

Predictors of Non-adherence in Patients Taking Psychotropic Medication and Suggestions to Improve

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ABSTRACT

Background: Non-adherence to treatment, especially medication is an important area of concern in psychiatry as it contributes to relapse and re-hospitalization of the patients. One of the ways to improve drug adherence is to know crucial factors responsible for poor medication adherence so that proper management strategies may be planned to improve patients' drug adherence. This article reviews the literature of non-adherence, discusses patients' reasons for failure to concord with medical advice, elect the predictors of and solutions to the problem of non-adherence.

Aims: To discuss the aspects of medication adherence and definition about health behavior and it will examine the predictors of non-adherence in those taking psychotropic medication and provide the physicians with various strategies for improving medication adherence among their patients.

Methods: We conducted a MEDLINE database literature search and science direct database were undertaken, limited to English language articles published between 1993 and 2014, using the following search terms: adherence, non-adherence, compliance, Improve medication adherence, strategies for physicians and pharmacists to ensure medication adherence, pharmacotherapy.

Conclusion: Medication non-adherence was significantly associated with an increased risk of rehospitalization, emergency room visits, homelessness and symptoms exacerbation. Non-adherence was significantly more likely to have a history of medication non-adherence, substance abuse or dependence, and difficulty recognizing her own symptoms. Patients who became medication non-adherence were significantly less likely to have a good therapeutic alliance form during hospitalization and were more likely to have family members who refused to become involved in their treatment. Community psychiatric services can potentially use effective clinical interventions, approved by scientific evidence, for reducing patient non-adherence.

Strategies for adherence include raising information and skill levels, altering characteristics of the regimen, and improving the relationship between the provider and the patient. Provider and the patient awareness with regard to medication adherence can be enhanced with the creative application of behavioral contracts. Adherence promoting efforts can also include rewards and improvement strategies.

1. Introduction

The most significant reason why individuals with schizophrenia fail to take their medication is because of their lack of awareness of their illness (anosognosia). Other reasons are concurrent alcohol or drug abuse and poor relationship between psychiatrists and patients. Medication side effects, widely assumed to be the most important reason for medication non-adherence, which also maybe a less important reason compared to other factors (1). Studies investigating the efficacy of clinical interventions for reducing treatment non-adherence have generated contrasting finding, and put the non-adherence phenomena most common in clinical practice. Fortunately there are effective clinical interventions that community psychiatric services can implement to reduce non-adherence (2).

2. Literature Review

Schizophrenia is a chronic and disabling illness that affects approximately 1% of the world's population. It is often accompanied by relapse even while on treatment (3). The failure of individuals with schizophrenia and

bipolar disorder to take prescribed medication is one of the most serious problems in psychiatric care. It often leads to relapse of symptoms, rehospitalizations, homelessness incarceration in jail or prison, victimization, or episodes of violence. The failure to take medication is referred to as non-compliance or non-adherence, the later is a better term (1). Patients with schizophrenia at high risk for medication non-compliance after acute hospitalization are characterized by history of medication non-compliance, recent substance use, difficulty recognizing their own symptoms, and weak alliance with inpatient staff and family who refuse to become involved in patient treatment (4). The interest in the topics of compliance, adherence and concordance in mental health disorders, and especially in schizophrenia, has increased substantially during the last few years. Focusing on these issues is overdue because non-compliance is a major problem in schizophrenia. Patients' who non-adherence to the antipsychotic medication relapse prevention could be difficult, and showed to have much higher relapse rates compared to patients who adhere to their medication antipsychotics. Patients with a history of taking antipsychotic medication and newly diagnosed with schizophrenia have relapse rates fivefold higher than those who did not take antipsychotic medication (5).

Antipsychotic medications represent the cornerstone of pharmacological treatment for patients with schizophrenia. Although these agents have shown to improve psychopathology, reduce relapse, and improve functioning (DSM-IV-TR), non-adherence to treatment with antipsychotic is common (6) and remains one of the greatest challenges in psychiatry (2, 7). Because adherence is an individual patient behavior, the following are some approaches that have been used to assess adherence behavior. **First**, subjective measurements obtained by asking patients family members, caregivers, and physicians about the patients' medication use. **Second**, objective measurements obtained by counting pills, examining pharmacy refill records (8), or using electronic medication event monitoring systems (7,8,9). **Third**, biochemical measurements obtained by adding a non-toxic marker to the medication and detecting its presence in blood or urine or measurement of serum drug levels. Currently, a combination of these measures is used to assess adherence behavior (7). In contrast to the cross sectional studies, examining this issue showed an association between severity of illness at hospital discharge and subsequent medication non-compliance (4).

In considering the nosology of concordance and adherence, a useful distinction is made between individuals who did not begin to take their medication and those who started the course of medication but with intermittent of non-adherence or discontinue prematurely against medical advice (10). Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.

