

# Comprehensive Review of Medical Literature on Treatment Adherence

## *Mental Illnesses and Physical Disorders*

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# Comprehensive Review

## Summary

Treatment adherence has assumed an increasingly important focus in all fields of medicine. With healthcare costs continuing to escalate and increasing awareness of the indirect costs associated with disease burden, the importance of delivering the right treatment to the right patient has grown. Policy makers, practitioners, consumers and advocates share a common voice in supporting the provision of treatment which is effective – efficacious, safe and well tolerated.

Medication adherence is a critical aspect in the treatment of and recovery from a psychiatric disorder. The personal and economic costs of non-adherence are profound and solutions to this problem have been less than desirable. Most non-adherence behaviors are partial with rates of adherence for severe psychiatric disorders less than that of general medical disorders.

Most current efforts to improve adherence are focused on patients alone. Treatments shown to be most effective are multi-modal and employ educational, behavioral and environmental techniques. While somewhat effective, these interventions have not been widely used as they are complex, expensive, and may be best implemented by interdisciplinary teams which are not always readily available to mental health consumers.

A program that reduces cost and complexity while improving treatment adherence and subsequent treatment outcomes is clearly needed. This literature review illustrates specific factors that can be utilized in an effective treatment adherence program.

1. Patients need a positive relationship with healthcare practitioners at every level of care delivery. The literature review has clearly shown that patients who have poor insight into their disorder and lack clear treatment instructions do poorly in adhering to medication treatment.
2. Healthcare practitioners should be adequately educated and embrace the importance of addressing adherence behavior in patient care. Healthcare practitioners need to be educated on the most recent findings regarding treatment adherence. Practitioners need practical resource tools to support their adherence interventions. Patient-specific information combined with easy to use adherence algorithms provide the practitioner with the tools needed to improve adherence behavior.

3. Healthcare practitioners must have accurate and timely information on a patient's adherence behavior readily available in order to effectively support and intervene. Adherence is misjudged by practitioners and underestimated by patients. With adequate information, practitioners are in the best position to assess clinical need, barriers, and levers to maximize treatment adherence. Pharmacy data analytics using medication possession ratios and dates of medication refill provides a cost efficient and practical method to inform the prescriber and patient on adherence behavior.

4. Consumers would benefit from easy to use adherence-education information when engaged in a supportive provider of care relationship. Patients often are unclear on many aspects of their medication treatment. Lack of insight, unclear treatment instructions, and poor communication skills can contribute to non-adherence behavior.


Given the many challenges associated with psychiatric practice of the severely ill, efforts to maximize information gathering for practitioners, facilitate practitioner-patient communication and mutual decision-making should significantly contribute to meeting the unmet need related to behavioral health treatment adherence.

## Treatment Adherence

### I. Understanding the impact of treatment adherence

Treatment adherence, the state of a patient's acceptance and follow through with treatment recommended by a healthcare professional, can be critical to recovery. C. Everett Koop, former US Surgeon General, has been quoted to say, "Drugs don't work in patients who don't take them." The growing importance of treatment effectiveness, identifying efficacious, safe and well-tolerated treatments shown to improve clinical and functional outcomes, has contributed to the national trend to emphasize evidence-based treatment guidelines. In addition, patients, advocates and policy makers place increasing emphasis on recovery and the importance of effective communication between patient and healthcare practitioner.

A variety of terms including compliance, adherence and concordance have been used to describe the phenomena of patient follow through with treatment. Many healthcare practitioners and patients prefer the term adherence because it connotes a collaborative agreement regarding a treatment plan that has been established in the context of a therapeutic alliance between patient and provider. In contrast, compliance suggests that the patient is passively following doctors' orders. Still, use of these terms risks stigmatizing these patients and can alter future relationships with practitioners.<sup>2</sup> The term concordance has been suggested as a third alternative and emphasizes patient rights, the need for information and the importance of two-way communication and decision-making. A concordance model suggests that patients have the right to make decisions even if the clinicians do



not agree with the decision. Throughout this paper, the term adherence will be used for consistency to denote what may have been referred to as adherence, compliance or concordance in primary literature sources.

The term partial adherence is preferred by some over non-adherence as it explicitly acknowledges the common situation in which a person takes some, but not all, of his or her prescribed medication. Partial adherence may include taking an amount that is consistently less than recommended or episodic (“on and off”) dosing behavior with discrete gaps in therapy. Most patients with schizophrenia are partially adherent.


Poor adherence accounts for significant worsening of disease, death and increased health care costs. By some estimates, 33-69% of all medication related hospital admissions are due to poor adherence and are associated with a cost of over \$100 billion a year.<sup>2</sup> One study reported over 60,000 Medline citations since 1980 related to adherence. While much is known about the problem, estimated in 1998 to cost US over \$100 billion, little effort to date has been made to implement both system wide and point of care changes to address it.

The impact of adherence in schizophrenia on morbidity, function and service use has been well established by several studies. Patients who were noted to be poorly adherent had a 75% relapse rate compared to 35% for adherent individuals. Relapse rates have been shown to be up to 5 times higher with non-adherence to anti-psychotic regimens in another study. A study measuring adherence using medication possession ratio (MPR), found adherent patients, with MPR of 0.8 or greater, to have the lowest rate of hospital admission. Patients with MPR less than 0.8 were 2.4 times more likely to be hospitalized.

