Patient Preference and Adherence

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EXPERT OPINION

Self-Report for Measuring and Predicting Medication Adherence: Experts' Experience in Predicting Adherence in Stable Psychiatric Outpatients and in Pharmacokinetics

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Patient Preference and Adherence

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The Problem: Poor adherence to appropriately prescribed medication is a global challenge for psychiatrists.

Prior Studies: Measuring adherence is complicated. In our recent three-country naturalistic study including more than 1000 patients and their adherence to multiple medication prescriptions at the same time, patients' self-report of adherence to each specific drug was the only practical option for measuring adherence. Systematic literature reviews provide inconsistent results for sociodemographic, clinical and medication variables as predictors of adherence to psychiatric drugs. Our studies over the last 10 years in relatively stable psychiatric outpatients have shown that some self-reported health beliefs had consistent, strong effects and a better predictive role. Three dimensions of these health beliefs are characteristics of the individual: 1) attitudes toward psychiatric medication such as pharmacophobia (fear of taking drugs or medicines), 2) health locus of control (the belief patients have about who or what agent determines the state of their health), 3) psychological reactance (an emotional reaction in direct contradiction to rules or regulations that threaten or suppress certain freedoms in behavior). They can be measured by the Patient Health Beliefs Questionnaire on Psychiatric Treatment. The attitude toward each specific medication can be measured by the necessity-concern framework and summarized as the presence or absence of skepticism about that drug. After 25 years conducting pharmacokinetic studies in psychiatric drugs, particularly antipsychotics, we have limited understanding of how to use blood levels to predict the effects of non-adherence or to establish it.

Expert Opinion on Future Studies: Future studies to predict adherence should include the inpatient setting and explore insight. Studying the pharmacokinetics associated with non-adherence in each psychiatric drug is a major challenge. Medication adherence is a complex and dynamic process changing over time in the same patient. Personalizing adherence using psychological or pharmacological variables are in their initial stages.

Keywords: attitude to health, drug monitoring, health behavior, medication adherence, psychiatry, psychopharmacology

Plain Language Summary

Why was the review done? Self-report can be used to measure medication adherence. Self-report can also be used to study some psychological attitudes that may predict adherence to psychiatric medications. The literature on predictors of adherence in psychiatric drugs provides inconsistent results for sociodemographic, clinical and medication variables.

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What did the authors do? In their recent three-country naturalistic study including more than 1000 patients and their adherence to multiple medication prescriptions at the same time, the authors found that patients' self-report of adherence to each specific drug was the only practical option for measuring adherence. The authors reviewed the literature, including systematic reviews on how sociodemographic, clinical and medication characteristics are being associated with adherence to prescribed psychiatric medications. They also compared these sociodemographic, clinical and medication characteristics against the self-reported psychological measures included in their studies over the last 10 years in relatively stable psychiatric outpatients.

What do these results mean? To summarize the self-reported dimensions that may predict medication adherence, the authors developed a new questionnaire. Future studies need to explore insight (recognition that one has a psychiatric disorder and awareness that treatment could be helpful) and include the inpatient setting. Medication adherence is a complex and dynamic variable that changes over time even in the same patient.

Introduction to Medication Adherence in Psychiatry

This Expert Opinion article reviews the literature in 3 sections: introduction to medication adherence in psychiatry, methods for measuring adherence as applied to psychiatry, and predictors of adherence in psychiatric patients. Then, it describes our psychiatric studies on medication adherence in stable outpatients and on pharmacokinetics as it relates to adherence. Finally, we provide sections on future studies and an expert opinion on the complexity of studying medication adherence in psychiatry.

This introduction to adherence in psychiatry has 4 subsections: defining medication adherence, relevance of adherence to psychiatric medications, adherence in severe mental illness in general and adherence in specific severe mental illnesses.