This poor adherence to medication leads to increased morbidity, mortality rate which was estimated to incur costs of approximately \$100 billion per year (7, 11). A large number of factors have been studied as possible determinants of medication non-compliance among patients with schizophrenia considering the variation exists in the strength and consistency of evidence supporting these risk factors (4). This non-adherence may due to factors that are patient-related (e.g., substance abuse, forgetfulness, anxiety about side effects, inadequate knowledge, lack of insight, lack of motivation, and fear of stigma (3,4,12); healthcare-related (e.g., poor patient/health care provider relationship, poor services and access to services, poor staff training (3,13); socioeconomically-related (e.g., illiteracy, low level of education) or treatment-related factors (e.g., polypharmacology, complex treatment regimens) (3,7,10,11).

There is a wide range of clinical interventions to reduce non-adherence in patients with psychosis. The focus of most of these studies has been the reduction of non-adherence to psychotropic medication or to schedule appointments (2). Improving adherence to treatment with antipsychotic medication in patients with psychotic disorders is a complex task. Identifying risk factors associated with non-adherence is an important initial step because modifiable risk factors might become targets for future interventions. Estimating the medical costs of non-adherence including those associated with psychiatric care, physical health care, and pharmaceuticals would provide information on the overall economic impact of adherence and might create an incentive for insures to allocate resources to improve adherence in this population (6).

This retrospective study will discuss the aspects of medication adherence and definition about health behavior and it will examine the predictors of non-adherence in those taking psychotropic medication and provide the physicians with various strategies for improving medication adherence among their patients.

3. Methodology

The researchers conducted a MEDLINE database literature search and science direct database were undertaken, limited to English language articles published between 1993 and 2014, using the following search

terms: adherence, non-adherence, compliance, Improve medication adherence, strategies for physicians and pharmacists to ensure medication adherence, pharmacotherapy, and factors associated with relapse. As articles were retrieved their references' were reviewed for potential studies to be included in the review.

4. The General Definition of Medication Adherence and Other Aspects of Health Behavior

The WHO defines adherence to long-term therapy as “the extent to which a person’s behavior-taking medication (2, 7, 14) (Box.1) (10), following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from health care providers (15). It is typically expressed as a percentage of total number of doses taken or theory-days available, in relation to the time period of observation during which compliance is measured (14).With respect to timing, dosage, and frequency of medication taking (11). The terms ‘compliance’, ‘adherence’ and ‘concordance’ are not used consistently in the literature (5); some authors use them synonymously (11) whereas others define compliance as the extent to which a person complies with medication and adherence or concordance as a wider concept, including habits and attitudes towards therapeutic strategies (5).

The use of the term “compliance” has been criticized by some authors as inferring an authoritarian and paternalistic attitude (5), often, the terms adherence and compliance are used interchangeably; however, their connotations are somewhat different. Adherence presumes the patient’s agreement with the recommendations, whereas compliance implies patient passively (7). *Steiner* and *Earnest* (2000) stated that both terms are problematic in describing medication-taking behavior because they “exaggerate the physician’s control over the process of taking medications” (16). More recently the concept of ‘partial compliance’ has emerged, acknowledging the actual, frequent situation in which a person takes some but not all of the prescribed medication (5). *Velligans et al.* (2007) suggest the term ‘medication refusers’, for those who do not accept medication, and ‘medication acceptors’. Divide by degrees of adherence (those who take medication but might have adherence problem in the future). The authors stress that this is very important because “complete refusal may begin as a function of missed or skipped doses, either intentional or accidental” (17).

Box 1 Working definitions about health behaviour

Adherence (compliance) is the extent to which an individual changes their health behaviour to coincide with medical advice

Concordance is the degree to which clinical advice and health behaviour agrees

Therapeutic alliance is an agreement between patients and health professionals to work together

Therapeutic disagreement is a divergence in the views of patients and doctors on the subject of treatment

The concept of concordance explicitly involves mutual respect and understanding between patients and their treating physician as well as shared decision-making in order to achieve a cooperative therapeutic alliance (5). Medication persistence is “the length of time from initiation to discontinuation of therapy (5, 14) and is measured on units of time” (14).

Providing specific definitions for compliance and persistence is important for sound quantitative expressions of patients’ dosing history and their explanatory power of clinical and economic events. Adoption of these definitions by health outcomes researchers will provide a consistent framework and lexicon for research (11).

5. Predictors of Non-Adherence/Poor Adherence to Medication

Several patient-related factors, including lack of understanding of their disease, lack of involvement in the treatment of decision-making process and suboptimal medical literacy, contribute to medication non-adherence.

The patients' health beliefs and attitudes concerning the effectiveness of the treatment, their previous experiences with pharmacological therapies, and lack of motivation also affect the degree of medication adherence (3, 7). Specific factors identified as barriers to medication adherence among inner city patients with low socioeconomic status were high medication costs, lack of transportation, poor understanding of medication instructions and long wait time at the pharmacy. A lack of family or social support is also predictive of non-adherence, as is poor mental health. In broader terms these factors fall into the categories of patient-related factors, physician-related factors, and health system/team building-related factors (7).