Long-term studies have reported that non-adherence accounts for 33%-73% of all instances of rehospitalization. Weiden and Olfson report that, when discharged patients stop their medication, relapse rates go up from about 3.4% a month to about 12% a month. They estimate that non-adherence accounts for at least 40% of all episodes of relapse and subsequent readmission to a psychiatric facility. In fact, while medication gaps for anti-psychotic use of greater than 3 months is associated with increased rates of hospitalization for individuals with schizophrenia, gaps as small as 10 days have been shown to double hospitalization rates. Missing or stopping anti-psychotic medications is also associated with increased emergency room visits and homelessness.

A definitive relationship exists between adherence and the economic costs of schizophrenia. Svarstad<sup>14</sup> and colleagues found that, in a Medicaid population, irregular users of antipsychotic medications had higher rates of hospitalization (42% vs 20%) resulting in higher mean hospital costs (\$3992 vs \$1048; year-1990 value). Another study by Gilmer and colleagues had similar findings. Hospitalization rates for non-compliant Medicaid patients were 35% (vs 14%) with associated hospital costs of \$3413 (vs \$1025).

The efficacy of antipsychotic medications in preventing relapses among persons who have schizophrenia has been established. On the basis of these findings, treatment guidelines have been developed with recommendations that medication regimens continue for at least one year after remission. While adherence in itself does



not guarantee a normal life for patients, it does lower the rate of relapse, an important precondition for achieving recovery.

Healthcare practitioners treating individuals with schizophrenia should be aware that medication non-adherence is prevalent despite the availability of newer antipsychotic medications with less severe and disabling side effects. In fact, up to 90% of patients with schizophrenia have been noted to be partially adherent with a varied pattern of taking less than prescribed dose, episodic self-administration of medication and/or failing to refill prescriptions.<sup>5</sup> Perkins has identified critical barriers to adherence despite availability of second generation antipsychotics. They include an individual's perceived risk of illness and benefits of treatment; the perceived costs of treatment, barriers to treatment and cues to act or engage in treatment. More specifically, lack of awareness of illness, poor relationship with one's healthcare provider, core psychiatric symptoms and medication side-effects can contribute to non-adherence. Interestingly, factors related to illness awareness and relationships with practitioners appear to impact adherence more than side effects. Several studies have failed to identify an association between side effects and non-adherence to treatment.<sup>24, 35</sup>

Treatment adherence is not an all or nothing phenomena. Incomplete or partial adherence is more common than non-adherence, when patients discontinue treatment. In spite of the introduction of psychotropic drugs that produce fewer side effects, partial or non-adherence in serious psychiatric disorders continues to be extremely prevalent. The relationship between adherence and the economic cost of schizophrenia is clear as non-adherence has been shown to be associated with higher frequency of relapse and more costly psychiatric hospitalizations.


## II. Treatment adherence in various disorders

Medication adherence differs for mental and physical disorders. A review of the literature between 1975 and 1996 found differing rates depending on the medication.

This large review of studies of non-psychiatric disorders including hypertension, hyperlipidemia and epilepsy report an average adherence rate of 76%. For antipsychotics the mean adherence rate was 58% compared to 65% for antidepressants.<sup>16</sup>

Adherence is generally better in acute disorders compared to chronic conditions with dramatic reductions occurring after the first 6 months of therapy. Several studies that investigated medical conditions in the elderly found that low adherence was associated with poorer understanding of their illness, treatment options, and satisfaction with and faith in the treating physician. Of note is the observation that depression is associated with medication non-adherence in outpatients with a variety of medical disorders. In a study of patients with coronary artery disease, depression was associated with a two-fold increase in non-adherence rates.

Non-adherence to second generation antipsychotic (SGAs) or atypical antipsychotic agents continues to be a ma-



major problem for 40-50% of patients with schizophrenia suggesting that improvement of side effects has not had the impact many people expected. By self-report, 20% of patients with schizophrenia reported missing one week or more of oral antipsychotic medications during the first three months after hospital discharge<sup>7</sup>. Another study found non-adherence following discharge from inpatient care to be at least 50% after 1 year and as high as 75% at 2 years.

It is estimated that half of patients being treated for depression either miss doses or prematurely discontinue antidepressant therapy. Discontinuation rates are highest during the first month of treatment with one third of primary care patients dropping out and a steady decline thereafter. Beliefs about medications are significantly associated with self-reported adherence as are severity of depressive symptoms. Worry about taking medications (such as becoming dependent or concern over effects of medications) and concerns that physicians overuse medications were associated with non-adherence. There is evidence to support that individuals with co-occurring medical and psychiatric disorders are less adherent than those with medical illness alone. Dolder and colleagues studied medication fill records for psychiatric and non-psychiatric drugs in 76 VA patients over 40 years old with schizophrenia or other psychotic disorders. The 12-month compliant fill rates or the proportion of total refills that were filled at the appropriate time ranged from 52% to 64% and did not differ between typical vs atypical antipsychotics or between psychiatric and non-psychiatric drugs.

Treatment non-adherence is identified as a frequent reason for hospitalization and suicide of bipolar patients. Up to a third of bipolar patients took only 30% of medications. Young, single, male bipolar patients are most likely to be non-adherent. Common reasons include negative personal attitudes toward illness, poor insight, mood symptoms, medication side effects, and comorbid conditions. A systematic study (using self report as a measure of adherence) of nearly 200 bipolar subjects participating in a VA clinical trial found that only current substance abuse was associated with non-adherence. Past substance abuse, psychiatric symptoms, prior hospitalizations, general health, gender or functional status did not differentiate highly compliant patients from those with substantial non-adherence<sup>26</sup>. The strength of this study included inclusion of subjects with diverse racial, ethnic and age composition. Women, however, were underrepresented.

