Compliance in Schizophrenia: Outpatients Taking Oral Antipsychotics

by

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Abstract

Noncompliance in schizophrenia has been linked to increased relapse rates and poorer outcome. We investigated noncompliance rate, distinguishable factors between compliant and noncompliant patients, and the correlation among different types of compliance measurements. Fifty-two outpatients with DSM-IV diagnoses of schizophrenia or schizoaffective disorder used MEMS® to record doses taken for a period of 4 weeks. Self-report, physician ratings, and pill counts were also used to measure compliance. On MEMS® reading, 25 patients (48%) were compliant, taking medications as prescribed 80% of the time or more, and 27 (52%) were noncompliant. Noncompliant patients were older with a longer duration of illness and more positive and total symptoms, and took medications more frequently. They reported lower family support and a lower alliance with their psychiatrists. Higher positive and total symptoms and lower alliance with psychiatrists were significantly correlated with lower readings on MEMS®. Only pill count was significantly correlated to MEMS® reading.

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I. Introduction

Since the introduction of antipsychotic medications in the 1950's, pharmacological treatment has been the cornerstone of schizophrenia treatment. One of the most important factors determining the success of pharmacological treatment is patient compliance with prescribed medication regimens (1). Unfortunately, noncompliance rates as high as 70% have been reported for patients with schizophrenia (1-3).

Noncompliance is not a unique problem to schizophrenia. Many patients with chronic medical conditions are at risk for noncompliance, especially when the condition is asymptomatic, the treatment is prophylactic or suppressive, and the consequences of noncompliance are delayed (4). However, in comparing compliance rates between mental and physical disorders, one study reports that patients taking antipsychotics showed average of 58% compliance, while patients with physical disorders showed average of 76% (5). Noncompliance in patients with schizophrenia is a significant problem due to the resultant increase in psychotic relapses and their disruptive effect on overall rehabilitation efforts, as well as more recent evidence indicating an association between number of relapses and poorer outcome (6).

The impact of medication noncompliance in patients with schizophrenia is reflected in increased hospital readmission rates. While the institutionalization of the mentally ill has dropped over the years possibly due to decrease in bed availability, and increase in outpatient care, hospital admissions and readmission rates have, in contrast, increased (7). One possible explanation for increase is "the revolving door" phenomenon (7), where many patients require frequent rehospitalizations after discharge. Noncompliance with medication has been shown to be significantly

associated with higher frequencies of rehospitalization in patients with schizophrenia who are on oral antipsychotic medications (7, 8). A case control study found that rehospitalized patients with schizophrenia were 8.18 times more noncompliant with medications and aftercare treatments compared to the their non-rehospitalized comparison group (9). At the same time, it has been suggested that maintenance medication treatment can prevent relapse in up to 90% of outpatients with schizophrenia in remission or in a stable clinical condition (10, 11), while up to 68% of patients receiving no medication experience relapse (10). In addition, noncompliant patients have more prominent psychotic features during relapse, resulting in longer hospital stays compared to their compliant counterparts (12, 13).

Added to this dilemma is the fact that hospitalization represents the greatest direct cost in the mental health care system (14). For example, the cost of readmission of patients with schizophrenia within 2 years of discharge is estimated to be $2 billion in the United States (15). Any factor that can reduce relapse rates, such as improved compliance, thus offers the opportunity for substantial cost savings (15).

Relapse costs must further be assessed within the context of the negative influence on families and rehabilitation. Families are often extensively burdened by the demanding role of caring for patients with schizophrenia, and relapse entails a worsening of symptoms and, at times, socially disruptive behaviour (16). Figures from 1985 in the United States indicate that the lost productivity of family members resulting from caring for patients with schizophrenia amounted to $4.5 billion in indirect costs (14).

To summarize, noncompliance in schizophrenia is extremely costly to the individual, his or her family, and society as a whole. Not surprisingly, much effort has gone into investigating compliance in patients with schizophrenia over the years. The picture emerging from these studies indicates that compliance is a complex, multi-dimensional behaviour best viewed along a continuum, rather than as an all-or-none phenomenon (1, 3, 4). Its complexity encompasses a variety of factors, including patient and illness profile, social variables, medication related issues, substance abuse and insight.

(A) Factors in compliance

(1) Patient profile and Demographic variables:

(1-1) Age:

Most studies agree that age is not consistently associated with compliance (17-20). However, there is some evidence that young adults, that is those younger than 30 years old, may represent a difficult group to treat in terms of compliance (21-23). Conversely, more positive attitudes toward compliance are associated with older age (24-26).

(1-2) Gender:

Gender is not found to be significantly associated with compliance in the majority of studies (1, 17, 19), although a few studies have reported an association between male gender and lowered compliance rates (21, 26). In several reports, post-discharge treatment compliance rates were dramatically better in females, including

compliance with both pharmacological and nonpharmacological interventions (27, 28).

(1-3) Socioeconomic class:

In alcoholism and drug addiction, low socioeconomic status or unemployment often predict poor compliance (29, 30). However, in patients with schizophrenia the finding of this trend is limited. Most studies found no association between socioeconomic class and compliance (1, 9, 19, 23). Interestingly, one study noted that most drug-refusing patients came from a higher socioeconomic class (31).

(2) Illness characteristics

(2-1) Course of illness:

Most studies have failed to show an association between the course of illness and compliance. For example, the age of onset of the illness, and duration of admissions have not been associated with compliance (13, 19). However, shorter duration of illness has been reported to be associated with noncompliance (23).

The relationship between the number of previous hospitalizations and compliance is conflicting, with evidence of poorer compliance as a function of number of hospitalizations in one report (13), but not in others (17, 20).

(2-2) Illness severity/Positive symptoms:

Noncompliance is consistently associated with more severe psychopathology. Noncompliant individuals show evidence of more severe psychosis, disturbed mood, conceptual disorganization, emotional withdrawal, and unusual thought content (32-34). It is also interesting to note that a specific symptom type, such as grandiosity,

stands out as distinguishing marker between compliant and noncompliant patients i.e. noncompliant patients had significantly higher ratings on grandiosity (34, 35). Studies have also reported an association between symptom severity at or after discharge and noncompliance (34, 36). One report has noted that noncompliance prior to rehospitalization is more common among patients with schizophrenia, paranoid subtype (37), although this finding was not replicated elsewhere (38).

(3) Insight and Cognitive function

(3-1) Insight:

Insight is now generally considered to be a multidimensional construct involving a patient's awareness of illness, ability to attribute symptoms to illness, and realization of need for treatment (39). It is worth noting that a patient's awareness of illness and resultant compliance are not always stable over time in schizophrenia (40).

Awareness of illness has been shown to be an important variable in compliance with treatment in schizophrenia (23, 40-42), with lack of insight in this respect strongly associated with poor compliance (35). In addition, patients with more awareness are significantly less likely to be readmitted to hospital due to relapse (42), whereas lack of insight or denial of illness represent a significant factor in frequent rehospitalizations (43). In the hospital setting, those who believe that they are not ill more often refuse medications (32). Patients who believe in more medical explanations for their illness make more visits to the clinic and follow treatment in a more compliant manner than patients who believe in nonmedical explanations for their illness (44). Along similar lines, patients with schizophrenia who recognize the

benefits of medication over and above symptom relief are more likely to comply with their medication regimen (2).

Despite the apparently significant relationship between insight and compliance, it is noteworthy that not all studies have found this to be the case. For example, in those on depot neuroleptics insight was not found to be related to compliance (45), and other studies have found no association between insight and compliance (2, 19). This suggests that there are patients who are not aware or do not believe that they are ill or need medication yet remain compliant, and vice versa.

(3-2) Neuropsychological impairments and cognitive deficits:

At this point, there are only two studies that have investigated the relationship between neuropsychological impairment and compliance. In one, specific neuropsychological impairments, as tested by a reading test, Verbal Fluency Test, the Cognitive Estimates Test and the Trail Making Test, were relatively poor predictors of compliance compared to other clinical variables such as diagnosis, attitudes to medication, side effects, and being a detained patient (25). In contrast, the other study reported that neurocognitive impairment was significantly related to compliance (40). The specific associations between neuropsychological impairment and compliance remain unclear and require further explanation. It is noteworthy that overall intelligence has not been associated with compliance (2, 19, 25, 40).

(4) Subjective experience of antipsychotic effects

Patients experiencing immediate benefits and a subjective sense of well being from medication have been shown to consent to and comply with antipsychotic

medications more than patients who experience medications to be of no benefit or harmful (19, 33, 38, 41, 46-48). For example, in one study, patients who experienced subjective dysphoria in response to a test dose of antipsychotic medication were more likely to refuse medications in both the short and long term (49). Patients' subjective perception of medication effects seems to be more closely related to compliance than logical understanding or learning of medication effects (38). It is also interesting to note that compliant patients focus more on positive effects and indirect benefits from medications, such as being able to stay out of the hospital (2).

(5) Medication related factors

(5-1) Side Effects:

Neuroleptic side effects can range from sedation, sexual dysfunction, and anticholinergic effects to disabling extrapyramidal symptoms (EPS). These side effects have been shown to be a contributing factor in noncompliance in a number of studies (36, 48, 50). Common negative beliefs among patients regarding medications are largely related to side effects (51), and a significant number of patients discontinue and/or change the dose of medication due to side effects (34), particularly EPS (50). However, not all studies have found this to be the case. One study, for example, reported that the occurrence of akathisia, drowsiness, tremor and dystonia are not significantly associated with compliance (19), while several others have indicated that a self-reported history of side effects is not related to noncompliance or drug refusal among in-patients (32, 37).

(5-2) Other factors:

In reviewing other medication related factors such as number of medications taken, dosage, and complexity of regimen, it is noted that findings on this topic are equivocal (1). There are reports indicating association between complexity of regimen and compliance (52), while others reported no such associations (17), as well as no association between the number of medications taken and compliance (19). Interestingly, similar rates of noncompliance have been reported across a wide range of antipsychotic doses (1).

A potential and practical problem related to medication is the cost of medication, and it has been reported that financial burden is a primary reason for noncompliance (9). Other financially related factors, such as lack of transportation to obtain medication, have also been identified as practical barriers to compliance (9).

(6) Alcohol and Substance Abuse

Alcohol and other substance abuse represent a serious problem among patients with schizophrenia. Thirty to 50 percent of schizophrenic patients have been reported to suffer from some form of substance abuse problem (18, 37, 53). Alcohol and substance abuse are closely associated with noncompliance (7, 9, 18, 37, 53, 54). For example, one study reported that substance abusers are 12.8 times more likely to be noncompliant than non-abusers (54). In addition, alcohol abusers or substance abusers are hospitalized more often due to noncompliance (7, 9, 53, 54). It has been reported, for example, that alcohol abusers are at 3.33 times higher risk of rehospitalization compared to case control subjects (9). Overall, alcohol and

substance abuse increase the risk of noncompliance and tend to result in poor clinical outcomes and more severe symptoms (54).

(7) Social Support

Social support, such as family and friends, is associated with outpatient compliance. Studies indicate that patients living with relatives who can help with medication taking are more likely to be compliant than those who lack this type of support (19, 34). For instance, one study found that important key relatives of noncompliant patients are more often employed and absent compared to those of compliant patients (23). In addition, patients with more extensive social networks and better social functioning have more positive attitudes toward compliance (24). As well, compliant patients demonstrate a broader array of daily activities involving social interaction (24), while noncompliant patients have fewer such contacts as outpatients, and show greater symptom severity than their compliant counterparts (18).