5.1 Patient Factors

5.1.1 Lack of Insight (illness belief and knowledge of medication; awareness):

many researchers argue that the relationship between insight and adherence is not always straightforward and may be without a direct relationship e.g., it is possible that the lack of insight in this population might be related to a lower level of formal education and a lack of understanding of mental illness and its phenomena (3). Health and disease are important factors in adherence in mental health. Patients' understanding of their condition and its need for treatment are positively related to adherence (10). Studies have shown that patients who understand the purpose of the prescription are twice as likely to collect it as those who do not understand. Awareness of treatment accounted for 20% and 34% of variation in subjective responses to atypical and typical antipsychotic drugs in one recent report (10). Awareness of psychotic illness may exist on several levels. *Olfson et al.* (2000) found that medication compliance was not related to whether a patient acknowledged having a mental illness or diagnosis of schizophrenia, but rather to the patients' ability to recognize clinical symptoms. Patients who have difficulty recognizing their own symptoms (4) (poor cognitive function) (10) may be less aware of their ongoing need for maintenance treatment and therefore less appreciative of the benefits of antipsychotic medication (4), and more likely to discontinue (10).

5.1.2 Side Effects: patients who default on their treatment said that treatment side-effects together with complex treatment regimens are the main reasons for their poor adherence (3). However, this association between medication side effects and adherence is not generally clearly established because many patients adhere to their medication despite treatment side-effects, and a history of adverse side-effects (3, 4) is not always predictive of future non-adherence (3). Some of these side effects are:

- a. **Weight gain:** due to medication has been linked with non-adherence and subjective distress. Obese individuals are more than twice as likely as those with a normal body mass index to miss their medication (10). *Fakhoury* (1999) found that more than 70% of patients described weight gain due to antipsychotics as extremely distressing which was higher than that for any other side effects (18).
- b. **Age education, life stressors, and stressful life events** are often associated with the onset of a psychotic relapse usually in the three weeks prior to the relapse. life stressors may be both internal (e.g., thoughts and feelings) and external (e.g., death of a close relative. other stressors include chronic interpersonal stress, poverty, homelessness, criminal victimization and stigma (3). other reported factors associated with relapse include age and education. the relapse tended to occur in the age group <50 years and, although this variable looked a statistically predictive power of relapse, there was a tend toward younger patients being more likely to relapse (3). *Gilmer et al.* (2004) found a low rate of adherence to treatment with antipsychotic medication in a sample of young and middle-aged (6).
- c. **Sexual dysfunction:** is a significant source of distress and may be linked to poor adherence (10). *Rosenberg et al.* (2003) examined the effects of sexual side-effects on adherence. They found that 62.5% of men and 38.5% of women felt that their psychiatric medication were causing sexual effects; 41.7% of men and 15.4% of women admitted that they had stopped their medication at some points during treatment because of sexual side-effects (19).
- d. **Motor retardation:** involves the general slowing down and weakening of voluntary of motor responses (e.g., speech is slowed, weakened in volume and reduced in amount (20).
- e. **Emotional withdrawal and uncooperativeness:** this construct is defined solely in term of the ability of the patient to relate in the interpersonal interview situation. Uncooperativeness is a term represents signs of hostility and resistance to the interviewer and interview situation (19).
- f. **Depressed mood:** Depression symptoms may appear at any time during the course of schizophrenia and contribute to relapse and a decrease in quality of life (3). The UK Public Campaign Defeat Depression revealed that many people were wary of taking antidepressants because they believed that individuals with depression should pull themselves together and more than three-quarters believed that the medication are addictive (10). *Kazadi et al.* (2008) showed in his study a quarter of all patients developed a depressed mood during the period studied increasing the risk of a relapse by 5.3 times. Other studies on depression associated with schizophrenia show a

variation ranging from a high of 75% to a low of 7% (3). *Sirey et al.* (2001) found that perceptions of stigma about depression at the start of treatment predicted subsequent medication adherence (21). Variation in adherence could be primarily explained by the balance between patient's perceptions of need versus perception of harm, with adherence being lowest when the perceived harm of the antidepressant exceeded the perceived need. Two consistent predictors of stopping medication are feeling better and adverse effects (10).

5.1.3 Substance Abuse: was very common among our study population. There was no significant association with relapses. This finding differs from previous findings of strong association with relapses and a greater risk of rehospitalization. Substance abuse exacerbates psychotic symptoms and drugs abused may also lead to transient symptom reduction. Commonly abused substances include nicotine, alcohol, cannabis and cocaine (3). *Sannibale et al.* (2003) found that younger male, heroine-dependant clients with poly-drug use who had refused opioid pharmacotherapy were more likely to drop out of treatment and to relapse early following treatment (22). Substance use disorders emerged as the strongest predictor of medication non-compliance (4, 6). This finding confirms and extends those of earlier cross-sectional studies and contrasts with the finding of *koraszny* and coworkers, who reported that a life time history of substance use disorder was not associated with medication non-compliance. A recent history of substance abuse or dependence may more accurately predict further medication compliance than a more remote history of a substance use disorder (4); however, some studies report no association between substance abuse and relapse (23).