Because stimulant effects dissipate rapidly, non-adherence is a likely reason for suboptimal outcome in ADHD. Most studies of adherence examine both discontinuation and adherence. One study found that about 50% of children stopped treatment within a few months, and 25% to 35% of pills prescribed were missing for the remaining subjects. Another study reported that 52% of children adhered to stimulant treatment over the 3 year observation period. Adherence was not predicted by parental knowledge of ADHD or opinions of treatment.

While non-adherence to a medication regimen is common in all forms of medical treatment, the literature indicates that individuals with psychiatric disorders have lower rates of treatment adherence than those with medical illnesses. Comorbid psychiatric and medical illnesses lead to lower rates of adherence than younger individuals or those individuals with medical illness alone.



### III. Treatment adherence assessment

Medication adherence is inherently difficult to define and measure. It is not a dichotomous variable but a set of behaviors which are dynamic and vary for individual patients. The ultimate goal is for a healthcare practitioner to know the percentage of prescribed dose of medication taken over a given time period<sup>2</sup>.

While many approaches have been developed and proven helpful, most are complex, time consuming, expensive and have not been widely implemented. Methods of assessment are either direct or indirect. The most stringent approaches include directly observed therapy, therapeutic drug monitoring of active drug and/or metabolite, or measurement of a biologic marker added to the medication, such as riboflavin that can be detected in the urine.

While therapeutic drug monitoring of lithium and anticonvulsants can provide accurate information about adherence, these tests are costly and require patient time, effort and adherence to monitoring efforts. Inter-individual variability of antipsychotic agents makes therapeutic drug monitoring inaccurate and impractical. Medication markers such as riboflavin are non-quantitative and only provide evidence that medication was taken.

Directly observed methods typically involve some form of case management, use of mobile treatment teams or integrated care in supportive housing settings in which a component of care is supportive observation of patients' self-administration of medication.

Indirect measures include use of electronic medication monitoring devices, self-report questionnaires, healthcare practitioner query, and analyses of refill rates and/or medication possession ratio. While indirect methods are more practical, some may sacrifice accuracy.

Electronic medication monitors, such as the Medication Event Monitoring System (MEMS<sup>®</sup>) are devices that can record the time bottles are opened or measure the number of drops dispensed. A feasibility study of adherence rates demonstrated significantly lower rates in patients who subsequently required hospitalization. Another study found MEMS to be much more sensitive than clinician rating in detecting non-adherence. In addition, use of pill counting is limited by the fact that patients can empty bottles prior to a visit and because it does not give information on dose timing.

Self-report questionnaires have been developed as an efficient and cost effective method to measure adherence. They include the Drug Attitude Inventory (DAI), the Medication Adherence Questionnaire (MAQ) and the Medication Adherence Rating Scale (MARS), specifically developed for use with psychiatric patients. The MAQ was validated in a more direct manner by correlating scores with blood pressure control. The MARS was validated against serum lithium and carbamazepine levels. However, while self-report measures have high specificity, they may overestimate actual adherence by about 15%. Administration requires healthcare practitioner

awareness and time during a clinical visit. Patients may want to present themselves favorably to practitioners.

Clinicians generally overestimate their own ability to identify and quantify non-adherence among their patients, highlighting the importance of objective and validated approaches to measurement . A study found that clinicians' best estimate of the proportion of their outpatients who missed 30 percent or more of their medication was approximately 6% whereas an electronic device in the cap of the medication bottle suggested that approximately 60% of the same patients met this threshold for non-adherence.

The medication possession ratio (MPR) is derived from the number of days' supply of medication a patient has received divided by the number of days' supply needed if the patient was taking the medication continuously<sup>11</sup>. Another variation of MPR is the cumulative mean gap ratio (the number of days when medication was unavailable in relation to the total number of days), or the compliant fill rate (the number of prescription fills indicating adherence in relation to the total number of prescription fills) . This approach to monitoring pharmacy data may be one of the few practical and cost effective methods for assessing adherence in large populations.

Treatment adherence is a common, clinically important non-dichotomous or episodic phenomenon, which is often misjudged by practitioners and under-estimated by patients.

An accurate, time sensitive and inexpensive proxy measure for medication adherence is critical to support non-adherence identification and behavior change strategies. Pharmacy data analytics tools which measure medication possession rates and date of refill are efficient and cost effective proxy measures.

## **IV. Factors that impact treatment adherence in severe behavioral health disorders**


A multitude of studies have been conducted to assess the contributions of medication characteristics, caregiver attitudes, patient and practitioner characteristics, and care delivery system variables to treatment adherence.

### **Medication Variables**

A variety of variables related to medication including efficacy, safety, tolerability, type of administration and dosing schedule have been examined. With the introduction of second generation atypicals (SGAs) came the hope of improved medication adherence. The literature is generally supportive of this conclusion.

There are few studies directly linking differences in medication efficacy to adherence. The CATIE study, however, provides some indirect insights into this relationship. One of the principle findings of CATIE was that the





time to the discontinuation of treatment for lack of efficacy was longer in the olanzapine group compared to the perphenazine, quetiapine, and risperidone group . Its apparent superior efficacy is also indicated by the greater reduction in psychopathology, longer duration of successful treatment, and lower rate of hospitalizations for an exacerbation of schizophrenia. All of these measures have been directly or indirectly linked to medication adherence.