Defining Medication Adherence

Medication-taking is a complex human health behavior discussed extensively in the literature amid notable controversy.[1] In the past, the literature used the term compliance, but lately, adherence has been used more often. Compliance, adherence and concordance are overlapping terms reflecting the complexity of medicine-taking behaviors.[2,3]

In 2003, the World Health Organization defined adherence as

> The extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.[4]

This wide definition extends adherence to successful self-management, since it emphasizes agreement and communication between the patient and the healthcare professional and includes more than strict compliance in taking prescribed medication. Treatment adherence can be considered in terms of points on a continuum ranging from treatment refusal to proper follow-up of prescriber instructions. It is essential to establish a sufficient level of treatment adherence to ensure effectiveness for each patient at each given moment.

Relevance of Adherence to Psychiatric Medications

Although the efficacy of psychiatric medications is frequently questioned,[5] taking psychiatric drugs at prescribed doses, at correct intervals, and for the period recommended is still essential for psychiatric patients to obtain the maximum possible benefits of these medications.[6] However, it is estimated that up to 45% of psychiatric medications are not taken as prescribed,[7] resulting in considerable cost for individual patients and healthcare systems.[4] At the patient level, inadequate adherence to prescribed psychiatric medications has been found to be associated with poorer outcomes for patients, including the early return of symptoms within the expected duration of a current episode (relapse) or new episodes (recurrence) following initial short-term improvement or remission, as well as hospital admissions.[8,9] Furthermore, inadequate adherence can be a risk factor for violence in psychotic disorders,[10] for suicide in major depressive disorders,[11,12] and for premature mortality in schizophrenia.[13] Finally, at the healthcare system level, psychiatric medication non-adherence represents a significant cost burden although related research is limited and of varying quality.[14,15]

Adherence in Severe Mental Illnesses in General

In principle, every psychiatric patient has the right to be treated and the right to refuse treatment, exceptions being emergency situations in which there is an imminent danger to self or others. Unfortunately, it is common that those patients with greater need of treatment (those with severe mental illnesses) are the more inclined to refuse it and this fact is posed in direct contradiction to the ethical principles of beneficence and respect for patient autonomy.[16]

It is assumed that psychiatric patients are able to choose; act rationally, intentionally, and responsibly; and make decisions in terms of costs and benefits.[17] However, patients with severe mental illnesses such as schizophrenia, bipolar disorder, and major depression can go through phases in which their awareness of illness is impaired; this lack of insight, or anosognosia, represents the most significant reason for treatment refusal when they are acutely ill.[18] Therefore, adherence is a process that requires time for its proper development, where people suffering a psychiatric disorder need to identify as patients, develop awareness of their mental illness, participate in their mental health care, and establish a relationship of trust and collaboration with mental health professionals. Adherence to prescribed psychiatric medication in severe mental illness is a dynamic variable and there are major differences between in- and outpatient treatments.

In acute inpatient treatment, clinicians hope that after refusal of essential medication, the patient will move to reacceptance of, and long-term compliance with, medication. The pathway to reacceptance of essential medication by patients who have refused medication can take various forms. Sometimes psychiatrists have no choice but to turn to involuntary medication. Patients may then voluntarily accept medication or it may be necessary to get a court order.[19] Although there are no systematic studies, during psychiatric hospitalization most, if not all, patients become adherent as a consequence of the close supervision of medicine-taking behaviors. Adherence is usually good after the initial hospital discharge but decreases substantially over time.[20]

Adherence in Specific Severe Mental Illnesses

There are controversies in the psychiatric literature about the benefits of psychiatric medications during acute exacerbations and maintenance in the three major severe mental illnesses. However, most expert reviews in schizophrenia,[21,22] bipolar disorder,[23,24] or major depression[25,26] agree on the need for medication in acute severe cases and for avoiding relapses.