5.1.4 Lack of Family and Social Support

The availability of family members who remind patients to take their medication is widely believed to lower the risk of medication non-compliance. Several cross-sectional studies have demonstrated lower rates of medication non-compliance among patients with schizophrenia who live with family members or with people who supervise their medication. At the same time, patients whose families are ambivalent about antipsychotic medication are at increased risk of medication non-compliance after hospital discharge (4). Individuals living with family members or in an assisted living facility were more likely to be adherent than those who lived independently. This might result from greater medication supervision and support of medication taking behavior by family members or staff and assisted living facilities or from greater access to outpatient services (6). Alternatively, it may be that characteristics of the patients themselves, rather than their living situations, determine rates of adherence. Patients who live with family members or in assisted living facilities are different in ways we have not measured from those who live independently and those who are homeless and it may be that these personal characteristics related to selection of living situation are driving our results (6). Family visits or family therapy session during the hospitalization were related to future medication compliance. However, patients whose families refused to participate in treatment were at high risk for stopping their medication. In previous research, a strong correlation has been found between family members and patients' attitudes toward antipsychotic medications (4).

5.1.5 Pharmacoeconomic Factors

According to a 2003 report published by WHO, adherence rates in developed countries average only about 50%. Adherence is a key factor associated with the effectiveness of all pharmacological therapies but is particularly critical for medications prescribed for chronic conditions (7). Reasons for non-adherence were lack of acceptance of the necessity, for pharmacological treatment and lack of insight (10). Missing or stopping antipsychotic medication was strongly associated with several untoward outcomes, including symptom exacerbation, non-compliance with out-patient treatment, homelessness, emergency room visit, and rehospitalization (4). Rate of non-adherence with psychotropic medication are difficult to summarize because they vary by setting, diagnosis and type of adherence difficulty (10). *Fenton et al.* (1997) found that non-adherent individuals with schizophrenia have a 3.7 fold greater risk of relapse than those who are adherent over 6-24 months (24). Pharmacoeconomic evaluations assess whether incremental improvements in outcome associated with a given drug justify the cost.

The specific nature of this assessment can take various forms, but essentially requires a comparison of alternative treatments costs and benefit. Many factors impact on these costs and benefits, one of which is how "well" the medicines are taken. Suboptimal compliance and/or failure to persist with therapy for the prescribed duration reduce the therapeutic potential of drug treatment, and account for many of the observed differences between efficacy and clinical effectiveness (14). *Gilmer et al.* (2004) found that the adherence rates of individuals treated with the atypical antipsychotics risperidone, and olanzapine and quetiapine were similar to those of patient treated with conventional antipsychotic medication. Results from previous research have been mixed regarding differences in adherence between typical and atypical antipsychotic (6). *Rosenheck et al.* (2000) found that patients taking clozapine had greater medication adherence than those taking haloperidol (because of greater

symptom improvement and fewer side effects) (25). *Doldar et al.* (2002) reported that patients treated at the San Diego Veterans Medical

Center who were taking atypical antipsychotics were more likely to be adherent than those taking typical antipsychotics, but this finding was sensitive to the exact definition of adherence (26). *Geddes et al.* (2000) found no clear evidence that atypical antipsychotics were more efficacious or better tolerated than conventional antipsychotics (27). *Gilmer et al.* (2004) found a lack of a significant difference in the adherence rates between conventional narcoleptics and atypical antipsychotics points to a need for continued research on improving adherence in patients with schizophrenia (6).

5.2. Physician-Related Factors

The importance of good communication between patients and health professional is increasingly acknowledged in relation to adherence (10). In practice, the process of making a joint therapeutic plan is often abbreviated. Doctors tend to overestimate the amount of information they have given to patients. At the same time, patients often misunderstand medical words (10). According to *Thompson and Pledger's* (1993) study, 22% of patients have difficulty with the word "symptom"; 38% with the word "orally"; and 76% with the word stroke (28). Poor relationship between psychiatric staff and patients is a factor in a patient's non-adherence to medication. It is referred to as a poor therapeutic alliance -such as relationships include psychiatrists, psychologists, nurses, social workers, and psychiatric aids in both in-patient and out-patient units. It involves things such as taking the time to listen to patients, treating them with respect, explaining things to them, and involving them in treatment decision in so far as this is feasible (10). Physicians' communication style during follow-up and clients' satisfaction were both predication of a better medication adherence. A collaborative communication style by the clinician enhanced client's knowledge of the medication, improved satisfaction with medication and improved reliability of medication use (10). Not only do physicians often fail to recognize medication non-adherence in their patients, they may also contribute to it by prescribing complex drug regimens. The complexity of a treatment regimen (number of tablets, number of medications and drug interval) adversely affect adherence (10). Regimens that require disruption of life style, or special techniques or arrangements are less welcomed by patients (10). In elderly patients, acceptable adherence is common in those taking only one medicine but rapidly fall in those taking four or more (10).