Rosenheck and colleagues evaluated adherence in 423 patients participating in a clinical trial comparing haloperidol to clozapine. While clozapine patients had longer times to discontinuation, they did not differ from the haloperidol group in terms of proportion of pills returned each week. In 2000, Olfson<sup>7</sup> reported on non-adherence, as defined by stopping medications for greater than 1 week, in patients discharged on either typicals or SGAs. There was a non-significant trend favoring SGAs although only 14.5% of the subjects were on SGAs. Two additional studies demonstrated partial adherence to be more prevalent in individuals on typical than atypical antipsychotic agents.

Dolder and colleagues<sup>38</sup> assessed adherence by examining pharmacy refill records in 288 patients over a 12-month period. Adherence rates were moderately higher at 6 and 12 months in patients receiving SGAs (olanzapine, risperidone, and quetiapine) compared to typical agents (haloperidol, perphenazine). Cumulative mean gap ratios were 23.2% for typical agents and 14.1% for SGAs at 12 months ( $p = 0.001$ ).

The CATIE study provides indirect evidence that side effects could be linked to adherence as the rates of treatment discontinuation due to intolerable side effects differed between treatments<sup>39</sup>. Risperidone had the lowest rate (10 percent), and olanzapine had the highest rate (18 percent). Moreover, more patients discontinued olanzapine owing to weight gain or metabolic effects (9 percent vs. 1 percent to 4 percent with the other four drugs,  $P < 0.001$ ) and more patients discontinued perphenazine owing to extrapyramidal effects.

There is a general belief that unwanted side effects, especially extrapyramidal symptoms (EPS), sexual disturbances and weight gain, have a negative influence on adherence . While there are reports linking non-adherence to specific side effects, most studies do not find a significant difference in frequency or intensity of side effects .

Extrapyramidal symptoms are perhaps the most studied side effect in terms of its relationship to medication adherence. The burden of EPS-related side effects, however, has greatly diminished over the past decade with the routine use of SGAs. When weight gain leads to obesity, there appears to be an influence on adherence. In a survey of 300 consumers (through NAMI and NMHA), body mass index (BMI) and subjective distress over weight gain were predictors of non-adherence. Obese individuals were more than twice as likely as those with a normal BMI to report missing their medication.

In a study of bipolar patients, medication side effects did not differentiate between adherent and non-adherent groups<sup>26</sup>. This was also confirmed in a study of 61 patients with schizophrenia with the exception of “psychological side effects.”<sup>42</sup>

Dolder and colleagues<sup>38</sup> demonstrated that the numbers of adjuvant psychotropic medications were not significantly correlated with the cumulative mean gap ratio, a measure of medication possession and adherence. In a study of bipolar patients, however, patients taking more medications were more likely to be adherent.<sup>26</sup>

Importantly, dosing frequency is inversely related to adherence.<sup>8, 43</sup> In a large review of 76 trials utilizing electronic monitoring, patients taking medications on a four times a day schedule were about 50% adherent compared to once daily dosing which was 80%. Twice daily and three times per day adherence rates were intermediate. Frequency of dosing rather than the number of medications or tablets that must be taken daily is most highly correlated with adherence rates.

In general, patients with higher out-of-pocket costs are more likely to forgo medications because of cost pressures. It is especially pronounced when physician trust is low which suggests that physician efforts to enhance patient trust may contribute to decreased rates of cost-related medication under use.

## Patient variables

A variety of patient factors have been found to contribute to adherence. Motivational factors related to adherence to antipsychotic medications include individuals' perceived vulnerability to relapse, perceived benefits derived from the medication, sense of support for treatment afforded by relatives and a positive clinician-patient relationship.<sup>21</sup> Poor clinician relationship, low insight, and an experience of coercion during admission were associated with a negative attitude toward treatment.

Key factors influencing adherence include clinical impairment and functional status. Paranoia, suspiciousness, grandiosity and delusional beliefs about medications have been related to non-adherence in some, but not all studies.<sup>5</sup> A study of 64 patients treated with depot medications where the severity of negative symptoms, as assessed by the Scale for Assessment of Negative Symptoms (SANS) was inversely related with adherence rates.

A study of pre-admission adherence patterns in 95 patients with schizophrenia found that non-adherent patients had lower means scores on the Global Assessment of Functioning, more often received compulsory treatment and more often had impaired insight both at admission and discharge. Non-adherence is reported to be related to disturbances in social adaptation and interaction behavior, a lack of insight into their condition, and a lack of feeling ill.<sup>43</sup> Non-adherent patients are less likely to recognize their clinical symptoms.<sup>7</sup> Stigma is also a patient reported barrier to medication adherence.<sup>20</sup>

Cognitive deficits, coupled with diminished insight, may decrease patients' ability to adhere to treatment regimens. Deficits in information processing can further undermine how a patient determines the benefits and subsequent need for treatment. Jeste and colleagues found that cognitive functions, especially conceptualization and memory, were strong predictors of abilities to manage medications, above effects of symptom severity or attitudes toward medications. Memory problems as well as untreated psychiatric symptoms were also identified as

a patient factor in a survey studying medication adherence in VA patients with schizophrenia.<sup>20</sup> Further studies are required to understand the link between cognitive function and medication adherence.

A 2 year prospective study of factors suspected to predict treatment discontinuation found that adherent patients had longer duration of illness (and were also older), were treated with higher doses of antipsychotic drugs and had more frequent extrapyramidal symptoms (EPS), were more cooperative and showed significantly higher scores in positive treatment expectations.<sup>43</sup>


Patients diagnosed with schizophrenia often have comorbid substance abuse as well as other medical disorders. Besides the consequences of worsening of psychotic symptoms, precipitating relapse, or prompting an increase medication dose, there is a strong link between substance abuse and medication non-adherence. Active substance use leads to disorganized lifestyle and can directly impair judgment about health behaviors. A prospective study over 4 years, found that those patients who regularly took their medication but also abused drugs were readmitted to the hospital sooner compared to adherent patients who did not use drugs.<sup>54</sup> The interval was further reduced in non-adherent drug using patients, a subgroup accounting for 57% of all hospital readmissions.