(8) Alliance with treatment team

Not surprisingly, the relationship between patients and their caregivers influences compliance. Noncompliant patients have been identified as having less confidence and trust in hospital ward staff (32). In the psychotherapy setting, patients with schizophrenia who have a good alliance with their therapists are significantly more likely to remain in the therapy, be more compliant with medications, and achieve better outcomes at 2 years (55).

II. Applicable models of compliance

Over the years, social and behavioural scientists have developed a number of theories and models that may be applied in our efforts to better understand compliance. Unfortunately, many of these are mostly focused on non-schizophrenic populations with medical illnesses, and have as one of their aims the goal of explaining preventative health behaviour in healthy public. Nonetheless, these models are relevant to the study of behaviours related to maintaining one's health, and may offer some insight into the study of compliance.

(1) Health Belief Model (HBM) (56)

This model was originally developed to explain preventative health behaviour in the early 1950s. It has subsequently been expanded to apply to patients' response to symptoms and compliance with medication regimens (57). It posits that an individual will take preventative action if he perceives himself to be susceptible to the illness in question, and the consequences of contracting the illness to be severe. Intertwined with this basic premise is that the individual must perceive the treatment to be beneficial and effective, and the cost or barriers to the treatment not unreasonable in order for the behaviour to occur. In the case of preventative health behaviour, the model also includes the concept of "cues to action", which refers to triggering stimuli in the environment such as posters, public announcements and so on which engage the individual to engage in preventative behaviours.

(2) Theory of Reasoned Action (58)

The intention to perform a behaviour is explained by a combination of an individual's attitudes about the action and their perception of likely normative reactions to the action from significant others. Thus, this model incorporates the role of social influences on behaviour and assumes that a cost-benefit analysis will be made by an individual before an action is performed. Formation of intention to perform an action is therefore influenced by one's own attitudes towards the behaviour as well as societal norms. This model has been applied in smoking cessation (59), and family planning (60).

(3) Theory of planned behaviour (61)

This theory is an extension of the theory of reasoned action, where the performance of the behaviour is a function of the strength of a person's attempt to perform a behaviour and the degree of control the person has over that behaviour. In other words, this model includes the notion of perceived behavioural control and perceived barriers. Perceived behavioural control describes the extent to which a person feels that performing an action is within their control, and perceived barriers are the cost or obstacles to overcome in order to perform an action. This model has been tested and supported in studies of weight loss regimens (62).

(4) Health Decision Model (63)

This theory posits that a combination of a patient's general and specific health beliefs and preferences, modified by personal experiences, knowledge,

sociodemographic factors and social interactions will determine health decisions, health behaviour compliance and health outcomes.

(5) Self-Regulation Model (64)

In this theory, individuals go through the following stages: extracting information; examining the dangers of the particular illness; planning and acting on the treatment course; and, monitoring and appraising the action(s) carried out in order to deal with the illness. This model views the patient as an active problem solver, whose health-related behaviour is an attempt to close the perceived gap between current health status and a future goal state. The choice of a specific coping response is influenced by whether it makes sense in light of their ideas about the illness and personal experience of symptoms.

(6) Social Learning Theory (65)

Behaviour is a function of expectations about the outcomes directly resulting from the behaviour and expectations about one's ability to engage in the behaviour. Thus it is the belief in one's own capabilities that influences the behaviour. This concept of "efficacy expectations" has been tested in smoking cessation, weight control, contraception, alcohol abuse, and exercise (66).

III. Evaluation of various models of compliance

One of many limitations facing these models is that they fall short in explaining health-related behaviour which is apparently irrational, such as failing to

obtain annual check-ups or seek medical treatment when it is clearly needed. Many researchers have attempted to use regression analytic techniques to find out the determinants of compliance, but compliance continues to be something more complicated than what one or two models combined can explain. For example, incorporation of the Theory of Reasoned Action into The Health Belief Model (HBM) only accounted for 29% of variance in compliance seen in individual patients taking antibiotics for urinary tract infection (67). In the same study, the Health Belief Model alone only accounted for 10% of the variance. Other models incorporating perceived strengths of the Health Belief Model together with a spectrum of other approaches such as the Health Decision Model, Health Locus of Control models and Social Learning Theory have produced inconsistent results (68).

A few studies have addressed schizophrenia using the Health Belief Model as a base model; unfortunately, the results are equivocal. Budd et al. found perceived severity of and susceptibility to an illness, and perceived benefits from the treatment to be related to compliance; however barriers or costs of treatment did not affect compliance (45). Somewhat similar to this finding, in a group that included patients with affective disorder or schizophrenia, perceived severity of illness and perceived benefits of treatment explained 43% of the variance in compliance (69). However, Nageotte et al. found only perceived vulnerability correlated with compliance (70). Kelly et al. found susceptibility, barriers and cues to action to significantly affect compliance, but not perceived benefits or severity (36). In examining a depot medication group, Pan and Tantam found no difference in HBM dimensions between compliant and noncompliant groups (71).

In addition to somewhat contradictory findings, there have been no theoretical models that have been operationalized and utilized to evaluate compliance in schizophrenia. A number of issues could act as barriers to this development because of special considerations required for patients with schizophrenia, such as the possibility of symptoms disrupting illness perception and limiting cognitive capacity to assess resources and formulate and act on a plan. By better understanding the factors influencing compliance in this group, it may be possible to then formulate a more comprehensive and relevant theoretical model.

IV. Problems in the Study of Compliance

Over the years, numerous studies have been published on the topic of compliance. A literature search (MedLine) indicates that between 1993-1998 over four thousand journal articles in this area have been published. The term itself has been called into question based on the argument that it fails to recognize the therapeutic relationship as a partnership and holds negative connotations for those individuals who do not follow treatment recommendations (72). As a result, more neutral terms have been suggested, including 'adherence', 'observance', and 'concordance' (72). Similarly, research into the topic has been approached from different directions. While some consider the problem from a behavioural perspective, focusing on why patients do not do as health care professionals feel they should, others view it as a systems or outcome issue, focusing on the impact of noncompliance on treatment and pharmacoeconomic outcomes. The most striking feature in the literature on compliance, however, is the lack of a clear and consistent definition and the absence of reliable and valid measurement tools.

(1) Definition of compliance

The most commonly cited definition defines compliance as "the extent to which a person's behaviour, in terms of taking medications, following diets, or executing lifestyle changes, coincides with medical or health advice"(73). Even though this definition has been widely available, it has not translated easily into a widely accepted operational definition of compliance.

Failure to comply with medication taking may occur in different ways. Examples include: omission of doses, taking medication for the wrong reason, errors in dosage or timing of doses, and discontinuing therapy before the end of the recommended course. Others include attendance at follow-up appointments as well (74). Many studies do not report on what criteria are used to define compliance versus noncompliance, making comparison among studies difficult. Even in those that do, the definition varies widely. In addition, definitions of noncompliance are frequently qualitative-for instance, "missed [taking medications] several times to stopped altogether" (18), "highly significant stressor or problem" (53)-again making comparisons difficult. Some investigators choose to report actual compliance rates, or the number of treatment units taken divided by the number of units prescribed, whereas others report as their compliance rates the percentage of patients judged compliant according to some predetermined standard.

(2) Measurement of compliance

Another problem facing compliance research is the difficulty in actually measuring compliance. Methods of measurement are often indirect, such as patient self-report, physician rating, and pill count. In contrast, direct methods of measuring compliance include blood and urine assays, although these may be neither available nor practical.

Measurement is especially questionable if it involves self-report as patients may deny noncompliance or demonstrate poor recall (75). Many patients simply over-report self-administration of medications (74), and as a result a number of

studies have used multiple measurements to address the limitations associated with self-report.

One such additional measurement includes physician estimates of patient compliance; however, it has been shown that physicians tend to overestimate patient compliance (74). Pill counts are a potentially more accurate indirect assessment method, although this method assumes that a patient is taking medication correctly if the count is right. In addition, it may be subject to a 'white coat' effect, where patients modify their behaviour in response to being observed (76).

Blood and urine assays can be used to assess compliance but such procedures are not available for all drugs (26), and those that are available may be expensive and time consuming. In addition, they are viewed as intrusive by patients. Further, serum levels only provide approximation of recent medication taking and are mainly that is mostly determined by a drug's half-life and most recent dose.

Some have suggested biochemical detection methods to evaluate compliance. An example of such a method would be adding a tracer to the target medication and doing urine assays (77). This method is still expensive, though, and also subject to the 'white coat' effect given that the patient is now instructed to take the additional pill with regular medications. In addition, the tracer has to be proven safe for patients to take.

In summary, much of the extensive body of literature on compliance lacks a clear and consistent definition of compliance as well as reliable measurement tools to measure compliance. The result is difficulty comparing studies and obtaining an accurate picture of compliance. Thus the problems of unclear and inconsistent

definition and unreliable measurement tools are the most important issues that compliance research is facing and that need to be addressed in order to better understand the complex issue of compliance.

V. Aims of this study

This study has been designed with the goals of evaluating the noncompliance rate in patients with schizophrenia and clarifying the relationship between compliance and a number of possible contributory factors. In doing so, this study aims to test the predictive power of these different variables with respect to compliance. Further, different types of compliance measurements will be compared. This information might then be used to design interventions to enhance and optimize compliance.

(a) Objectives of study

(1) Establish the rate of noncompliance in patients with schizophrenia taking oral antipsychotics.

(2) Compare and correlate different types of compliance measurements.

(3) Investigate the characteristics that distinguish compliant patients from noncompliant patients.

(4) Evaluate the predictive power of a number of factors identified in the literature on compliance.

(b) Hypotheses of study

Based on existing literature, the following are hypothesized.

(1) Compliant patients will show higher level of insight.

(2) Noncompliant patients will show more severe symptoms.

(3) Alcohol and/or substance abuse will be more prevalent in the noncompliant patient group.

(4) Comparison of different measurements of compliance will indicate that pill count, physician's rating, and patient self-report do not correlate with objective measurement such as MEMS® rating.

VI. Methods

(1) Subjects:

We approached the psychiatrists in the Schizophrenia and Continuing Care Program at the Centre for Addiction and Mental Health, Clarke Division in Toronto, Ontario to refer their outpatients who may be eligible for this study. When patients were contacted, the project was explained to them, and voluntary consents were obtained. This project was also advertised by posting a poster, recruiting patients to call the principal investigator. The majority of patients, however, were referred by their psychiatrists.

To avoid a "white coat effect" (i.e. patient's compliance changing due to being in a compliance study), with the approval of the Ethics Committee, subjects were told that the objectives of this study were to survey their opinions regarding medications and to evaluate the effects of medications on memory. Subjects were recruited according to the following inclusion and exclusion criteria.