Failing to explain benefits and adverse effects of a medication effectively and inadequately is considered the financial burden to the patient. Ineffective communication between the primary care physician and the patient with mental disease further compromises the patient's understanding of his or her disease, its potential complications, and the importance of medication adherence failing to elicit a history of alternative, herbal or supplemental therapies from patients is another source of ineffective communication(7). *Joyce et al.* (1969) demonstrated that patients were unable to recall half of the information given to them by their physicians (29). Two-third of individuals recently discharged from hospital did not know what time to take medication and less than 15% recalled the common side-effects (10).

The lack of any association between patient-provider relationship and non-adherence should be viewed in the working context, in our setting, doctors' change every 6 month. Chronic schizophrenic patients; furthermore, could be compromised by their illness and unable to establish a committed therapeutic alliance with their psychiatrists (3). Involvement the patients in the treatment decision-making process, patients who are very unwell or without insight are unlikely to tolerate an extensive dialogue about possibilities. Yet collaborative decision-making has been shown to be consistent predictor of health outcomes (10). Most patients do not feel involved in treatment decisions and state that they take medication only because they are told to. Patients typically leave the clinic with a poor understanding of the rationale for therapy. In one study, two-thirds of psychiatric in-patients did not understand why they were taking medication, and the vast majority could not be said to have given informed consent to their treatment. Similarly, many patients misunderstand prescription instructions (10).

5.3. Health System/Team Building Related Factors:

Medical disorder exacerbates the relapse process. In South Africa, mental health services remain marginalized and poorly integrated with general medical services in the primary health care system. Co-morbid medical illnesses are managed by different services, and it is possible that adequate attention is not paid to recording these co-morbid medical disorders in case note at mental health clinics (3). Fragmented health care systems create barriers to medication adherence by limiting the health care coordination and the patients' access to care prohibitive drug costs and/or copayments also contribute to poor medication adherence. Health information technology is not widely available, preventing physicians from easily accessing information from different patient's care-related venues, which in turn compromises patient care, timely medication refills and patient-

physician communication (7). The early period of contact between clinician and patient is important in terms of forming a therapeutic alliance and making a joint-therapeutic plan. Most patients with mental health problems themselves recognize the difficulty in adhering to complex medication regimen (10). Before starting a new psychotropic drug, we suggest that clinicians should explicitly acknowledge to the patient the difficulties of taking medication outline realistic benefits and discuss possible adverse effects, and consideration of treatment alternatives (10). Patients who receive this kind of communication are more acknowledgeable and have more positive initial beliefs about their medication (10). Out-patients with schizophrenia who form strong alliances with their therapists seem to be more likely to comply with prescribed medications than patients who form weaker alliance. The development of a trusting collaborative clinical relationship may lead patients to perceive practical advantages of continuing with prescribed medications. In-patients who consent to receive antipsychotic medication have also been found to be more satisfied with and trusting of hospital staff than those who refuse medication (4). In an overtaxed health care system in which clinicians see a large volume of patients without resources to meet individual patients' needs, the amount of time a clinician spends with patients may be insufficient to properly assess and understand their medication-taking behaviors. Slow access to services, length of intake process, therapist related barriers, employee policies and ineffective training of staff, lack of time may preclude engaging the patient in a discussion on the importance of medication adherence and strategies to achieve success (7). 40% of youth in low income communities display mental health difficulties mental. Health providers must ask themselves how can they improve services and access their finding for the programs that are essential (30). This indeed is not just an obstacle for the programs, but for the individual clinicians as well, as they are the ones who are charged with engaging consumers in treatment (30).

Communication among physicians is often insufficient and may contribute to medication non-adherence. Direct communication between hospitalists and primary care physicians occurs in less than 20 % of hospitalizations, and discharge summaries are available at less than 34% of first post discharge visits. Inadequate communication between physicians, hospitalists, primary care physicians, and consultants also contributes to medication errors and potentially avoidable hospital readmissions (7).

Patients with schizophrenia are usually discharged from hospitals to follow up at their nearest community mental health clinics, which focus mainly on pharmacotherapy, with little psychosocial support services owing to a lack of human and material resources, and the difficulties of integrating various treatment modalities in community based, out-reach teams-even where the appropriate range of services is available. Despite these constraints, relapse rates are similar to those of developed countries. Notwithstanding the other benefits and qualities that are brought about by psychosocial approaches (3).

6. Strategies to Improve Medication Adherence

Poor adherence to medical treatment severely compromises patient outcomes and increases patient mortality. According to the WHO, improving adherence to medical therapy would yield very substantial health and economic benefits. To improve medication adherence, the multifactorial causes of decreased adherence must be understood (7). The WHO classifies these factors into 5 categories: socioeconomic factors, factors associated with the health care team system in place, disease-related factors, therapy-related factors, and patient related factors (7).