Unfortunately, the literature on adherence for these three severe mental illnesses does not appear to be very helpful in providing specific recommendations to clinicians regarding predicting adherence in individual patients, although experts agree on the importance of medication adherence.[27]

Recent expert reviews on adherence in schizophrenia tend to describe general aspects and rarely provide specific recommendations which can be used by practicing clinicians. Tham et al[28] state that greater insight and less severe psychotic symptoms are associated with increased adherence in general but they do not integrate their review in the context of the phases of the illness and the differences between in- and outpatients. Kikkert and Dekker[29] say that, although it is an intensively studied phenomenon, we have little understanding of underlying mechanisms leading to nonadherence. Kane and Correll[30] emphasized the role of long-acting injection (LAI) antipsychotics in increasing adherence during maintenance treatment in outpatients. Bright[31] focused on difficulties in measuring adherence but in our experience with stable outpatients this problem is common to all patients with severe mental illnesses. Weiden[32] stresses that patients with schizophrenia frequently do not disclose to their treating physicians that they are not adherent. This explains why, in a relatively small study using blood levels to identify schizophrenia patients considered by their psychiatrists to be treatment-resistant, one-third of them had subtherapeutic serum concentrations which in many cases may be associated with lack of consistent adherence.[33]

Recent reviews focused on adherence during maintenance treatment of bipolar disorder also tend to provide limited specific information for orienting practicing clinicians. Levin et al[34] provided a narrative review with no specific data on the significance of the variables in the various studies concerning what they call barriers to adherence, including those related to 1) bipolar pathology, 2) an individual's circumstances and 3) external factors such as treatment setting or healthcare system. Systematic reviews of interventions for improving adherence stressed the limitations of methodology for establishing long-term adherence in patients with bipolar disorder.[35,36] In the last five years, as new formulations of second-generation LAIs are being developed by pharmaceutical companies, the companies have realized that the LAI market may not only include patients with chronic schizophrenia but also patients needing maintenance in bipolar disorder.[37] Therefore, some recent reviews focus on the potential role of LAI antipsychotics[38] but there are no long-term studies with these compounds in bipolar disorder. After a systematic review of drug discontinuation in both schizophrenia and bipolar disorder, Gentile[39] had the opinion that new second-generation LAIs may not be any better

than the less expensive compounds (oral or first-generation LAIs) for individualizing treatment.

There are fewer expert reviews of adherence in major depression than in schizophrenia and bipolar disorder. In a narrative review of adherence to antidepressants in general, Hung[40] stressed the multiple factors that may contribute to non-adherence. The most significant contributors to poor adherence that they list include minority status, immigrant status, low income, lack of health insurance, adverse effects, pregnancy, dissatisfaction with treatment, poor relationship of patients with healthcare professionals and lack of information. The factors they listed as contributing to better adherence were old age, positive attitudes to depression and antidepressants, previous experiences and vicarious experiences of depression and antidepressant treatment. Rush and Thase[41] maintain that, for improving adherence in major depression, clinicians need to practice patient-centered medical management.

Measuring Medication Adherence in Psychiatry

A prior Expert Opinion article in this journal was completely dedicated to medication adherence. In that article, Whalley Buono et al[42] stressed three important facts: 1) the most robust medication adherence measures are often ill-suited for large-scale use, 2) less robust measures including self-report are commonly misinterpreted in population-level analyses, and 3) in the absence of a gold standard, the choice of the method for measuring adherence must consider the purposes of the study.

We completely agree with these 3 facts, which have become obvious as we have moved toward greater complexity in our medication adherence studies in relatively stable outpatients. In 2013, the first author[43] recruited only at one site and only patients with one diagnosis in a cross-sectional sample. Moreover, he assumed that a global measure of self-reported adherence was a good reflection of adherence, ignoring the fact that most psychiatric patients take several medications and thus may have differing levels of adherence for these different medications. Our most recent study[44,45] with a similar cross-sectional design included 1372 patients from 3 recruitment sites in 3 different countries (Argentina, Spain and Venezuela), having different levels of access to health care. After consecutive recruitment of patients willing to sign a consent form at each site, we were able to collect adherence levels for 2454 oral psychiatric medications which reflected 80 different pharmacological compounds.

After almost 10 years of research, we have a very practical approach to the issue of measuring medication adherence in psychiatric patients. We propose to review the subject in 4 subsections: measuring adherence to a single oral medication, measuring adherence to multiple oral psychiatric medications in large samples, adherence to LAI psychiatric medications and the limitation of clinical samples.