In a study of bipolar patients perceived barriers to care (travel difficulties, communication, life commitments) did not differentiate between adherent and non-adherent groups.<sup>26</sup> Other studies, however, have shown a relationship of non-adherence to distance to the clinic. Discharge instructions including those related to medication administration were routinely misunderstood according to Velligan and colleagues who performed daily home visits for 2 weeks following hospitalization. In many cases, as a result of short lengths of stay, individuals still had high levels of psychotic symptoms. Frequently discharge medications were confused with pre-hospitalization medications. Multiple problems with living environment (living in cars, different homes) and daily routines (lack of regular meals, sleeping through dosing times) were identified as barriers to treatment adherence.

Non-adherent patients who gained insight during treatment had significantly fewer days of inpatient treatment during the next year than those whose insight was still low at discharge. Another study found insight to be a factor only when patients with comorbid substance abuse were excluded. Lack of insight has been suggested to have two components, unawareness of illness and incorrect attributions about the causes of illness, both of which can be addressed in the context of therapeutic relationship.<sup>48</sup> Adherence was significantly better among those in regular contact with their psychiatrist.

## Practitioner Variables

Currently, more than three-quarters of mental health practitioners in the US have a bachelor's degree or less and a large proportion of clinicians lack the skills necessary to deliver evidence-based practices. They often have negative attitudes towards rehabilitation and mutual support, and underestimate consumers' interest in collaborative treatment planning, all factors relevant to adherence. These attitudes also hinder the adoption of innovations.




Studies conducted over ten years ago showed that a significant proportion of physicians failed to prescribe anti-psychotics by guideline recommendations when such medications were indicated.<sup>60</sup> In a follow up study continued gaps in following consensus guidelines were observed. This study also identified the effectiveness of clinicians' ability to communicate important information to the patient. Despite good theoretical knowledge about relapse prevention many psychiatrists did not give clear recommendations about the duration of maintenance therapy to their patients. Perhaps there was fear that patients would have rejected these recommendations. It is becoming clear, however, that effective communication improves health outcomes. This study also found that physicians did not routinely use adherence-enhancing strategies such as depot medication use or behavioral interventions.

Communication skills underlie any relationship. Cruz and Pincus reviewed 34 articles on health communications in the psychiatric literature published between 1950 and 2001 . The goal of the psychiatric encounter has shifted over this time and now focuses on assessment of symptom severity, education, negotiating a treatment plan, providing psychopharmacological treatment, and coordinating treatment provided by multiple caregivers. These data gathering functions must be balanced with development of a trusting, caring and participatory relationship with the patient. This changed role is consistent with the paradigm shift observed in mental health services where there is a focus on disease management and recovery. Therefore, it is critical for the practitioner to have mastered psychotherapy and communication skills, knowledge of pharmacology and recovery principles to be maximally effective.

The provider-patient relationship has been suggested by some to impart the greatest value in influencing treatment adherence . The physician must understand the patient's wishes and allow participation in discussions about therapy.<sup>43</sup> Therapeutic alliance was important in a study of 213 patients with schizophrenia or schizoaffective disorder.<sup>7</sup> Patients who became non-adherent scored significantly poorer on four of six Active Engagement Scale subscales: optimism about the usefulness of treatment, meaningful involvement in therapy, interest in understanding their illness, and realistic perceptions of therapist. In contrast, however, a study of bipolar patients found that working alliance between patient and provider along with patient satisfaction and number of months under care with provider did not differentiate between adherent and non-adherent groups.<sup>26</sup>

A review of the literature demonstrates several key medication, patient and practitioner variables which contribute to medication adherence. Key medication variables include the fact that atypical antipsychotics produce higher adherence rates than typicals. Additionally, medication dosing frequency is inversely related to adherence.

Key patient variables include patient mental status, as significant difficulties with cognition, executive functioning and affect interfere with treatment adherence. A patient's lack of insight regarding their illness and the resulting need for medications is a significant factor in treatment non-adherence. Poor insight, combined with treatment instructions that are at times unclear and misunderstood also creates negative adherence outcomes. A positive expectation regarding the outcome of treatment is a significant factor in obtaining treatment adherence.



Practitioner factors contributing to non-adherence are varied and significant. Studies reveal that inadequate listening to and communication with patients limits treatment adherence as does difficulties with the practitioner/patient relationship. This results in a lack of understanding of how to respond to a patient who is exhibiting non-adherence to treatment. In addition, limited education and experience related to clinical practice for some and best practice guidelines for others, impacts care and treatment adherence. This critical area appears to be the one that might be most easily impacted by effective interventions.

## V. Improving treatment adherence

The evidence presented above highlights the importance of healthcare practitioners appreciating the prevalence of partial or non-adherence, working to maximize patient factors contributing to it and having practical and timely information relating to patient adherence. In clinical practice, healthcare practitioners rely on cross-sectional and longitudinal history. They review current symptoms in the context of past medical history. As past history is the best way to predict future behavior, ideally practitioners would have an accurate assessment of adherence to support clinical decision-making.

### Addressing Patient Factors


Efforts to improve treatment adherence have varied approaches including educational, behavioral changing, environmentally supportive and monitoring efforts. Most interventions are patient-focused and specific. They are delivered through clinical settings and via community treatment teams as well as through payors' disease or care management efforts. For interventions specifically targeting adherence, greatest improvement appears to occur in approaches with varying combinations of educational, behavioral, and affective (family support, home visits, counseling) components .