(1-1) Inclusion criteria:

-18 to 55 years of age

-DSM-IV and SCID diagnosis for schizophrenia or schizoaffective disorder

-Ability to understand and communicate in English

-Ability to give voluntary informed consent

-Taking oral antipsychotic medications

(1-2) Exclusion criteria:

-Previous medical diagnosis which may possibly affect the outcome of measures within this study e.g., mental retardation, ECT in last 6 months

-Patients on depot antipsychotic medications

-Patients on clozapine

(2) Measurements:

Table 1
Measurements used in the study

Dimensions	**Tests**
Diagnoses	DSM-IV. SCID
Demographic information	Patient Interview
Compliance with medication	Self-report. Physician rating, Pill count. MEMS®
Insight	Schedule for the Assessment of Insight (SAI)
Severity of illness	PANSS
Alcohol and substance abuse	DSM-IV criteria for alcohol and other substance abuse
Side effects	UKU. Simpson Angus. Barnes' Rating Scale for Drug-Induced Akathisia. AIMS
Subjective experience with antipsychotics	Drug Attitude Inventory (DAI)
Perceived level of family support	PSS-Fa
Alliance with treatment team	WAI
Medication related factors (cost. regimen. # of medications)	Patient interview
Cognitive functioning	Neuropsychological Battery

(2-1) Diagnostic:

DSM IV (78) and SCID (79)

DSM-IV defines the criteria to be met in order for the diagnosis to be made. SCID is a commonly used formalized structured interview designed to extract all information necessary for a number of diagnoses. We used these scales in this study to confirm the diagnoses of schizophrenia or schizoaffective disorder.

(2-2) Demographic variables:

Participants were interviewed regarding demographic information (e.g. age, gender, length of illness since the first onset of symptoms, and education)

(2-3) Compliance:

Four different measurements of compliance were used in this study. First, patients were asked to rate their own compliance on a scale of 0 to 100%. Their treating psychiatrists were also asked to provide a rating of compliance, in this case treating compliance as a dichotomous variable: taking medications on greater than or equal to 80% of time versus less than 80% of time. Physicians rated compliance dichotomously because physicians expressed difficulty with rating patients' compliance on a scale of 0 to 100%. Pill counts were performed by asking patients to bring their medications on the first interview and once again at the subsequent interview. The result of the pill count was converted to a scale of 0 to 100%. Lastly, MEMS® rating (Aprex Ltd.)-a special bottle cap that records the times during the day when the bottle is opened-was used during the study (80).

As discussed earlier, only a few studies have clearly indicated a definition of compliance used in their studies. After surveying the studies that have reported

numerical values (e.g. percentage) for the definition of compliance, we decided to use 80% as the cutoff mark for the compliance versus noncompliance in this study. For example, previously, Porter has defined a patient as compliant if at least 80% of his prescribed drug is consumed for general medical illness (81). Garavan et al. defined compliance as 76 to 100% consumption of prescribed doses in schizophrenia (47). Duncan and Rogers defined the compliant group to be patients who had taken their antipsychotic medication as prescribed more than 80% of the time in schizophrenia (82).

In addition, MEMS® rating is used as a gold standard of compliance in this study. Even though MEMS® rating is still an indirect method that cannot prove patient's ingestion of medications, it has been shown in other areas of medicine that self-reported compliance, physician rating, and pill count indicated significantly higher compliance than MEMS®. MEMS®, thus, may be providing more accurate picture for daily patterns of medication consumption (72, 83, 84).

(2-3-note) MEMS® TrackCap CR (Child Resistant):

The MEMS® is a medication bottle cap containing microelectronics that record each time the bottle is opened. Its electronic memory can also store information about the patient and drug. TheTrackCap CR meets child resistant standards and can be used when a child resistant closure is required. The MEMS® provides a means of measuring a patient's compliance to prescribed drug regimens. Once a patient returns the MEMS® cap, its data can be read off on the MEMS® communicator, which can be analyzed by the proprietary software. Data can be read as a calendar plot, which shows how many times a patient has taken a dose each day.

The program also gives a chart to show the time of the day patients took the doses. Additionally, uncovered hours, the percent of time within the analysis period that the medication was not therapeutically active, can be shown on a graph.

(2-4) Insight:

Schedule for the Assessment of Insight (SAI) (85)

This scale covers three overlapping dimensions: (a) awareness of illness; (b) the capacity to re-label psychotic experiences as abnormal; and (c) willingness to accept medication treatment. Each dimension has two or three questions scored from 0 (no insight) to 2 (good insight) with a maximum total score of 14. This scale has been developed specifically for the patients with schizophrenia. Its validity and reliability have been tested by correlation of this scale to other scales that measures insight in patients with schizophrenia (86). We chose this scale for our study, because it measures global, multidimensional aspects of insight in patients with schizophrenia with relative ease of administering the scale. To further validate the use of this scale in our study, we correlated the outcome of this scale to the outcome of the item G12 on the PANSS (Lack of judgment and insight).

(2-5) Severity of Illness:

PANSS (The Positive and Negative Syndrome Scale) (87)

The PANSS consist of 3 subscales: Positive, Negative and General Psychopathology. This scale has been developed for the patients with schizophrenia, and the study of 101 patients with schizophrenia found the scale to be normally distributed and supported its reliability and stability (87). It has been used frequently in recent years, reflecting a shift in emphasis from evaluating positive symptom alone

to recognizing the significance of other symptoms as well. We chose to use this scale because of its comprehensive approach in detecting positive, negative and total symptoms in patients with schizophrenia.

(2-6) Alcohol and substance abuse:

DSM-IV criteria for alcohol and other substance abuse (78).

DSM-IV defines the criteria to be met in order for the diagnosis to be made. We used these scales in this study to confirm the diagnoses of alcohol and/or substance abuse.

(2-7) Side effects:

Extrapyramidal Side effects (EPS): Simpson Angus (88).

This scale describes the methods and scoring in terms of assessing patients for acute EPS. It was developed for the patients with schizophrenia, and it has been used as gold standard measure for the acute EPS for many years. Validity and reliability of the scale were tested during a double-blind study involving two dose levels of haloperidol and a placebo, and reported to be high (89). We chose to use this scale because it is one of most frequently used scales to measure acute EPS.

Other Side effects: UKU (Udvalg of Kliniske Undersogelses) (90).

The UKU is a comprehensive scale measuring 4 distinct types of side effects: psychic, neurologic, autonomic, and other. It also provides for an item assessing the impact of these side effects on an individual's functioning. Face, content, concurrent, and construct validity of the scale have been reported to be sound, in addition to its acceptable reliability (90). This scale was developed specifically for the patients

using antipsychotic medications. We used this scale because it encompasses a broad range of side effects that may arise from using antipsychotic medications.

Akathisia Side effects: Barnes' Rating Scale for Drug-Induced Akathisia (91).

This scale incorporates diagnostic criteria for pseudoakathisia, and mild, moderate, and severe akathisia. It was developed for the patients with schizophrenia. Validity of the scale derives from its basis in signs and symptoms found to be characteristic of the condition of both acute and chronic schizophrenia. In addition, the inter-rater reliability has been reported to be high (91). We chose this scale because it is widely used to measure akathisia in patients with schizophrenia.

Tardive dyskinesia Side effects: AIMS (92).

Developed by the Psychopharmacology Research Branch (PRB) of the National Institute of Mental Health (NIMH), this scale incorporates the following aspects: (1) global severity of abnormal movements as seen by an observer; (2) global severity of the patient's reaction to movements; (3) incapacitation due to abnormal movement rating; and global dyskinesia ratings of the face, lips, jaw, tongue, arm, leg, and trunk. This scale has been specifically developed for the patients with schizophrenia and reported to have sound face validity (93). We chose to use this scale because it is widely used as a standard measuring tool in detecting tardive dyskinesia in schizophrenia.

(2-8) Subjective experience of antipsychotic effects:

The Drug Attitude Inventory (DAI-30) (48)

The DAI-30 is a 30 item self-report inventory that focuses on the subjective effects of antipsychotic medications in patients with schizophrenia. This inventory is

designed to measure patient's subjective experience with medications as well as values and attitudes toward illness and health. Good internal consistency has been demonstrated, and high test-retest reliability has also been demonstrated for this scale (17). We chose to use this scale because of it is one of the few scales directly measuring patients' subjective experience with medications as well as their attitudes towards taking medications.

(2-9) Social Support:

Perceived Social Support-Family Scale (PSS-Fa) (94):

This is a self-report scale and measures an individual's perception of one's fulfillment of needs for social support from family. Normative data for this scale were derived from a sample of 222 (mean age=19 years) undergraduate psychology students. The PSS-Fa has excellent internal consistency, with an alpha of 0.90. The test-retest coefficient of stability over a one-month period was 0.83 (94). It also has good concurrent validity reported by correlations to the California Personality Inventory and interpersonal dependency (94). Even though this scale was not designed for the patients with schizophrenia, we decided to use it in this study because of its good reliability and validity in addition to the lack of such scales in schizophrenia.

(2-10) Alliance with treatment team:

Working Alliance Inventory (WAI) (95):

This self-administered scale measures 3 aspects of alliance between a patient and a clinician: (1) tasks being relevant and efficacious, (2) mutually shared goals, (3) bonds, including trust, acceptance and confidence. Norms are not reported in the

primary references for this scale. It has good reliability in term of internal consistency with alphas of 0.87. In addition, its concurrent validity is supported by correlations between the three subscale scores and measures of perceived attractiveness, expertness, and trustworthiness that clients feel towards clinicians, and correlates with clinicians' empathy (95). Even though this scale was not designed for the patients with schizophrenia, we decided to use it in this study because of its good reliability and validity as well as lack of such scales in schizophrenia. In this study, patients were instructed to answer questions according to their relationship with treating psychiatrists only.

(2-11) Other medication related factors:

Complexity of regimen (how often taken and how many medications) and cost of medication (paying for medications or not paying, i.e. subsidized by drug plan, hospital, or family). These were asked during the patient interview.

(2-12) Cognitive functioning

A number of neuropsychological tests have been put together to test different dimensions of cognitive functioning and neuropsychological impairments. The tests used for each dimensions are the following as listed in Table 2:

Table 2

Neuropsychological Battery

Domain	Test(s)
Global cognitive functioning	Wechsler Adult Intelligence Test-R (Information Subtest, Block Design Subtest)
Attention	Woodcock-Johnson-Revised: Word span Stroop Color-Word Test
Executive functioning	Wisconsin Card Sorting Test
Memory	Wechsler Memory Scale-R (Logical memory I, II, Visual memory I, II) Hopkins Verbal Learning Test
Visuospatial functioning	Benton Judgement of Line Orientation Test

Global cognitive functioning: Wechsler Adult Intelligence Test-Revised (Information subtest & Block Design test) (96)

The information subtest tests general knowledge normally available to people growing up in the North America. The Block Design subtest is a construction test in which the subject is asked to construct an image using blocks. These two tests give a general indication of a person's level of global cognitive functioning.

Attention: Woodcock-Johnson-Revised Word Span (96)

This test asks the subject to recall number of words played by a tape recorder. The number of words to remember each time gets larger, making the task more difficult. This test is designed to test attention level.

Attention: Stroop Color-Word test (96)

This test asks the subject to read out loud the color of ink for each word, actually ignoring the word itself. It is a measure of concentration and attention.

Executive Functioning: Computerized WCST (The Wisconsin Card Sorting Test) (97):

This widely used test was devised to study abstract behavior and shift of set. The WCST is often used in schizophrenia, especially related to frontal function. This test is self-administered.

Memory: Wechsler Memory Scale-Revised (Logical Memory I & II, Visual Memory I & II) (96)

The Logical memory I tests for free recall after hearing a story, thus testing for immediate memory. Similarly, Visual Memory I tests for recall of image after being shown a picture. In the Logical and the Visual Memory II tests, subjects are asked to remember as much as possible of the story and the picture after 30 minutes, thus testing for delayed recall or memory.