6.1 Patient-Related Factors

Medication adherence is primarily in the domain of the patient; effective patient education must be individualized, multifactorial, and delivered in a variety of methods and settings outside of the examining room. A key component of any adherence improving plan is patient education (7). Formal health education programs, such as diabetes self-management education, have been shown to be effective (31); however access to similar non-disease-specific program is limited. In the absence of a formal program, physicians would do well to emphasize the availability of other educational resources, but not limited to pharmacists, community health programs, and interactive Web-based materials. It might also be beneficial to recommend to patients that they engage local librarians to help them access the internet (7). It is possible that psychoeducational strategies that help patients develop more accurate subjective health assessments may improve compliance with maintenance antipsychotic treatment. Cross sectional studies have reported that patients who deny being mentally ill have higher rates of medication non-compliance than patients with greater insight into their illness. And improvements in insight have been linked to improved medication compliance (4).

Thus, another key factors that can improve patients-related medication adherence is actively involving patients in treatment decisions when possible. One simple way to involve patients is to ask what time of day they would prefer to take their medications. One patient may be more likely to adhere to his or her medication if they were

taken in the evening, whereas for another, the morning may be preferred. Only patients can make these decisions (7). Treatment does not progress unless the client is engaged and actively participates in his treatment. This is the basis of effective intervention (30). If a number of alternative treatment options are recommended, offering patients choices encourages active participation in their treatment. Similarly, the physicians should avoid prescribing numerous medications and behavioral modifications at any one visit because this may overwhelm the patient and induce a sense of futility. If it is necessary to prescribe more than one drug or intervention during a given visit, a rationale should be provided for which are most important because it will help insure that, if patients decide to stop taking their medications for any reason, they will discontinue the most important medication last (7). Pharmacogenetic differences in the rate of metabolism of antipsychotic medication and in the response to antipsychotic medications have also been reported (6). There was an association between excess amounts of antipsychotic medication and a greater likelihood of being hospitalized. Excess medication fills might have resulted from overuse of antipsychotics leading to increase the risk of medication side effects and associated medical care. Alternatively, excess filling of medication may be indicative of other problems, such as having an unsatisfactory response to antipsychotics requiring numerous medication changes, or being in a situation in which medications are often lost or stolen, or sold (6). *Parikh et al (1996)* stated that almost half of patients with low literacy admitted shame, which prevented them from seeking needed help. Of patients who admitted having reading problems and being ashamed, more than 85% hid their limited literacy from co-workers or supervisors, and approximately 50% hid it from their children (32). To help combat poor health literacy and its negative effect on medication adherence, a “shame-free” environment must be created. Possible solutions to poor patient literacy include providing the patient with pictorial and audiovisual educational material instead of written instructions (7). Unlike a number of previous investigations, *Gilmer et al. (2004)* found a significant association between adherence to treatment with antipsychotic medication and age and ethnicity (6).

Investigators examining the course of schizophrenia have observed; which indicate that positive symptoms show a modest improvement over time and it may be that adherence improve along with a decline in severe psychotic symptoms. It is also possible that younger people with schizophrenia, presumably with a shorter duration of illness than older individuals, may not have had a sufficient time to appreciate the consequences of non-adherence (6). *Valenstein et al. (2002)* reported that African Americans were significantly less likely to be adherent to their antipsychotic medication, but the low rate adherence among Latinos is a new finding (33). Despite the widespread use of a typical antipsychotic medication, alarmingly high rates of both underuse and excessive filling of antipsychotic prescriptions were found in Medicaid beneficiaries with antipsychotic adherence and associated negative consequences suggest interventions in multiple levels (6).

Adherence of any particular ethnic group is likely to be affected by a unique combination of factors. Psychosocial and other non-biological factors such as cultural beliefs and expectations, as well as access to care, may play an important role in determining adherence (6). In mentally ill patient, partial adherence to treatment remains a therapeutic challenge and a factor that is difficult to quantify. It is compounded by the fact that adherence rate varies for different psychotropic medication: 58% for antipsychotic and 65% for antidepressants (3). Recognizing and treating mental illness must be a priority when treating patients for others chronic conditions such as cardiovascular disease (CVD) often, successful treatment of patients' coexisting illness depend on the first treating any underlying mental illness (7). Difficulties with medication compliance are considered to be one of the most important risk factors for relapse and rehospitalization among patients with schizophrenia which form approximately 40-50% of relapse patients (5). Individuals who were non-adherent, partially adherent, or excess fillers were more likely to be hospitalized. There is growing body of literature suggesting that individuals with schizophrenia receive worse physical health care and experience poorer outcomes than individuals with depression or without mental illness. Patients who are non-adherent to their antipsychotic treatment are likely to be more antipsychotic and, presumably, less able to comply with outpatient treatment for other medical illness (6). 10% of patients prescribed antidepressants fail to pick up their first-prescription. Of those who start take their medication, non-adherent rates increase with time. Individuals with depression generally want more information about their condition than they are offered and want to be involved in decision-making. In depression, as in other areas, the more information that is given the better is adherence (10).