It is essential for healthcare practitioners to understand how an individual conceptualizes and deals with health and illness. Several conceptual models have been developed to allow practitioners to appreciate how best to interface with individual patients in an effort to maximize adherence and recovery.

The “Health Belief Model” views the process by which patients weigh the cost of treatment against benefits as core. If individuals complete this personal analytic process and the benefits are seen to be greater than the costs and risks, treatment adherence is more likely to occur <sup>43</sup>. Patients are more likely to adhere to treatments when they perceive the recommended treatment makes “common sense” in light of their personal beliefs about the illness and their past experiences with illness and/or current symptoms<sup>1</sup>.

Adherent patients consider the medication to be helpful in treating their illness and have a positive attitude toward medication. Conversely, non-adherent patients see no reason for taking medication due to lack of insight that they are ill or faith in medications to help them. A biologically oriented view of illness (where schizophrenia





is seen as a neurochemical imbalance) increases adherence while a psychosocial model of illness (schizophrenia is a consequence of problems with the environment) reduces adherence. It is therefore important to consider these attitudes in the overall approach to improving treatment adherence.

Other models focus on the treatment and communication process and the extent to which patients understand and implement the treatment regimen. Still other models focus on parallel processing on the cognitive level through disease and treatment schemas and on the motivational level through emotional response. These models illustrate the importance of specific coping plans to implement intent.

It is apparent that the highly rational assumptions of these models have limited value in understanding and predicting adherence in schizophrenia<sup>64</sup>. Approaches must go beyond the usual individual psychological focus of these models and give attention to contextual cues and reinforcements that are more amenable to intervention within treatment programs.


The recovery model suggests that rather than being cured, one learns to live with mental illness. There are four stages of recovery including hope, empowerment, self-responsibility, and establishing a meaningful role in life. This model is a reflection of efforts to give more authority to the consumer, a position some practitioners find uncomfortable due to a lack of experience. Critical to an individual's development of hope and ability to formulate goals is gaining mastery over symptoms and relapses. Thus, illness management and recovery are closely related with the former primarily focused on minimizing symptoms and relapses and recovery focused primarily on helping people develop and pursue goals.

The first step in addressing patient factors is to identify patients at risk for non-adherence. One approach is by assessing the number of barriers to medication adherence, presence of substance abuse, and symptom severity.<sup>20</sup> Barriers include stigma of taking medications, side effects, memory problems, and lack of social support. Once these broad areas have been assessed a comprehensive intervention plan can be devised and implemented.

Psycho-education is a therapeutic approach to reduce relapse and rehospitalization rates of schizophrenic patients. It is supposed that, through increased knowledge and insight, people with schizophrenia will cope in a more effective way with their illness, thereby improving prognosis. Patient education is aimed at improving knowledge about both illness and treatment with the hope that a more developed rationale for treatment will be developed and adherence will be improved. Social skills' training involves teaching people skills to improve interactions with prescribers, such as how to discuss medication side effects.

Psycho-education by itself is largely ineffective in improving adherence with antipsychotic medications. In a review of 39 studies evaluating various adherence improvement interventions, psycho-educational interventions without accompanying behavioral components and supportive services were less likely to be effective.<sup>64</sup> This was confirmed by other reviews conducted by Dolder<sup>64</sup> and Mueser<sup>67</sup> and may reflect an impact of memory problems, common in schizophrenia.<sup>67</sup>





Even in group settings, the evidence for the impact of education on adherence is weak. Of 4 reviewed studies only one that combined psychoeducation (9 lectures about illness and medication) with behavioral reinforcement for desirable medication-taking routines improved adherence after 5 months, but suffered from significant attrition bias.


There is one study in which psychoeducation that focused specifically on bipolar illness appeared effective in improving adherence. Effectiveness was maximized when the intervention was longitudinal and interactive.<sup>25</sup> Poor insight is closely linked with non-adherence and presents a major stumbling in the recovery of patients with schizophrenia.<sup>12</sup> Cognitive-behavioral interventions target attitudes and beliefs about medications and center on the assumption that adherence is a coping behavior heavily determined by the personal construction of the meaning of medication and illness.

The goal of cognitive behavioral therapy (CBT) is to improve insight into illness, increase adherence to medication, ameliorate the severity of symptoms and mitigate other negative consequences of schizophrenia<sup>12</sup>. There are a variety of CBT interventions. In general they share several common features. The first is addressing distorted beliefs about illness and developing cues to support adherence behavior. The second is improving the ability to recognize clinical symptoms which helps to make patients more aware of their ongoing need for maintenance treatment and more appreciative of the benefits of medication. The third is linking the positive effects of medications to the patient's personal goals and desires for better functioning and quality of life. CBT has been shown to be effective in reducing residual psychotic symptoms, which is indirectly linked to improved medication adherence<sup>15</sup>.

Motivational interviewing is a CBT technique that involves helping people articulate goals and explores how medication may aid in achieving those goals. Motivational interviewing techniques must be customized for application in psychotic disorders as negative symptoms and passivity can undermine motivation for change and ability to develop goals.

Compliance therapy is an example of a CBT influenced intervention program using a combination of cognitive approaches and motivational interviewing. Patients are encouraged to articulate their beliefs and ambivalence about antipsychotic medications while focusing on adaptive behaviors and the importance of staying well.<sup>64</sup> A randomized controlled study demonstrated sustained gains in medication adherence, attitudes about medication, and insight.<sup>12</sup> Compliance therapy, however, was not associated with improvements in adherence in another study of 30 patients.