Memory: Hopkins Verbal Learning Test (96)

In this test four words on each of six 12-word lists come from three semantic categories, which differ for each of the lists. Three learning trials are followed by a 24-word recognition list. This test is designed to test for memory.

Visuospatial functioning: Benton Judgment of Line Orientation test (96)

This test examines the ability to estimate angular relationships between line Segments by visually matching angled line pairs to 11 numbered radii forming a semicircle.

(3) Statistical analysis of data

First, the data were analyzed to check for normality. Any data found to be skewed were transformed through log transformation. For measurements of cognitive functioning, all sub scores from various neuropsychological tests, as specified, were

entered into a factor analysis using varimax rotation (SPSS statistical program). Factors were then selected to be entered into further statistical analyses.

To investigate the different characteristics between compliant and noncompliant patients. Hotelling's T^2 test was used for the continuous variables, while the chi-square test was used for the dichotomous variables.

To look for the predictive power of a number of variables that are indicated in the literature to be associated with compliance (total symptoms, alliance with treatment team, support from family, side effects, length of illness, insight), a multiple regression analysis model was employed.

The results of MEMS® readings were tested for correlations with other variables studied in this project using Pearson correlation coefficients tests. To find out the correlations between the different compliance measurements, the results were dichotomized using 80% as a cutoff mark for compliance versus noncompliance. These dichotomized variables were then evaluated using the Kendall's tau-b Test.

VII. Results

(1) Description

A total of 60 patients participated in this project, out of which 52 patients agreed to use MEMS® special medication containers. Out of eight patients who refused to use MEMS®, 3 patients were using blister packs, 4 patients were distrustful and suspicious of MEMS®, and 1 patient never returned the MEMS® container. There were 26 men and 26 women; 46 patients were single, while 6 were married. Seventeen patients had schizoaffective disorder, while 35 patients met diagnostic criteria for schizophrenia. As shown in table 3, the mean age was 35.96 years old, and illness duration 13.75 years. Six patients met DSM-IV criteria for concomitant alcohol or drug abuse. Thirty-six patients (69%) were taking novel antipsychotics (e.g. olanzapine, risperidone, and quetiapine), while 16 patients (31%) were taking conventional antipsychotics (e.g. loxapine, haloperidol, perphenazine, and so on).

Table 3
Description of Sample

	Minimum	Maximum	Mean	Std. Deviation
Age (years)	19.00	55.00	35.96	10.27
Education (years)	9.00	18.00	13.75	2.15
Length of illness (years)	.50	38.00	13.16	11.10
Number of hospitalizations	.00	40.00	5.23	6.98

In terms of symptom severity, the patient sample was relatively mild to moderately ill. Table 4 illustrates the positive, negative and total symptom scores on the PANSS.

Table 4
Severity of Symptoms

	Minimum	Maximum	Mean	Standard Deviation	Corresponding T score
Positive	14.00	29.00	18.12	3.99	47
Negative	14.00	27.00	18.60	3.50	44
Total	60.00	99.00	74.29	10.24	

For measuring side effects, the UKU has been modified to evaluate psychic, autonomic, and other side effects. For neurologic side effects; i.e., EPS, the Simpson Angus, Barnes, and AIMS have been used. With modification, the UKU allows for a maximum total score of maximum 111. The findings are summarized in the following table 5.

Table 5
Severity and Types of Side Effects Suffered

	Minimum	Maximum	Mean	Standard Deviation	Maximum Possible Score
UKU	0.00	29.00	8.40	6.80	111
Simpson Angus	0.00	8.00	1.15	2.09	40
Barnes	0.00	3.00	0.38	0.75	14
AIMS	0.00	1.00	8.750E-02	0.22	4

As shown, majority of the patients did not manifest clinically evident EPS. Other types of side effects were also minimal, as measured by the UKU. It is interesting to note that EPS measured by the Simpson Angus was significantly

correlated with the types of medications patients were on. Higher EPS score was significantly correlated with usage of the conventional antipsychotics rather than the novel antipsychotics (r=0.313, p=0.024).

Patients' insight into their illness, psychiatric symptoms, and need for treatments were assessed by the Schedule to Assess Insight. The scale allows for a maximum score of 14, higher scores indicating greater insight. It is felt that the insight level in this group was high: about 43% of patients scored 10-12 (71-86%) of 14 maximum on the insight scale as shown in table 6. Mean level of insight in this patient group was 8.13 (SD 4.13, range 0 to 14).

Table 6
Insight Score Distribution

Scores	Frequency	Percent	Cumulative Percent
.00	1	1.9	1.9
1.00	4	7.7	9.6
2.00	5	9.6	19.2
4.00	3	5.8	25.0
5.00	1	1.9	26.9
7.00	7	13.5	40.4
8.00	2	3.8	44.2
9.00	3	5.8	50.0
10.00	7	13.5	63.5
11.00	4	7.7	71.2
12.00	11	21.2	92.3
13.00	2	3.8	96.2
14.00	2	3.8	100.0

Subjective experience of antipsychotic effects was investigated using the Drug Attitude Inventory. This scale is comprised of 30 self-report questions regarding patients' own views on taking medications and experience of unpleasant side effects. This scale produces scores range from –30 to +30; negative scores are associated with

more negative perceptions and experiences. The mean score on this scale was +17.79 (SD 10.24, range −10.00 to +30.00). The following table of distribution indicates that the majority of patients had positive scores, with only 3 patients recording negative scores.

Table 7
Distribution of the Drug Attitude Inventory Scores

Scores	Frequency	Percent	Cumulative Percent
-10.00	1	1.9	1.9
-2.00	2	3.8	5.8
4.00	1	1.9	7.7
6.00	3	5.8	13.5
8.00	3	5.8	19.2
10.00	3	5.8	25.0
12.00	2	3.8	28.8
14.00	4	7.7	36.5
16.00	3	5.8	42.3
17.00	2	3.8	46.2
18.00	1	1.9	48.1
20.00	5	9.6	57.7
24.00	6	11.5	69.2
26.00	8	15.4	84.6
28.00	4	7.7	92.3
29.00	1	1.9	94.2
30.00	3	5.8	100.0

Rapport patients felt with their treating physicians were measured by using the Working Alliance Inventory (WAI-Short Form, the maximum score of 84). The mean score was 65.17 (SD 16.08, range 20 to 84). Considering the score of 84 as 100%, mean score would indicate that on average, patients felt 78% alliance with their treating physicians (population norm is not reported for this scale).

Table 8
Distribution of the WAIS Scores

Scores	Frequency	Percent	Cumulative Percent
20.00	1	1.9	1.9
30.00	2	3.8	5.8
33.00	1	1.9	7.7
42.00	1	1.9	9.6
45.00	1	1.9	11.5
48.00	1	1.9	13.5
50.00	3	5.8	19.2
51.00	2	3.8	23.1
54.00	2	3.8	26.9
56.00	1	1.9	28.8
60.00	3	5.8	34.6
63.00	1	1.9	36.5
66.00	7	13.5	50.0
68.00	2	3.8	53.8
69.00	2	3.8	57.7
72.00	3	5.8	63.5
75.00	3	5.8	69.2
78.00	5	9.6	78.8
81.00	3	5.8	84.6
84.00	8	15.4	100.0

The Perceived Social Support-Family Scale (PSS-Fa) was used to measure the degree of fulfillment each subject perceived on his or her needs for support from family. Population normative data have been derived for this scale (mean 13.40, SD 4.83) (94). In our patient group, the mean score was 10.65 (SD 6.35), indicating that this sample felt less support from their family than the normative population.

Table 9
Distribution of the PSS-Fa Scores

Scores	Frequency	Percent	Cumulative Percent
1.00	4	7.7	7.7
2.00	2	3.8	11.5
3.00	2	3.8	15.4
4.00	1	1.9	17.3
5.00	6	11.5	28.8
6.00	2	3.8	32.7
7.00	3	5.8	38.5
8.00	2	3.8	42.3
9.00	2	3.8	46.2
10.00	2	3.8	50.0
11.00	3	5.8	55.8
12.00	4	7.7	63.5
13.00	1	1.9	65.4
14.00	2	3.8	69.2
15.00	1	1.9	71.2
16.00	1	1.9	73.1
17.00	2	3.8	76.9
18.00	2	3.8	80.8
19.00	4	7.7	88.5
20.00	6	11.5	100.0

The level of cognitive functioning was tested by a number of neuropsychological tests previously outlined. As shown in table 10, the result of these tests showed that patients in this group have relatively normal cognitive functioning, without any sign of severe impairments.

Table 10
Neuropsychological Battery Results

	Minimum	Maximum	Mean	Standard Deviation
WCST Perseverative Errors Z score	-1.44	3.24	0.0040	1.15
Immediate Memory (Max. 200)	4	192	90.17	47.81
Delayed Memory (Max. 200)	3	182	75.06	44.43
Wechsler Intelligence Full Scale IQ	66	138	99.38	15.68
Hopkins Verbal Learning (Max. 36)	11.00	32.00	25.30	4.39
Hopkins Delayed Recall (Max. 12)	4.00	12.00	10.50	1.57
Stroop Interference T Score	38.00	63.00	50.15	6.11
Memory for Words W (375-598)	458.00	534.00	497.50	21.21
Judgement of Line Orientation (Max. 15)	2.00	15.00	13.12	2.20

The Wisconson Card Sorting Test was used to test for executive functioning, and its mean for perseverative errors Z score indicated that this group is close to the population norm (i.e. mean Z score is almost zero). Average patients in this group could recall about 45% of what they heard as a story immediately and about 38% of the original story on delayed recall. In remembering 12 words which were consecutively read out to them, patients could remember about 70% of the list on 3 trials in. In testing for memory, an average of 10.50 of 12 words were recalled. In testing for attention with the Stroop Interference Test the mean T score was 50.15, indicating average performance compared to the population norm. Another attention test, the Woodcock-Johnson-Revised: Word Span Memory For Words, once again indicated non-impaired performance on attention. Mean score was 497.50 out of 598

functioning, as indicated by the Judgement of Line Orientation Test (average 13.12 out of a maximum of 15 (87%)). Taken together, there was no indication of cognitive impairment in this group beyond a slight reduction in memory.

Dosage regimen in this population consisted of once, twice, and three times daily: (OD, BID, or TID). 75% of patients took their medications OD, while 23% took it as BID regimen. In one individual medication was administered TID.

Table 11
Dosing Regimen

Number of times to take Medications	Number of Patients	Percent	Cumulative Percent
Once a day	39	75.0	75.0
Twice a day	12	23.1	98.1
Three times a day	1	1.9	100.0

The average numbers of medications taken on a daily basis in this group was 2.69 (range 1 to11).

Table 12
Number of Medications to be taken

Number of medications	Frequency	Percent	Cumulative Percent
1	16	30.8	30.8
2	14	26.9	57.7
3	10	19.2	76.9
4	5	9.6	86.5
5	3	5.8	92.3
6	2	3.8	96.2
8	1	1.9	98.1
11	1	1.9	100.0

In this group, all the patients were receiving medications free of charge; therefore, the cost variable was not entered into analysis.

