude is the physician's goal. However, for patients who do not object to taking medication but do not take it because of logistical problems, environmental interventions may help adherence.

In clinical practice. Physicians need to carefully evaluate the patient's behavior and attitude toward medication and assess whether either is a problem causing nonadherence. For example, a person may be completely adherent because his medication is currently being supervised by a family member. If there is no interest in gauging the patient's attitude about the medication, the clinician will not be able to anticipate future nonadherence that would arise if the family member stops monitoring the medication. The take-home message is that clinicians need to consider behavior and attitude as distinct entities, and assess both simultaneously.

Theory 4: Patient Beliefs That Underlie Attitude Toward Medication Are Always "True"

Perception is reality where patient beliefs about medication are concerned. In practice, medication benefits and side effects are what the patient perceives and believes them to be—no more, no less—not what the clinician judges them to be. Therefore, clinicians and patients should discuss attitudes and beliefs regarding medication. Obstacles that prevent patients from understanding the benefits of medication include cognition limitations, inconsistent and fluctuating beliefs, and reluctance to share information with the clinician. The same obstacles may make it harder to elicit adherence attitudes, yet these are the kinds of challenges that come with the territory of working with symptomatic patients, and it can be done. Because patients know that the clinician wants them to take medication and fear that displaying negative attitudes toward medication may be met with disapproval, patients may not readily report their attitudes. Clinicians need to discuss the subject with patients in a manner that helps the patients feel comfortable revealing their real attitudes.

Obstacles also prevent clinicians from understanding patient attitudes and beliefs. Some clinicians were trained in giving "medical model" psychoeducation that is a monologue about medication benefits, rather than in listening to patients. Clinicians should gently interview patients about medication attitudes rather than solely about their medication-taking behavior. This change of emphasis has the advantage that patients can discuss beliefs truthfully without feeling a necessity to lie about actual adherence behavior. Other health-promoting behaviors and reasons for taking or not taking medication, such as achieving life goals and improving functional status, can be included in the discussion (Table 3). Clinicians need to practice active listening, take the patient's beliefs at face value, and avoid interrupting to correct mistaken perceptions or beliefs.

Several factors may contribute to the patient's attitude toward medication. Patients may perceive both benefits and problems regarding taking medication. If a patient perceives benefits to taking medication, his or her attitude is more likely to be favorable even if there are problems such as partial efficacy. For example, if Mr. A hears voices, takes a medication that has only partial efficacy, and continues to hear some voices, but then finds that when he stops taking medication the voices get worse, Mr. A will realize the benefit of taking medication, even though the efficacy is only partial. Conversely, if a patient does not perceive any benefits of medication, his or her attitude to medication is likely to be unfavorable, even if there are few side effects. If Mr. A is switched to another medication that has complete efficacy but, now having no symptoms, he believes that he was cured and no longer needs medication, then the perceived efficacy of

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medication has declined although the actual efficacy of medication rose.

A patient's attitude toward medication may fluctuate just as opinions regarding other areas of life change. Opinions expressed by doctors, family members, friends, peers, and the media can all influence a patient's attitude toward medication.

In clinical practice. A nonjudgmental interview about attitudes toward medication can be structured as a dialogue in which beliefs about health, including adherence to medication, are discussed together with other health-promoting behaviors, life goals, and functional status.

Theory 5: Adherence Behavior Changes and Fluctuates Over Time and Should Be Considered Part of the Illness

Adherence is often conceptualized as a complication that is separate from schizophrenia; however, it may be more helpful to view nonadherence as an essential and almost necessary part of having the illness, learning how to take medication, and eventually learning how to engage in the process of remission and recovery.

When patients experience a first episode of schizophrenia and begin to take medication for it, they are likely to respond well to treatment. However, from the patient's perspective, there is no absolute proof that the improvement is related to the medication. A young adult may reason that he or she has been ill, has recovered, and has now reached the time to stop medication and get on with life.

Despite the introduction of newer antipsychotic medications that are generally better tolerated than conventional antipsychotic medications, patients still discontinue medication at high rates. Robinson and colleagues[12] found that 26% of patients with first-episode schizophrenia or schizoaffective disorder stopped taking antipsychotic medication during the first year of treatment; those with poorer premorbid cognitive functioning were more likely to discontinue. The same research group[5] showed that discontinuing antipsychotic medication increased the risk of initial relapse by almost 5 times (hazard ratio = 4.89, 99% CI = 2.49 to 9.60). A recent randomized, double-blind study[13] of patients in the early course of psychotic illness who were taking olanzapine, quetiapine, or risperidone found discontinuation rates of 68.4%, 70.9%, and 71.4%, respectively, at week 52. For all 3 agents, the major reason for cessation was patient decision (41.5%) rather than efficacy or adverse events.

Clinicians can avoid clinical disappointment in and frustration with individual patients if they expect nonadherence, use it as a learning tool for the patient, and maintain the therapeutic alliance with the patient while the patient learns to accept and integrate medication into life as part of the recovery process, an attitude that can only come from within the patient.[14,15] Clinicians can maintain the alliance with the patient and mitigate the disruptive effects of nonadherence by maintaining a nonadversarial approach that emphasizes a shared desire to help the patient live a full and healthy life and reach life goals, despite disagreements about how best to achieve recovery. Clinicians should view stability as just the beginning of recovery, aim for full remission of symptoms, maintain a hopeful stance and be interested in the patient's life as well as his or her medication-taking, focus on helping the patient achieve life goals, and have a medication dialogue that concentrates on the role of medication in achieving life goals.

In clinical practice. It is important to consider nonadherence as an integral part of the illness and recovery. In devising treatment strategies to achieve remission, recovery, and life goals without a power struggle between clinician and patient, the clinician should integrate medication adherence into a recovery orientation, expect nonadherence at some point, and make managing nonadherence a learning experience for the patient.

CONCLUSION

These 5 theories about nonadherence can be applied in clinical practice to help improve adherence to antipsychotic medication and to assist patients with schizophrenia achieve remission and recovery. The theories remind clinicians that adherence itself is not the goal of treatment for patients with schizophrenia; symptom control, improved health, and better opportunities for recovery are the true goals. Inasmuch as adherence problems can represent barriers to medication-taking behavior or unfavorable attitudes toward taking medication, adherence attitude needs to be considered separately from adherence behavior. When it comes to addressing the patient's unfavorable or ambivalent attitudes about medication, clinicians should start by asking about the patient's belief and initially take that belief at face value. When it comes to addressing problems with adherence behavior, clinicians should carefully evaluate for medication gaps triggered by persistent negative or cognition symptoms or nonadherence episodes triggered by breakthrough positive symptoms. No matter how pervasive the current adherence problems appear, clinicians should remember that antipsychotic nonadherence is in many ways part of the overall disease process and that many schizophrenia patients who ultimately recover have extensive histories of nonadherence that were changed by a positive therapeutic experience. By viewing adherence and nonadherence as part of the illness and recovery process, this perspective can help defuse the adversarial power struggles between doctor and patient that all too often are part of the way adherence challenges are managed today.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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