Illness management is defined as professional-based interventions designed to help people collaborate with professionals in their treatment, reduce susceptibility to relapse, and cope more effectively with symptoms.<sup>66</sup> This is in contrast to illness self-management that which emphasizes peer-facilitated services. Many illness management programs strive to improve self-efficacy and self-esteem and to foster skills that help people pursue their personal goals. Enhancing coping and the ability to formulate and achieve goals are in line with the current emphasis on recovery.



Behavioral interventions assume that adherence is modified by frequent repetition and behavioral modeling. Common strategies include providing patients with detailed instructions and concrete problem-solving strategies such as reminders (pill boxes, calendars, electronic reminders, reminder phone call), self-monitoring tools (medication logs), cues (placement of medications), and reinforcements (phone calls). Behavioral tailoring involves development of strategies for incorporating medication into daily routine (environmental cues) or simplifying the medication regimen. Behavioral tailoring has been shown to consistently improve adherence in four studies.<sup>66</sup> Comparison studies have shown behavioral therapy to be superior to psycho-education.<sup>64</sup>

Family therapy alone does not have a large effect on adherence. Of 12 family intervention studies reviewed, only three reported significant differences in adherence<sup>64</sup>. Two of the successful interventions included a behavioral component (including medication adjustment), and the provision of stable housing and other supportive services. While not specifically studying adherence, a number of studies have shown reductions in relapse rates among patients whose families received psycho-education. Those that were most effective also included a combination of illness education, family support, crisis intervention and problem solving over a period of time spanning at least nine months. The evidence of support for this approach has been strong enough to be included in PORT recommendations. Despite the growing evidence for an impact of family interventions on outcomes (including relapse and adherence to treatment), only 10% of families of outpatients with schizophrenia receive support or education .

There are many strategies described for addressing medication side effects. However, as has been reviewed, side effects do not appear to be a prominent driver for non-adherence. Some general strategies for addressing side effects include dose reduction to the minimal effective dose, medication switching, dose schedule modification and use of adjunctive medications to treat persistent EPS, akathisia, and sexual dysfunction. Dietary counseling and promotion of lifestyle changes can be helpful in addressing metabolic side effects and weight gain.

Inadequate clinical response to apparently adequate dosages of antipsychotic medications warrants assessment of plasma levels to rule out unusual or altered drug metabolism or non-adherence.

While depot medications cannot ensure adherence, they can enhance it (non-adherence is immediately apparent)<sup>35</sup>. Depot medications appear to have a beneficial effect of adherence and rate of relapse.<sup>43</sup> PORT recommendations state that depot antipsychotic medication treatment should be available and considered for persons who have a history of problems with adherence on oral medication.<sup>72</sup>

Medication counseling combined with behavioral techniques including provision of a medication calendar and a mini-pillbox, as well as a follow-up telephone call was shown to improve adherence to a short term (3 week) treatment for a medical disorder. The goal was to improve patients' attitudes toward treatment and their knowledge about disease and medication as well as provide reminders.

## Addressing Care Delivery Factors

The rapid rise of organized health care systems offers new opportunities for addressing adherence problems. Many patients with serious mental illness (SMI) are enrolled in managed Medicaid or Medicare programs or are cared for in other public-sector organizations such as Veterans Administration (VA) hospitals. These organizations often have comprehensive pharmacy data, which can provide systematic identification of poorly adherent patients and can serve as an important front-end component of a comprehensive adherence improvement program when coupled with treatment as with an illness management program.<sup>11</sup>

Use of disability funds or other forms of leverage (housing, outpatient commitment) in an attempt to improve treatment adherence are ubiquitous (44-59%) in the treatment of public sector patients . While there is little empirical data to assess effectiveness of leverage, this approach is often perceived by consumers as coercive and unhelpful .


At the clinic level, factors known for improving adherence include routinely scheduled visits, shorter intervisit interval, and incorporating some form of psychotherapy during the visit<sup>56</sup>. Systems should be in place to follow up on missed appointments. As medical comorbidities can impact overall recovery, systems should ensure access to general medical health care.

Peer support, a form of social emotional support, is frequently coupled with instrumental support, which is mutually offered by persons having mental illness to others sharing a similar mental health contention. This approach has been shown to be a cost effective supplement to other treatment approaches. In addition, a number of studies have shown it to be associated with improved medication adherence as well as reduced hospitalization.

Therapeutic communities blend a range of mental health approaches, such as psychiatric care, psychosocial rehabilitation, assertive case management, and consumer empowerment, along with other enhancements to promote recovery. These programs are cost effective and have been shown to reduce hospitalization and help patients reach important milestones of recovery . While cost effective when considering overall service and community burden, implementing these programs requires significant financial and infrastructure support.

Adherence was improved for patients with comorbid schizophrenia and substance abuse who attended a self-help group that encouraged the responsible use of effective psychiatric medication. Other baseline variables associated with adherence were living in supported housing, having fewer stressful life events, and having a lower severity of psychiatric symptoms.<sup>55</sup>

Directly observed therapy has its origins in the public health treatment of tuberculosis as a method to ensure as close to 100% adherence as possible. In 2002, Comprehensive Neuroscience, Inc. (CNS) was asked to implement the Medication Adherence Project (MAP), a directly observed therapy program for individuals with schizophrenia, in the San Francisco area with support from Eli Lilly and Company. While the primary goal was to improve medication adherence, secondary goals were to assess client function and impact on psychiatric service utilization.