Consideration of patient's economic status is of paramount importance. Recognizing that patient's economic constraint will limit their ability to adhere to their medication, the physician may direct patients to programs that provide financial assistance (7). As expected, hospital costs were lower and pharmacy costs were higher for those who were adherent to their antipsychotic medications than for those who were non-adherent. Overall, improving medication adherence has the potential to improve health for individuals with schizophrenia without seriously increasing costs. Thus, interventions that efficiently improve medication adherence are likely to be

cost-effective (6). In contrast, excess filters had higher pharmacy, hospital, out-patients, and total costs. Targetting excess medication fills has the potential to save more than \$1.000 per person per year in medication costs alone (6). Studies for intervention aimed at reducing homelessness have found that homeless individuals assigned to community housing, group homes, and residences providing a higher level of services were more likely to remain stably housed than homeless individuals attempting to live independently (10). To the extent that assisted living facilities provide a residence with improved medication oversight, they could be viewed as preferred alternative to homelessness. Policy makers interested in reducing homelessness might consider subsidizing these facilities for certain subgroup of homeless individuals and evaluating whether these subsidies improving long-term residential and treatment outcomes (6). Inpatient staffs who take a careful history to the recent medication non-compliance patients may improve their prediction to who are at risk for stopping their antipsychotic medication. The availability of family to help patients has been consistently shown to be associated with improved medication compliance (4). Individuals who were homeless had the lowest probability of being adherent. They were also the least likely to receive medication supervision, to have the support of family members, and to have access to outpatient care (6).

In the general population, it is recognized that social support acts as a protective factor against stressful life events and improves recovery from health conditions. The literature has established that there is a positive correlation between social support with health, functioning and quality of life.

6.2 Physician-Related Factors

Effective communication is the key to a good physician-patient relationship. Thus, perhaps the foremost strategy; physicians can promote medication adherence by using a follow up patient-centered approach of care that increase active patient involvement in the medical decision-making process. As a part of the patient centered approach, physician should consider patient 'cultural beliefs and attitudes' (7).

If physicians are aware that patients plan to ration their medication, they will be able to discuss the importance of taking the medication as ordered or to prescribe a different medication that is more 'forgiving'. Forgiving drugs are defined as those for which a missed dose is less detrimental to long-term outcomes. Physicians have several opportunities to improve medication adherence especially when take in consideration the type of drugs that prescribed (7). Clinical outcomes of treatment are affected not only by how well patients take their medication but also by how long they take their medication (11).

Prescribing the maximum number of possible doses at one time, thereby limiting the frequency of pharmacy visits, and acknowledging the patients' economic status by adhering to their formulary improve adherence by minimizing economic barriers. An increased number of bills ingested per day may also decrease adherence. To help combat the decreased adherence associated with polypharmacy, physicians should consider prescribing fixed-dose combination pills when possible (7).

The long term benefit of these interventions that showed by most studies is a positive effect as soon as early the implementation of the intervention done for reducing pharmaceutical non-adherence (2). Medications with once daily dosing may be preferable than medications that are taken in multiple doses per day because minimizing the frequency of dosing has shown to improve adherence (7). A review of studies that measure compliance confirmed that the prescribed number of doses per day is inversely related to compliance. Simpler, this frequent dosing regimens resulted in better compliance across a variety of therapeutic classes. *Marie et al.* (2011) suggest that a 10% decrease in adherence will occur with each additional daily dose. Because complex treatment regimens are associated with decreased adherence, physicians would be wise to prescribe drugs that can be taken at the same time of day. If complex treatment regimens cannot be avoided, open acknowledgement of this by the physician may improve the physician-patient relationship, thus increasing adherence (7).

When prescribing a new medication, the physician or clinical pharmacist should provide the patient with all necessary and important information, including the name of the medication, its purpose (e.g., to lower BP); the rationale for choosing it (e.g., other drugs to lower your BP, but this one is equally effective and is available on your insurance plan's formulary list); the frequency of dosing (e.g., once daily); when it should be taken (e.g., in the morning with your other medications); how long it should be taken (e.g., for one year or lifelong); and any potential adverse effects, their likelihood of occurring, whether they will resolve without intervention, and how the treatment plan may change if they do not resolve (7). Mental health professionals can sometimes, increase the effectiveness of their treatments, by inviting the client's family or friends to a session therapy, this of course, occurs only if evidence in the client's clinical assessments supports the need (30).