(2) Compliance Rates

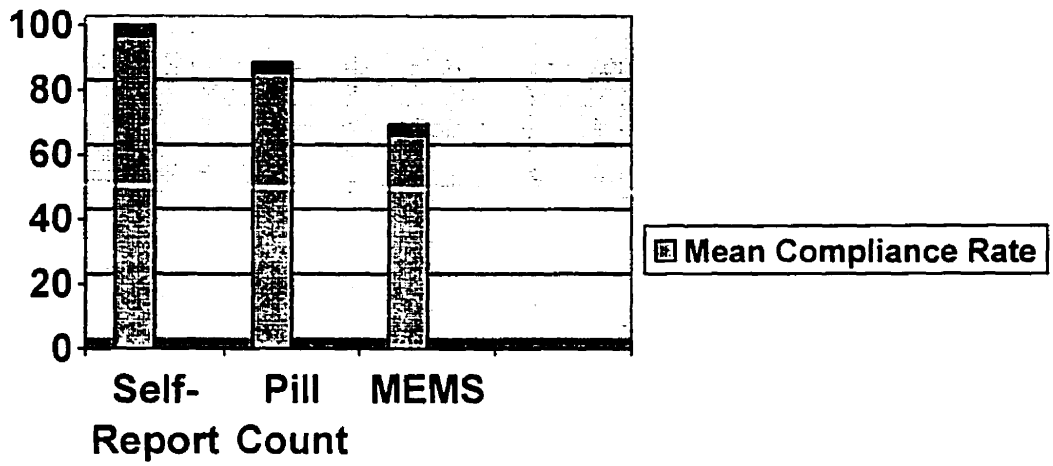
In this project, compliance has been measured in four ways: patient self-report, physician's rating, pill count and MEMS®. Patient self-report, pill count, and MEMS® were measured on a scale of 0 to 100 %, then dichotomized as compliant and noncompliant using 80% as the cutoff mark. Physicians rated their patients as either compliant or noncompliant based on this same 80% cutoff.

Mean rate of compliance was as follows: patient self-report 96.94%, pill count, 85.45%, and MEMS® rating 66.12%. The following table and figure compare the discrepancy reported by three different types of compliance measurements.

Table 13
Compliance Rates

	Mean	Standard Deviation	Range	Median
Self-Report	96.94%	6.53	75-100%	100%
Pill Count	85.45%	16.09	40-100%	90%
MEMS®	66.12%	31.00	0-100%	77%

Figure 1
Comparison of mean compliance rates by different measurements



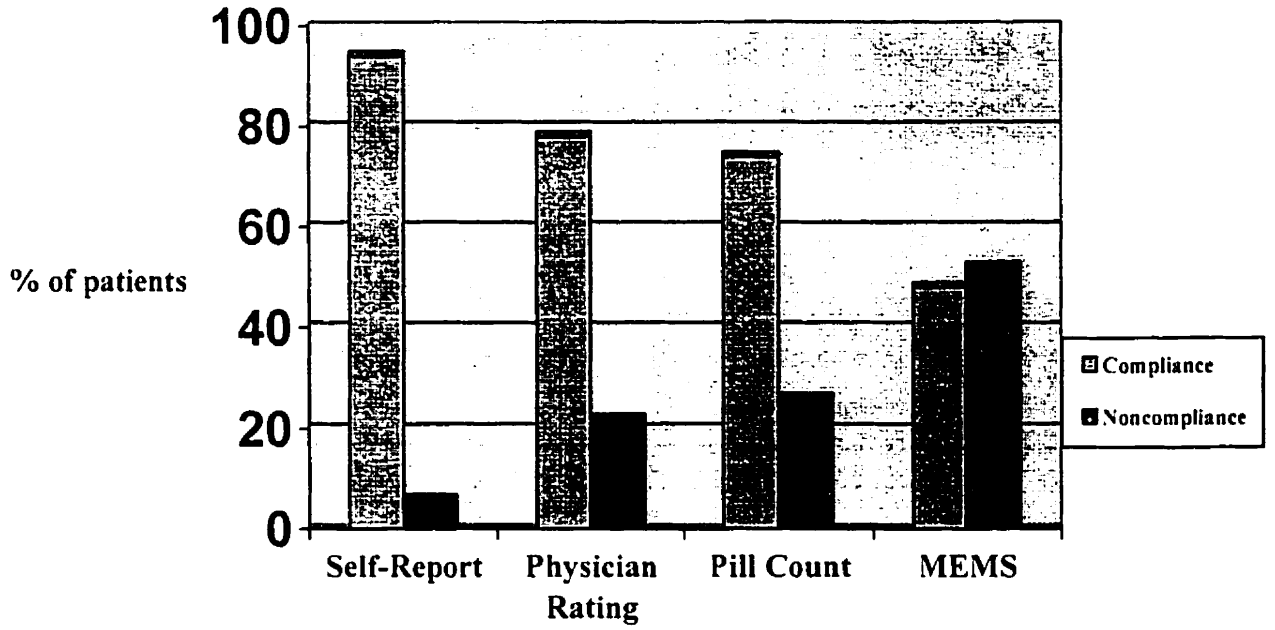
Of 52 patients who participated in using MEMS®, 40 patients had their compliance rated by their physicians. Thirty-one (77.5%) were rated as compliant by their physicians, and 9 patients (22.5%) were rated as noncompliant. In comparing this with the self-report estimates, 30 patients who reported compliance were judged compliant by their physician as well. However, the physicians rated 9 self-reported compliant patients as noncompliant, and 13 individuals rated compliant by their physician were actually noncompliant according to the MEMS® reading.

Similarly, when compared to pill count 10 self-reported compliant patients were rated as noncompliant. This contrast increased in magnitude when MEMS® reading was compared with self-report: 27 self-reported compliant patients were rated as noncompliant according to MEMS®.

There were 27 noncompliant patients (i.e. taking medications less than 80% of time) and 25 compliant patients according to MEMS® reading. Twelve patients

(23%) took medications < 55% of the time, while 15 (29%) took medications between 55 % and 79% of the time. Twenty-five patients (48.1%) took medications ≥80% of the time. These outcomes are depicted on the figure 2.

Figure 2
Comparison of compliance vs. noncompliance rates by different measurements



(3) Comparison between compliant and noncompliant patients

For dichotomous variables such as gender, marriage status, diagnosis, and alcohol/drug abuse, chi square tests were used. Results indicated that none of these variables were significantly different between compliant and noncompliant groups as shown in Table 14.

Table 14
Summary of Chi-Square Analysis

		MEMS® Reading		Chi-Square P Value
		Compliant	Noncompliant	
Sex	**Male**	11	15	0.405 (Non significant)
	Female	14	12	
Marriage Status	**Single**	23	23	0.442 (Non significant)
	Married	2	4	
Diagnoses	**Schizophrenia**	18	17	0.488 (Non significant)
	Schizoaffective Disorder	7	10	
Alcohol/Drug Abuse	**Positive**	1	5	0.102 (Non significant)
	Negative	24	22	

All other continuous variables were evaluated using Hotelling's T^2 test. Age, length of illness, positive symptoms, total symptoms, alliance with physician, family support, and dosage regimen were shown to be significantly different between the compliant and noncompliant groups (See Table 15).

Noncompliant patients were significantly older (39.44 vs 32.20, p=0.01), with longer duration of illness (17.70 vs 8.25, p=0.001). This group also scored significantly higher on the PANSS for positive (p=0.04) and total symptoms (p=0.004). Noncompliant patients were less likely to be taking their medications once daily; 37% of noncompliant patients were taking medications twice daily compared to 12% for the compliant group (p=0.03). In addition, compliant patients felt significantly stronger family support (p=0.01) and a significantly higher level of alliance with their psychiatrist (p=0.04) compared to noncompliant group.

Table 15
Group Statistics and Significant Differences

	MEMS® Rating	Mean	Standard Deviation	Hotelling's Trace P value
Age	**Compliant**	32.2000	10.8244	0.010
	Noncompliant	39.4444	8.5275	(Significant)
Length of Illness	**Compliant**	8.2480	9.6320	0.001
	Noncompliant	17.7037	10.5459	(Significant)
Positive Symptoms	**Compliant**	16.9600	3.3476	0.037
	Noncompliant	19.1852	4.2881	(Significant)
Negative Symptoms	**Compliant**	17.8400	2.9394	0.135
	Noncompliant	19.2963	3.8711	(Nonsignificant)
Total Symptoms	**Compliant**	70.1200	7.1258	0.004
	Noncompliant	78.1481	11.2445	(Significant)
Insight (SAI)	**Compliant**	8.4400	3.9484	0.612
	Noncompliant	7.8519	4.3386	(Nonsignificant)
Side effects (UKU)	**Compliant**	8.9600	7.2312	0.575
	Noncompliant	7.8889	6.4708	(Nonsignificant)
EPS SE (SA)	**Compliant**	.6800	1.6000	0.117
	Noncompliant	1.5926	2.4061	(Nonsignificant)
EPS SE (BARNES)	**Compliant**	.3600	.7000	0.821
	Noncompliant	.4074	.7971	(Nonsignificant)
EPS SE (AIM)	**Compliant**	5.640E-02	.1774	0.336
	Noncompliant	.1163	.2568	(Nonsignificant)
Subjective Response (DAI)	**Compliant**	18.0000	9.0323	0.878
	Noncompliant	17.5926	9.9856	(Nonsignificant)
Alliance with treatment team (WAIS)	**Compliant**	69.8800	12.2791	0.041
	Noncompliant	60.8148	18.0853	(Significant)
Family Support (PSSFA)	**Compliant**	12.9600	6.2549	0.010
	Noncompliant	8.5185	5.7470	(Significant)
Dosing Regimen	**Compliant**	1.1200	.3317	0.033
	Noncompliant	1.4074	.5724	(Significant)
# of medications	**Compliant**	2.7200	1.4866	0.923
	Noncompliant	2.6667	2.3534	(Nonsignificant)
Cognitive Functioning Factor	**Compliant**	.1971019	.9718600	0.300
	Noncompliant	-.1023510	1.0810669	(Nonsignificant)

(4) Correlation of MEMS® readings with other variables

In addition to using an 80% cutoff mark in evaluating the difference between compliant and noncompliant patients, MEMS® readings were further analyzed using the Pearson Correlation Coefficient test. Results indicated that more severe positive symptoms, and more severe total symptoms were significantly associated with lower MEMS® readings. Conversely, higher self-reported levels of alliance with treating psychiatrists were significantly associated with higher MEMS® readings.

The following table depicts the significant correlation to MEMS® readings.

Table 16
Significant correlation to MEMS® readings

	Correlation Coefficient	P value
Positive symptoms	-0.326	0.018
Total symptoms	-0.420	0.002
Alliance with treating MD	0.330	0.017

(5) Regression analysis of multiple factors for compliance

A number of variables that are often indicated in the literature as being important factors in determining compliance were identified and entered into a multiple regression analysis to evaluate their predictive power for compliance in this group. Variables included:

(1) Symptom severity (PANSS total symptom scores)

(2) Length of illness

(3) Insight (SAI score)

(4) Severity of side effects (UKU score)

(5) Alliance with treatment team (WAI score)

(6) Family support (PSS-Fa score)

This model was significant (p=0.024), and the combination of variables explained 27% of the total variance shown in compliance rating for this group (R square =0.267).