The participants received their medications in daily pre-packaged bubble packs which were prepared by a local pharmacist. The daily pack included that day's entire dose of medications. Participants received weekend and holiday packets on Fridays and the day before holidays. The staff also inquired and recorded whether the participant had taken their PM dose. It should be noted that some participants were only on a PM regimen. Staff observed adherence for morning dose was 83%. For a two-year period prior to enrollment the cohort of subjects had combined 25 acute hospital episodes for a total of 193 days and 10 acute diversion unit episodes for a total of 126 days (intensive community residential placements that serve as an alternative to hospitalization). For a nine-month period after enrollment, there was 1 acute hospital episode for a total of 6 days and 1 acute diversion unit episode for a total of 12 days.

The results of this pilot project suggest that a focus on medication administration can have an impact on outcomes in terms of service utilization. There are no other reports to our knowledge using this approach in a SMI population. Unfortunately, the project was found too costly to continue or bring to scale in other regions and was discontinued.

There is agreement among some researchers that adherence is maximized when there is a strong positive individual relationship with the patient<sup>62</sup>. Physician trust is likely to foster more effective patient-physician communication which in turn heightens patients' understanding of their medications' importance for their health and well-being.<sup>47</sup> Trust, in turn, is most closely linked to physician communication style including behaviors such as active listening, providing emotional support, providing clear and thorough information, eliciting patients' input in treatment decision making, and allowing adequate time for patients to ask questions.

Practitioners should convey a sense of acting out of concern for the patient. Similarly, through careful solicitation and monitoring of patients' response to treatment it should be possible to maximize the perceived benefits of treatment, which can be adjusted if the patient is distressed by adverse effects or if the subjective well-being of the patient does not improve.<sup>48</sup> One way for prescribers to enhance their relationships with patients is to actively seek their views and encourage collaboration.

A variety of models exist to address patients' beliefs, knowledge of illness, striving for recovery and decision making when attempting to maximize treatment adherence. The most effective methods to improve treatment adherence combine patient education, efforts to link treatment adherent behavior with environmental cues and reinforcement and application of cognitive strategies to deal with health beliefs and impediments to adherence. The delivery of these interventions requires practitioner training, time and often multidisciplinary team support to deliver. Systems of care and payors must provide financial support and needed infrastructure to implement them.

Individualization of medication choice based upon clinical needs and efficacy while optimizing dosing levels and schedules contributes significantly to adherence. Practitioners, who are knowledgeable about factors leading to treatment adherence, well versed in communication techniques, and educated about best practices and guide-

lines, are best poised to engage patients. Given that even the best intended practitioners and patients misjudge adherence, both must be aided in the adherence effort by adherence data.

## VI. Unmet medical need in treatment adherence

Medication adherence is a critical aspect in the treatment and recovery of a psychiatric disorder. The personal and economic costs of non-adherence are profound and solutions to this problem have been less than desirable. Most non-adherence behaviors are partial with rates of adherence for severe psychiatric disorders less than that of general medical disorders.

Most current efforts to improve adherence are focused on patients alone. Those shown to be most effective are multi-modal and employ educational, behavioral and environmental techniques. While somewhat effective, these interventions have not been widely used as they are complex, expensive, and may be best implemented by interdisciplinary teams which are not always readily available to mental health consumers.

A program that reduces cost and complexity while improving treatment adherence and subsequent treatment outcomes is clearly needed. This literature review illustrates specific factors that can be utilized in an effective treatment adherence program.


1. The patient has a positive relationship with healthcare practitioners at every level of care delivery.

The literature review has clearly shown that patients who have poor insight into their disorder and lack clear treatment instructions do poorly in adhering to medication treatment. Healthcare providers are in the optimal position to provide a patient with a clear understanding of their psychiatric disorder and resulting treatment needs. Additionally, the patient's healthcare practitioners can create positive patient expectations of treatment outcomes which result in improved treatment adherence.

2. Healthcare practitioners are adequately educated and embrace the importance of addressing adherence behavior in the care.

Healthcare practitioners need to be educated on the most recent findings regarding treatment adherence. The most effective treatment interventions as identified in the literature should be discussed and new techniques disseminated.

Practitioners also are in need of practical resource tools to support their adherence efforts. While practitioner-specific barriers to adherence have been long identified, there are few interventions focused on improving practitioner/patient relationships and communication specifically addressing treatment adherence. With adequate information, practitioners are in the best position to assess clinical need, barriers, and levers to maximize treatment adherence. Given the many challenges associated with psychiatric prac-



tice of the severely ill, efforts to maximize information gathering for practitioners, facilitate practitioner-patient communication and mutual decision-making should significantly contribute to meeting unmet need related to behavioral health treatment adherence. Patient-specific information combined with easy to use adherence algorithms provide the practitioner with the tools needed to improve adherence behavior.

3. Healthcare practitioners have accurate and timely information on a patient's adherence behavior readily available in order to effectively support and intervene.

Adherence is misjudged by practitioners and underestimated by patients. Pharmacy data analytics using medication possession ratios and dates of medication refill provides a cost efficient and practical method to inform the prescriber and patient on adherence behavior.

4. Consumers can benefit from easy to use adherence-education information when engaged in a supportive provider of care relationship.

As highlighted in this review, patients often are unclear on many aspects of their medication treatment. Lack of insight, unclear treatment instructions, and poor communication skills can contribute to non-adherence behavior. Patients clearly benefit from supportive practitioner relationships that provide clear answers to patient's questions and concerns. Easy to read and utilize patient education material that assist the patient in seeking needed answers to illness and medication questions facilitates adherence behavior.



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