Patients' perceptions of adverse effects contribute significantly to decisions regarding medication adherence. Non-adherence to medications secondary to adverse effects is termed rational non-adherence, which *Garner* (2010) defines as "the cessation of a prescribed therapy because of concern for, or the presence of, medication side effects", *Garner* further states that rational non-adherence "is nearly impossible to circumvent if a patient's specific side-effect concern are not substantially addressed". Therefore, it is critical that adverse effect profiles are considered when prescribing a medication and discussed with the patient before the initial prescription and at every visit thereafter (34). The use of motivational interviewing is another effective communication tool. Motivational interviewing is a counseling technique originally developed to help patients face threat addiction, also designed to help patients identify and overcome reasons they may be reluctant to change their behavior (7). Doctors do not diagnose perfectly or prescribe carefully all of the time. Thus the patient is not always acting irrationally if he attempts to allow for adverse effects or minimize stigma by adjusting doses or times of administration, a substantial minority do not tell their doctor after stopping or interrupting medication. Partially because of fear of rejection or being disbelieved, or embarrassment about discussing adverse effects such as weight gain or sexual problems (10). Overall by acknowledging the presence of cultural beliefs and attitudes, physicians can build trust with their patients and proactively address any culture or belief related adherence barriers. An essential component of effective physician-patient relationships is the creation of an encouraging, "blame free" environment, in which patients are praised for achieving treatment goals and are given "permission" to honestly answer any questions related to their treatment. By asking the appropriate questions, physicians can accurately assess which medications patients are taking and how they are taking those (7).

6.3 Health System/Team Building-Related Factors

The health system in which a physician practices is integrated to achieving the ultimate goal of improved patients' health. Because medication adherence is an important contributor to improved patient health, health care systems must evolve in a way that emphasizes its importance. According to *Marie et al.* (2011), constraints may be addressed by developing a patient-based health care team approach. The team-based approach includes training non-physician staff to perform duties traditionally completed by physicians, thus allowing the physicians more time to discuss the patient's medication adherence patterns. For example, during a telephone reminder for an upcoming appointment, clerical staff might remind patients to bring in all their medications and pill boxes for review at the office appointment (7). Other aspects of a team-based approach to health care include assessment of non-adherence by office staff and pharmacists; pharmacist-based patient education, phone call reminders, web-based tools, and assignment of a case manager. Because these activities occur outside of the physician-patient encounter, they will not lengthen the visit and may increase efficiency. Increased implementation of electronic medical records and electronic risk of non-adherence and targeting them for intervention may limit the antipsychotic treatment (7).

Initially long-term medications during hospitalization for an acute event, rather than initiation the therapy session after discharge, may improve adherence. Initiating therapy while patients are hospitalized is thought to improve adherence because patients and their caregivers are focused on psychiatry risk and how it can be reduced during this "teachable moment". Many patients perceive that medications initiated while they are in the hospital are essential for their health (7). Until long term data become available and until studies establish which intervention maintains its effect in the long term, clinical interventions should be implemented in practice as short-term measures. For example, orientation and education about treatment modalities and medications is essential to keep patients in treatment, but this intervention should be frequently and routinely repeated in the same patients, because it is unknown whether its effect is maintained in the long term. Similarly, pre-discharge contacts between patients and the out-patients team, or pre-discharge psychotherapeutic interventions, must become a routinely delivered service policy, offered each time evaluate the schedule for patient discharge, even for patients who have already received it during previous admissions (2). Community psychiatric services can provide effective clinical interventions, approved by scientific evidence, for reducing patients' non-adherence, who conducted a narrative review of clinical interventions in psychoses, recommended a schedule appointments before discharge from in-patient care unit, using prompts in the forms of letters and telephone calls (5) to encourage patients to keep their appointments and offering education about treatment and medication (2). A critically important health system-related factor that improves medication adherence, also keeps patient safety, is the appropriate medication reconciliation. Medication reconciliation is the process of creating the most accurate list of alternative medications that ensures patient safety, including drug name, dosage frequency, and route, and comparing that list against admission, transfer, and/or discharge orders. The goal of medication reconciliation, a national priority of the Joint Commission on Accreditation of Healthcare Organizations, is to ensure provision of correct medications to patients at all transition points and avoid medication duplication and errors (7).

7. Conclusions

Medication non-adherence was significantly associated with an increased risk of rehospitalization, emergency room visits, homelessness and symptoms exacerbation. Non-adherence was significantly more likely to have a history of medication non-adherence, substance abuse or dependence, and difficulty recognizing her own symptoms. Patients who became medication non-adherence were significantly less likely to have a good therapeutic alliance form during hospitalization and were more likely to have family members who refused to become involved in their treatment. Community psychiatric services can potentially use effective clinical interventions, approved by scientific evidence, for reducing patient non-adherence.

Future promising of pharmacologic approach that lowers the risk of medication non-compliance should motivate clinicians to identify and provide appropriate preventive interventions to those patients during the critical period of transition from inpatient to outpatient care. Physicians must recognize that poor medication adherence contributes to suboptimal clinical benefits, particularly in light of the WHO's statement ensure that increasing adherence may have a greater effect on health than any improvement specific treatment.

Strategies for adherence include raising information and skill levels, altering characteristics of the regimen, and improving the relationship between the provider and the patient. Provider and the patient awareness with regard to medication adherence can be enhanced with the creative application of behavioral contracts. Adherence promoting efforts can also include rewards and improvement strategies.

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