(6) Correlations among different measures of compliance

The 4 different types of compliance measurements (self-report, physician rating, pill count, MEMS®) used in this study were evaluated using Kendall's tau_b test to determine correlations. The only significant correlation found was between pill count and MEMS® (correlation coefficient 0.455, p=0.005). Interestingly, MEMS® and patient self-report were negatively correlated, although this was not significant (correlation coefficient –0.257, p =0.066).

VIII. Discussion

Patients in this project were mostly chronic schizophrenic adult patients. They showed slightly lower symptom severity compared to schizophrenia population norms. Alcohol and/or substance abuse was not a common problem in this group, and side effects were minimal. In addition, the majority reported positive perceptions and experiences with regards to antipsychotic medication effects, and a relatively high level of insight into illness. However, the group felt that their family was providing support at a level lower than the normal population norm. Level of alliance with treating psychiatrist was again relatively high, indicating long-standing relationships between these patients and their treating physicians. This group did not show any signs of cognitive impairments based on a number of neuropsychological tests.

It is true that this sample group does not represent a severely ill schizophrenic inpatient group or a group that doesn't have any contacts with healthcare system. However, this group represents a schizophrenia outpatient group, those who are followed regularly by a psychiatrist and a case manger. This is the group, to which the outcomes of this study can be applied.

According to MEMS® rating, patients on average took their medications 66% of time. Using an 80% cutoff mark as an a priori definition of compliance, 52 % (27 patients) of patients were noncompliant. This figure is in agreement with what have been reported previously in the literature. For example, a 1997 review of 15 studies evaluating compliance among outpatients with schizophrenia found a median noncompliance rate of 55 % (1).

It is noteworthy that compliance rates observed using other types of measurement were higher than rates seen with MEMS®. For example, in this study, compliance based on pill count was 85.5%, while MEMS® reading indicated average compliance rate of 66%. This trend has been shown in other studies as well. For instance, in diabetic patients, pill count and pharmacy refill data overestimated compliance compared to MEMS® (98). In patients with alcohol dependence, pill count also yielded a significantly higher estimate of compliance than MEMS®, and the compliance estimate obtained with MEMS® was more consistently correlated with treatment outcome (99). Similar results were reported for patients with hypercholesterolmia (100). In a study involving patients with tuberculosis, pill count and urine test for isoniazid overestimated compliance when compared to MEMS® (101).

Similarly, many studies have reported that patient self-report substantially overestimates compliance when compared to MEMS® (102-104). For example, in patients taking doxycyline for chlamydia, patient self-reported compliance rate was 90%, but MEMS® reading indicated only 16% (104). Similarly, the patient self-reported compliance rate in this study of schizophrenia was 96.94%, substantially higher than the 66% rate recorded with MEMS® .

Physician ratings of compliance-78% in this study-exceeded MEMS® ratings. Moreover, according to MEMS® reading, 42% of physician-rated compliant patients were actually noncompliant. This trend has also been noted elsewhere in the literature. In one study, for example, medical residents could not estimate levels of antacid compliance in their patients with accuracy any better than chance (105).

Only pill count was significantly correlated with MEMS® readings in this study. This finding has practical clinical implications, for the use of MEMS® is really confined to research protocols. However, these data would suggest that pill count represents a reliable and practical alternative for the evaluation of compliance.

Noncompliant patients in this report differed significantly on a number of dimensions compared to their compliant counterparts. Specifically, noncompliant patients were older, with a longer duration of illness. This finding is somewhat at odds with the literature. For instance, several studies have reported that younger patients are more noncompliant (22, 23, 82), while another report indicated more favorable attitudes towards taking medications among older patients (24). Other investigations found no age difference between compliant and noncompliant patients (19, 47, 106). There is, however, at least one report indicating that patients who refused antipsychotic treatment in an inpatient setting were significantly older (31).

Also at odds with existing literature was the finding of decreased compliance with longer duration of illness. Several reports have noted an association between shorter length of illness and noncompliance (23), while others reported no relationship between length of illness and compliance (19, 47). The fact that both age and duration of illness produced similar results here in terms of compliance is, perhaps, not so surprising given how interrelated they are.

A further analysis of these variables suggested that the present findings might have been influenced, at least in part, by the definition of compliance. Specifically, noncompliance was further subdivided into 2 ranges: 50-79% and <50%. Fifteen patients showing 50 to 79% compliance rates on MEMS® were significantly older

(mean 41.44 years old) and had longer duration of illness (18.8 years) than the 25 patients who showed ≥80% compliance on MEMS®. However, the 12 non-compliant patients who showed < 50% compliance were not significantly different in terms of age or length of illness from the compliant population. This finding reminds us that while for research purposes we may chose to define compliance as a categorical variable, degree of compliance is distinguishable and represents a continuum model.

Consistent with other reports, noncompliant patients in this project were suffering from more severe positive symptoms. Most studies in the literature have reported that positive symptoms are significantly related to noncompliance (24, 32, 35, 82). In addition, total symptom scores of noncompliant patients were significantly higher than those of compliant patients. What is not clear is whether these symptoms were the primary cause for the noncompliance, or whether noncompliance with medication resulted in heightened symptom severity.

Insight was not related to compliance. Compliant patients did have higher average insight scores but not significantly different from that of noncompliant patients. This finding is at odds with those studies in the literature, suggesting that insight is an important factor in compliance (13, 19, 23, 28, 32, 35, 40, 41, 107). However, it is in keeping with other studies where insight was not found to be significantly related to compliance (45, 47). It is worth pointing out that the majority of studies, which found a significant relationship between insight and compliance, used patient self-report as a primary means of measuring compliance. However, in a study that was able to precisely measure compliance rate through depot injection appointments, a significant relationship between insight and compliance was not

found (45). Interestingly, level of insight here was significantly negatively correlated with other variables linked to compliance, including both positive and total symptoms (correlations –0.484, -0.489, p=0.000).

Another point to be mentioned on the lack of significant relationship between insight and compliance in this project is that perhaps this finding indicates the complexity of insight. It is now generally accepted that insight should be thought of a continuum rather than all-or-none categorical concept (85). As well, many indicated that insight in schizophrenia is not stable as it changes over the course of illness (39). Given these, it is not difficult to see that measuring insight cross-sectionally to correlate to the behaviour over a period of time may be inadequate. More studies are needed to clarify this point.

There are different types of insight scales available for the use in patients with schizophrenia, and there has been debate over which one of them is more accurately reflective of insight in these patients (86). In this study, we used the David Schedule for the Assessment of Insight (85). The scores from this scale were correlated with the scores on the G12, Lack of judgment and insight item on the PANSS (87). The results indicated that these two scores are highly correlated (correlation coefficient – 0.817, higher scores on the G12 indicates lower level of insight; p=0.000). This high correlation supports the use of the David Schedule for the Assessment of Insight in this study.

Majority of the patients (69%) was taking novel antipsychotics and reported minimal side effects in this study. Interestingly, higher level of EPS reported on the Simpson Angus was significantly correlated with the conventional antipsychotic use. However, prominent EPS was rare in this study even with the correlation being

reported for the use of conventional anitpsychotics with this side effect. Thus side effects did not play a significant role in compliance in this study. The literature itself is contradictory regarding this point. While many studies have reported side effects to be an important determinant in compliance (17, 19, 36), others have not found this to be the case (32, 37). It is possible that had the intensity of side effects been greater in this population, a more significant role may have been established.

Data from the Drug Attitude Inventory (DAI), where patients' subjective views on taking medications and subjective experience of effectiveness and side effects are asked, provide indirect support for the low incidence of side effects in our sample. All but 3 patients scored positively on this scale, indicating that most individuals felt positively about their experience in taking medications for their illness. There was, in fact, a significant negative correlation between DAI score and UKU side effect score (correlation –0.398, p=0.003). However, DAI scores were not significantly different between compliant and noncompliant patients, despite evidence elsewhere indicating that this scale can be used to predict drug compliance, especially clinician global assessment of patient compliance (2, 17, 19, 23, 24, 32, 47, 49). Patient's subjective neuroleptic response did not play a role here possibly due to lower number of patients reporting negative outcomes and almost all patients reporting positive outcomes on this scale. Clinicians' ratings of compliance and DAI dichotomized scores i.e. positive vs. negative experience were correlated here but only approached significance (correlation 0.301 p=0.060).

In this study, patients were asked to evaluate their perceived level of alliance or rapport with treating physicians. Compliant patients felt significantly stronger rapport with their physicians, in keeping with the literature, indicating a positive

therapeutic alliance facilitates medication compliance (32, 55, 108). One study actually identified the perception of the physician's interest in him or her as the single best predictor of medication compliance among discharged schizophrenic patients (108). Many studies outside of schizophrenia have reported similar findings. Compliance improves when the doctor is perceived as emotionally supportive, and the affective quality of the doctor-patient relationship represents a key determinant in both patient satisfaction and compliance (109-112). Indeed, in one report, the association between therapeutic alliance and medication compliance was independent of the patient's severity of psychopathology, dosage regimen, or inpatient/outpatient status (55), emphasizing how important this dimension can be in compliance.

Along a similar vein is the relationship between patients' perceived level of family support and compliance. As a group, patients in this study felt that they were getting less than the general population average with respect to family support. However, compliant patients felt a level of family support in keeping with the population average, whereas the noncompliant group felt about 35% less support. This contrast was statistically significant, and in concordance with the numerous reports linking social support and the availability of family or friends to assist or supervise medications with improved compliance (19, 23, 24, 34, 108). In other areas of medicine, family involvement has also been shown to have a significant impact on a patient's adjustment to chronic illness and compliance with daily treatment regimens (113, 114). The benefit of family support with respect to compliance may be more than emotional as regular medication taking is a task that demands organization and structure on a daily basis. The support of family and/or

friends in this respect may be particularly useful in an illness like schizophrenia, with its features that include not only positive, but also negative and cognitive symptoms.

Further to this point, patients here had relatively normal cognitive functioning, with no significant differences between the compliant and noncompliant subgroups. A previous report noted that cognitive functioning showed no relationship to compliance when measured by 7 point observer-rated scale (25), although in another study neurocognitive impairment was associated with lower overall compliance to treatment as measured by collaterals reporting at baseline and 6-month follow-up (40). In terms of our findings, the degree of cognitive impairment, like side effects, may not have been severe enough to adversely influence compliance.

It has been demonstrated that complex dosing regimens can negatively influence compliance (1). While numbers of different medications taken were not significantly different between compliant and noncompliant patients in this study, significantly more compliant patients were taking medication once daily, whereas more non-compliant patients were taking medication twice daily.

Other factors, namely gender, marital status, and diagnosis, did not have any significant relationship with compliance here. Similarly, there was a no significant relationship between alcohol and/or substance abuse and compliance. However, the sample was small, with only 6 patients (12%) meeting DSM-IV criteria for alcohol and /or substance abuse. Of this group; however, 5 (83%) were noncompliant, although this did not reach statistical significance. Nonetheless, alcohol and substance abuse has been identified as one of the most important factors in determining compliance (54), and in this report a larger sample of such patients may have provided statistically meaningful differences.

Underscoring the complexity of compliance, a regression analysis to evaluate the contribution of 6 factors, identified as important in compliance in the literature (1), reached significance, but it was capable of explaining only 27% of the total variance. Had the severity of side effects and symptoms been higher in this group, this combination of factors might have explained the larger amount of the variance. In addition, other factors such as alcohol/substance abuse may play a substantial role that was not detected in this study.

Strengths of this study include the use of objective measure of compliance, MEMS® to report the compliance rate and to examine the relationships among different variables and compliance. Second strong point in this project is that we used the holistic approach in investigating compliance. We looked at most of the variables mentioned in the literature, while many of the studies so far only examined the relationship between compliance and one variables. Thirdly, sample in this group is representative of outpatients with schizophrenia, those who are being followed closely with the care of psychiatrists and case manager, and functioning relatively well. Those are the patients who usually get sent into the community to manage their own medications, and the relevance of compliance or medication management is an important issue in this group.

Limitations of this study include the inherent limitation of MEMS® system. Even though it records the opening of the bottle, it cannot guarantee the ingestion of medications occurred. Additionally, to accommodate the project within reasonable time period and to ensure patients come back for the second appointment, the project was limited to 4-week follow-up period. It is not hard to imagine that compliance may be different in longer follow-up period. Third limitation is the selective nature

of sample we had in the study. This group is not representative of whole patient population with schizophrenia, especially for the more severely ill groups, such as inpatient group. Thus the findings of this study cannot be generalized to the whole patient population with schizophrenia. In addition, a relatively small sample size limits our ability to explore a number of important issues in schizophrenia. For instance, only 6 patients were identified in this report as having alcohol/substance abuse. Had there been a larger sample, this number might have been larger, allowing us to fully examine the impact of this prevalent problem on compliance.

For future directions, it is important that compliance studies are done using objective measures of compliance rather than self-report or physician rating alone. As shown in this study, these methods tend to overestimate compliance, and this may result in an incorrect understanding of compliance. In addition, a larger sample that includes more diverse patient groups such as more severely ill patients with longer a follow-up period would be recommendable.

IX. Conclusion

In this study, 54% of patients were identified as noncompliant. These individuals were significantly older and had a longer duration of illness, significantly higher scores for positive symptoms, as well as total symptoms, and their medication regimen reflected more frequent dosing. In addition, they perceived themselves as having less family support, and they reported a lower therapeutic alliance with their psychiatrist. Consequently, interventions that may enhance compliance include the following: a supportive doctor-patient relationship, family involvement, simplification of dosing regimens, and optimal symptom control. Compliance is clearly a complex behavior, as evidenced by the fact that a select group of factors strongly associated with compliance in the literature could explain less than 1/3 of the variance.

Neither self-report nor physician rating correlated significantly with an objective measure of compliance (MEMS®), whereas pill count did. While the use of MEMS® may not be practical in routine clinical practice, evidence from this report suggests that pill count may prove useful in evaluating compliance in the everyday practice setting.

Given how prevalent noncompliance is as well as its profound impact on relapse rates and outcome, efforts must be made to better understand the mechanisms underlying noncompliance. It appears somewhat simplistic to believe that newer antipsychotics, regardless of whether they are more effective and/or tolerable, will eliminate noncompliance in the clinical setting.

References

1. Fenton WS, Blyler CR, Heinssen RK: Determinants of medication compliance in schizophrenia: empirical and clinical findings. Schizophr Bull 1997; 23(4):637-51

2. Adams SG, Jr., Howe JT: Predicting medication compliance in a psychotic population. J Nerv Ment Dis 1993; 181(9):558-60

3. Kane JM: Compliance issues in outpatient treatment. J Clin Psychopharmacol 1985; 5(3 Suppl):22S-27S

4. Blackwell B: Drug therapy: patient compliance. N Engl J Med 1973; 289(5):249-52

5. Cramer JA, Rosenheck R: Compliance with medication regimens for mental and physical disorders [see comments]. Psychiatr Serv 1998; 49(2):196-201

6. Wyatt RJ: Neuroleptics and the natural course of schizophrenia. Schizophr Bull 1991; 17(2):325-51

7. Haywood TW, Kravitz HM, Grossman LS, Cavanaugh JL, Jr., Davis JM, Lewis DA: Predicting the "revolving door" phenomenon among patients with schizophrenic, schizoaffective, and affective disorders [see comments]. Am J Psychiatry 1995; 152(6):856-61

8. Green JH: Frequent rehospitalization and noncompliance with treatment. Hosp Community Psychiatry 1988; 39(9):963-6

10. Rifkin A, Quitkin F, Rabiner CJ, Klein DF: Fluphenazine decanoate, fluphenazine hydrochloride given orally, and placebo in remitted schizophrenics. I. Relapse rates after one year. Arch Gen Psychiatry 1977; 34(1):43-7

11. Leff JP, Wing JK: Trial of maintenance therapy in schizophrenia. Br Med J 1971; 3(775):599-604

12. Hale T: Will the new antipsychotics improve the treatment of schizophrenia? [editorial]. Bmj 1993; 307(6907):749-50

13. McEvoy JP, Howe AC, Hogarty GE: Differences in the nature of relapse and subsequent inpatient course between medication-compliant and noncompliant schizophrenic patients. J Nerv Ment Dis 1984; 172(7):412-6

14. Wasylenki DA: The cost of schizophrenia. Can J Psychiatry 1994; 39(9 Suppl 2):S65-9

15. Weiden PJ, Olfson M: Cost of relapse in schizophrenia. Schizophr Bull 1995; 21(3):419-29

16. Kuiper L: Family burden in schizophrenia: implications for services. Social Psychiatry and Psychiatric Epidemiology 1993; 28:207-210

17. Hogan TP, Awad AG, Eastwood R: A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med 1983; 13(1):177-83

18. Owen RR, Fischer EP, Booth BM, Cuffel BJ: Medication noncompliance and substance abuse among patients with schizophrenia. Psychiatr Serv 1996; 47(8):853-8

19. Buchanan A: A two-year prospective study of treatment compliance in patients with schizophrenia. Psychol Med 1992; 22(3):787-97

20. Axelrod S, Wetzler S: Factors associated with better compliance with psychiatric aftercare. Hosp Community Psychiatry 1989; 40(4):397-401

21. Bebbington PE: The content and context of compliance. Int Clin Psychopharmacol 1995; 9 Suppl 5:41-50

22. Hoffmann H, Wyler A, Kupper Z: Age as a factor in identifying young adult chronic patients who are difficult to treat. Psychiatr Serv 1995; 46(4):404-6

23. Agarwal MR, Sharma VK, Kishore Kumar KV, Lowe D: Non-compliance with treatment in patients suffering from schizophrenia: a study to evaluate possible contributing factors. Int J Soc Psychiatry 1998; 44(2):92-106

24. Draine J, Solomon P: Explaining attitudes toward medication compliance among a seriously mentally ill population. J Nerv Ment Dis 1994; 182(1):50-4

25. Kemp R, David A: Psychological predictors of insight and compliance in psychotic patients. Br J Psychiatry 1996; 169(4):444-50

26. Marken PA, Stanislav, S.W.: Schizophrenia, in Applied Therapeutics: The clinical use of drugs. Edited by Young LY, Koda-Kimble, M.A. Vancouver, WA, Applied Therapeutics, Inc, 1995, pp 75-12-75-13

27. Salokangas RK, Stengard E: Gender and short-term outcome in schizophrenia. Schizophr Res 1990; 3(5-6):333-45

28. Smith TE, Hull JW, Anthony DT, Goodman M, Hedayat-Harris A, Felger T, Kentros MK, MacKain SJ, Romanelli S: Post-hospitalization

treatment adherence of schizophrenic patients: gender differences in skill acquisition. Psychiatry Res 1997; 69(2-3):123-9

29. Rosenberg CM, Davidson, G.E., Patch, V.D.: Patterns of drop-outs from a methadone program for narcotic addicts. The International Journal of the Addictions 1972; 7(3):415-425

30. Pisani VC, Motanky, G.U.: Predictors of premature termination of outpatient-followup group psychotherapy among male alcoholics. The International Journal of the Addictions 1970; 5(4):731-737

31. Hoge SK, Appelbaum PS, Lawlor T, Beck JC, Litman R, Greer A, Gutheil TG, Kaplan E: A prospective, multicenter study of patients' refusal of antipsychotic medication. Arch Gen Psychiatry 1990; 47(10):949-56

32. Marder SR, Mebane A, Chien CP, Winslade WJ, Swann E, Van Putten T: A comparison of patients who refuse and consent to neuroleptic treatment. Am J Psychiatry 1983; 140(4):470-2

33. Marder SR, Swann E, Winslade WJ, Van Putten T, Chien CP, Wilkins JN: A study of medication refusal by involuntary psychiatric patients. Hosp Community Psychiatry 1984; 35(7):724-6

34. Van Putten T, Crumpton E, Yale C: Drug refusal in schizophrenia and the wish to be crazy. Arch Gen Psychiatry 1976; 33(12):1443-6

35. Bartko G, Herczeg I, Zador G: Clinical symptomatology and drug compliance in schizophrenic patients. Acta Psychiatr Scand 1988; 77(1):74-6

36. Kelly GR, Mamon JA, Scott JE: Utility of the health belief model in examining medication compliance among psychiatric outpatients. Soc Sci Med 1987; 25(11):1205-11

37. Pristach CA, Smith CM: Medication compliance and substance abuse among schizophrenic patients. Hosp Community Psychiatry 1990; 41(12):1345-8

38. Soskis DA: Schizophrenic and medical inpatients as informed drug consumers. Arch Gen Psychiatry 1978; 35(5):645-7

39. Swanson CL, Jr., Freudenreich O, McEvoy JP, Nelson L, Kamaraju L, Wilson WH: Insight in schizophrenia and mania. J Nerv Ment Dis 1995; 183(12):752-5

40. Cuffel BJ, Alford J, Fischer EP, Owen RR: Awareness of illness in schizophrenia and outpatient treatment adherence. J Nerv Ment Dis 1996; 184(11):653-9

41. Lin IF, Spiga R, Fortsch W: Insight and adherence to medication in chronic schizophrenics. J Clin Psychiatry 1979; 40(10):430-2

42. McEvoy JP, Freter S, Everett G, Geller JL, Appelbaum P, Apperson LJ, Roth L: Insight and the clinical outcome of schizophrenic patients. J Nerv Ment Dis 1989; 177(1):48-51

43. Kent S, Yellowlees P: Psychiatric and social reasons for frequent rehospitalization. Hosp Community Psychiatry 1994; 45(4):347-50

44. Foulks EF, Persons JB, Merkel RL: The effect of patients' beliefs about their illnesses on compliance in psychotherapy. Am J Psychiatry 1986; 143(3):340-4

45. Budd RJ, Hughes IC, Smith JA: Health beliefs and compliance with antipsychotic medication. Br J Clin Psychol 1996; 35(Pt 3):393-7

46. Herz MI, Melville C: Relapse in schizophrenia. Am J Psychiatry 1980; 137(7):801-5

47. Garavan J, Browne S, Gervin M, Lane A, Larkin C, O'Callaghan E: Compliance with neuroleptic medication in outpatients with schizophrenia; relationship to subjective response to neuroleptics: attitudes to medication and insight. Compr Psychiatry 1998; 39(4):215-9

48. Awad AG: Subjective response to neuroleptics in schizophrenia. Schizophr Bull 1993; 19(3):609-18

49. Van Putten T, May PR, Marder SR, Wittmann LA: Subjective response to antipsychotic drugs. Arch Gen Psychiatry 1981; 38(2):187-90

50. Van Putten T: Why do schizophrenic patients refuse to take their drugs? Arch Gen Psychiatry 1974; 31(1):67-72

51. Davidhizar RE, Austin JK, McBride AB: Attitudes of patients with schizophrenia toward taking medication. Res Nurs Health 1986; 9(2):139-46

52. Razali MS, Yahya H: Compliance with treatment in schizophrenia: a drug intervention program in a developing country. Acta Psychiatr Scand 1995; 91(5):331-5

53. Drake RE, Osher FC, Wallach MA: Alcohol use and abuse in schizophrenia. A prospective community study. J Nerv Ment Dis 1989; 177(7):408-14

54. Kashner TM, Rader LE, Rodell DE, Beck CM, Rodell LR, Muller K: Family characteristics, substance abuse, and hospitalization patterns of patients with schizophrenia. Hosp Community Psychiatry 1991; 42(2):195-6

55. Frank AF, Gunderson JG: The role of the therapeutic alliance in the treatment of schizophrenia. Relationship to course and outcome. Arch Gen Psychiatry 1990; 47(3):228-36

56. Rosenstock IM: Historical origins of the health belief model. Health Education Monographs 1974; 2:328-335

57. Kirscht JP: The health belief model and illness behavior. Health Education Monographs 1974; 2:387-408

58. Ajzen I, Fishbein, M.: Understanding attitudes and predicting social behavior. Englewood Cliffs, New Jersey, Prentice-Hall, 1980

59. Jaccard J: A theoretical analysis of selected factors important to health education strategies. Health Education Monographs 1975; 3:152-167

60. Fishbein M, Jaccard, J.: Theoretical and methodological considerations in the prediction of family planning intentions and behavior. Representative Research in Social Psychology 1973; 4:37-51

61. Ajzen I: From intentions to actions: A theory of planned behavior. in Action control: From cognition to behavior. Edited by Kuhl J, Beckman, J. New York, Springer-Verlag, 1985, pp 11-39

62. Schifter DE, Ajzen I: Intention, perceived control, and weight loss: an application of the theory of planned behavior. J Pers Soc Psychol 1985; 49(3):843-51

63. Eraker SA, Kirscht JP, Becker MH: Understanding and improving patient compliance. Ann Intern Med 1984; 100(2):258-68

64. Leventhal H: Theories of compliance, and turning necessities into preferences: Application to adolescent health action, in Developmental

aspects of health compliance behavior. Edited by Krasnegor NA, Epstein, L.H, Bennett-Johnson, S., Yaffe, S.J. Hillsdale, NJ, Lawrence Erlbaum Associates, 1993

65. Bandura A: Social Learning Theory. Englewood Cliffs, NJ, Prentice-Hall, 1977

66. Strecher VJ, Champion, V.L., and Rosenstock, I.M.: The Health Belief Model and Health Behavior, in Handbook of Health Behavior Research I: Personal and Social Determinants. Edited by Gochman DS. New York, Plenum Press, 1997, pp 71-91

67. Ried LD, Christensen DB: A psychosocial perspective in the explanation of patients' drug-taking behavior. Soc Sci Med 1988; 27(3):277-85

68. Schlenk EA, Hart LK: Relationship between health locus of control, health value, and social support and compliance of persons with diabetes mellitus. Diabetes Care 1984; 7(6):566-74

69. Adams J, Scott J: Predicting medication adherence in severe mental disorders. Acta Psychiatr Scand 2000; 101(2):119-24

70. Nageotte C, Sullivan G, Duan N, Camp PL: Medication compliance among the seriously mentally ill in a public mental health system. Soc Psychiatry Psychiatr Epidemiol 1997; 32(2):49-56

71. Pan PC, Tantam D: Clinical characteristics, health beliefs and compliance with maintenance treatment: a comparison between regular and irregular attenders at a depot clinic. Acta Psychiatr Scand 1989; 79(6):564-70

72. Metry J-M: Measuring compliance in clinical trials and ambulatory care. in Drug Regimen Compliance: Issues in Clinical Trials and Patient Management. Edited by Metry J-M. and Meyeer. U.A. West Sussex. John wiley & Sons Ltd.. 1999. pp 1-21

73. Haynes RB: Introduction. in Compliance in health care. Edited by Haynes RB. Taylor. D.W.. Sackett. D.L. Baltimore. Johns Hopkins University Press. 1979

74. Epstein LH. Cluss PA: A behavioral medicine perspective on adherence to long-term medical regimens. J Consult Clin Psychol 1982; 50(6):950-71

75. Weiden P. Rapkin B. Mott T. Zygmunt A. Goldman D. Horvitz-Lennon M. Frances A: Rating of medication influences (ROMI) scale in schizophrenia. Schizophr Bull 1994; 20(2):297-310

76. Blackwell B: Compliance. Psychother Psychosom 1992; 58(3-4):161-9

77. Kapur S. Ganguli R. Ulrich R. Raghu U: Use of random-sequence riboflavin as a marker of medication compliance in chronic schizophrenics. Schizophr Res 1991; 6(1):49-53

78. APA: Diagnostic and Statistical Manual of Mental Disorders. Washington. DC. American Psychiatric Association. 1994

79. First MB. Spitzer. R.L. Gibbon. M.. Williams. J.B.W.: Structured Clinical Interview for DSM-IV Axis I Disorders: SCID Clinician Version. New York. Biometrics Research Department. Columbia University. 1995

80. Aprex: MEMS TrackCap CR. Menlo Park. CA. Apria HealthCare INC. 1994

81. Porter AM: Drug defaulting in a general practice. Br Med J 1969; 1(638):218-22

82. Duncan JC, Rogers R: Medication compliance in patients with chronic schizophrenia: implications for the community management of mentally disordered offenders. J Forensic Sci 1998; 43(6):1133-7

83. Matsui D, Hermann C, Klein J, Berkovitch M, Olivieri N, Koren G: Critical comparison of novel and existing methods of compliance assessment during a clinical trial of an oral iron chelator. J Clin Pharmacol 1994; 34(9):944-9

84. Waterhouse DM, Calzone KA, Mele C, Brenner DE: Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring [see comments]. J Clin Oncol 1993; 11(6):1189-97

85. David AS: Insight and psychosis [see comments]. Br J Psychiatry 1990; 156:798-808

86. Sanz M, Constable G, Lopez-Ibor I, Kemp R, David AS: A comparative study of insight scales and their relationship to psychopathological and clinical variables. Psychol Med 1998; 28(2):437-46

87. Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13(2):261-76

88. Simpson GM, Angus, J.W.S.: A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 1970; 45(212):11-19

89. Simpson GM. Angus JW. Edwards JG: A controlled study of haloperidol in chronic schizophrenia. Curr Ther Res Clin Exp 1967; 9(8):407-12

90. Lingjaerde O. Ahlfors. U.G.. Bech. P.. Dencker. S.J.. Elgen. K.: The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatrica Scandinavica 1987; 76(334):1-100

91. Barnes TRE: A Rating Scale for Drug-Induced Akathisia. British Journal of Psychiatry 1989: 154:672-676

92. Guy W: Assessment manual for psychopharmacology. Publication (ADH). Washington. DC. US Dept. of Health. Education. and Welfare. ECDEU. 1976

93. Gardos G. Cole JO. La Brie R: The assessment of tardive dyskinesia. Arch Gen Psychiatry 1977: 34(10):1206-12

94. Procidano ME. Heller. K.: Perceived social support-family scale (PSS-Fa). in Measures for clinical practice. A sourcebook. vol 2. Edited by Fischer J. Corcoran. K. New York. The Free Press. 1987. pp 421-425

95. Horvath AO: Working Alliance Inventory (WAI). in Measures for clinical practice. A sourcebook. vol 2. Edited by Fischer J. Corcoran. K. New York. The Free Press. 1987. pp 691-694

96. Lezak MD: Neuropsychological Assessment Third Edition. New York. Oxford University Press. 1995

97. Heaton RK. Harris. M.E.: Wisconsin Card Sorting Test: Computer Version. U.S.. Psychological Assessment Resources. INC.. 1990

98. Paes AH, Bakker A, Soe-Agnie CJ: Measurement of patient compliance. Pharm World Sci 1998; 20(2):73-7

99. Namkoong K, Farren CK, O'Connor PG, O'Malley SS: Measurement of compliance with naltrexone in the treatment of alcohol dependence: research and clinical implications. J Clin Psychiatry 1999; 60(7):449-53

100. Schwed A, Fallab CL, Burnier M, Waeber B, Kappenberger L, Burnand B, Darioli R: Electronic monitoring of compliance to lipid-lowering therapy in clinical practice. J Clin Pharmacol 1999; 39(4):402-9

101. Fallab-Stubi CL, Zellweger JP, Sauty A, Uldry C, Iorillo D, Burnier M: Electronic monitoring of adherence to treatment in the preventive chemotherapy of tuberculosis. Int J Tuberc Lung Dis 1998; 2(7):525-30

102. Straka RJ, Fish JT, Benson SR, Suh JT: Patient self-reporting of compliance does not correspond with electronic monitoring: an evaluation using isosorbide dinitrate as a model drug. Pharmacotherapy 1997; 17(1):126-32

103. Choo PW, Rand CS, Inui TS, Lee ML, Cain E, Cordeiro-Breault M, Canning C, Platt R: Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. Med Care 1999; 37(9):846-57

104. Bachmann LH, Stephens J, Richey CM, Hook EW, 3rd: Measured versus self-reported compliance with doxycycline therapy for chlamydia-associated syndromes: high therapeutic success rates despite poor compliance [see comments]. Sex Transm Dis 1999; 26(5):272-8

105. Caron HS, Roth HP: Objective assessment of cooperation with an ulcer diet: relation to antacid intake and to assigned physician. Am J Med Sci 1971; 261(2):61-6

106. Sellwood W, Tarrier N: Demographic factors associated with extreme non-compliance in schizophrenia. Soc Psychiatry Psychiatr Epidemiol 1994; 29(4):172-7

107. Smith TE, Hull JW, Goodman M, Hedayat-Harris A, Willson DF, Israel LM, Munich RL: The relative influences of symptoms, insight, and neurocognition on social adjustment in schizophrenia and schizoaffective disorder. J Nerv Ment Dis 1999; 187(2):102-8

108. Nelson AA, Jr., Gold BH, Hutchinson RA, Benezra E: Drug default among schizophrenic patients. Am J Hosp Pharm 1975; 32(12):1237-42

109. DiMatteo MR, Hays RD, Prince LM: Relationship of physicians' nonverbal communication skill to patient satisfaction, appointment noncompliance, and physician workload. Health Psychol 1986; 5(6):581-94

110. Hall JA, Roter DL, Katz NR: Meta-analysis of correlates of provider behavior in medical encounters. Med Care 1988; 26(7):657-75

111. Heszen-Klemens I, Lapinska E: Doctor-patient interaction, patients' health behavior and effects of treatment. Soc Sci Med 1984; 19(1):9-18

112. Squier RW: A model of empathic understanding and adherence to treatment regimens in practitioner-patient relationships. Soc Sci Med 1990; 30(3):325-39

113. Cromer BA, Tarnowski KJ: Noncompliance in adolescents: a review. J Dev Behav Pediatr 1989; 10(4):207-15

114. Friedman IM, Litt IF: Promoting adolescents' compliance with therapeutic regimens. Pediatr Clin North Am 1986; 33(4):955-73