Adherence to a Single Oral Medication

Based on our experience and, more importantly, on recent review articles,[42,46,47] Table 1 provides a brief summary of the direct and indirect methods which can be used to study medication adherence to a single psychiatric drug, along with their strengths and weaknesses.

Adherence to Multiple Oral Psychiatric Medications in Large Samples

Objective methods such as blood levels or pill counts are not possible in countries with limited resources and are not practical when dealing with patients who may be taking as many as 6 psychiatric medications at the same time; each patient could adhere differently to the various medications prescribed. This type of study was not possible until the introduction of the Sidorkiewicz adherence tool, which uses self-report of adherence to each medication.[48] This tool has five questions and each question has two or three possible answers. The tool uses non-threatening language to reduce social desirability bias and features practical examples and pictographs to help patients recognize their medicine-taking behaviors. The instrument defines six medication adherence levels for a given medication which are dichotomously classified as adherence (levels 1–3) or non-adherence (levels 4–6, ranging from poor medication adherence to discontinuation).[48]

On 09/10/20 a PubMed search using "Sidorkiewicz adherence" provided 8 articles, of which 4 were on psychiatry.[44,49–51] All of them were from our group, so no other psychiatric researcher has yet published results using this adherence tool.

Adherence to LAI Antipsychotic Medications

As indicated in the introduction: 1) schizophrenia experts recommend using LAI antipsychotics to

Table 1 Methods to Assess Adherence to Oral Medications

Test	Advantages	Disadvantages
Direct Methods		
Medication consumed under direct observation	Most accurate	Impractical for routine use. Patients can hide pills in the mouth and discard them.
Measurement of the level of medicine or metabolite in blood	Objective	Lower metabolism and "white coat" adherence can give a false impression of adherence; expensive; invasive; requires laboratory; need multiple levels to calculate individual variability; validity of therapeutic ranges varies; each drug has its pharmacokinetic profile, which is poorly investigated; can over- or underestimate depending on behavior immediately prior to test; metabolism is influence by genetic, environmental and personal variables
Measurement of a biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids; impractical
Indirect Methods		
Self-reporting by the patient (interview, diary, questionnaire)	Subjective; simple and easy to use; noninvasive; readily available; inexpensive; sensitive for non-adherence; the most useful in a clinical setting for large studies	No evidence that the drug is actually ingested; not accurate, results are easily distorted by the patient; patient is aware of the measurement
Physician perception	Subjective; simple; non-invasive	Validity is extremely poor; physicians overestimate adherence
Pill counts	Objective, quantifiable and easy to perform	Time consuming; data easily altered by the patient (eg, pill dumping); provides no information about timing of missed doses or about times of day that medications are taken; requires patients bring pills for counting
Rates of prescription refills	Objective: easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; poorly integrates with the elderly; assumes medication is consumed when bottle/compartment is opened; requires return visits and downloading data from medication vials and expertise in interpreting data
Measurement of physiologic markers (eg, heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for another reason

decrease the risk of non-adherence and 2) some experts are also promoting the use of LAI antipsychotics for the maintenance of bipolar disorder, although the benefits are less well established.

Measuring LAI adherence is conceptually different that measuring adherence to oral medications since the only issue is whether or not the patient comes to receive the injection. Thus, patients on LAI may need to be considered separately when considering representativeness in schizophrenia samples. On the other hand, the use of LAI antipsychotics across different countries is extremely variable[52,53] and is probably influenced by medical, pharmaceutical and legal issues. Clinical experience and training on the use of LAI appears to be quite variable among psychiatrists across different countries. Moreover, different countries have different levels of access to different LAI compounds. First-generation compounds tend to be cheap while second-generation compounds tend to be

expensive. Many states in the USA and some other countries[54] offer involuntary outpatient or community treatment laws that may facilitate the use of LAIs, but these forced outpatient treatment orders are not present in many European countries which, on the other hand, offer easy access to free psychiatric treatment including free medications.

Limitations When Using Clinical Sampling

Our three-country study has opened our eyes to the limitations when clinical sampling is used for the study of adherence. Any study using self-report of adherence in clinical samples is "doomed" from the start since patients who not sign the consent form will not be included. Although in our studies, the research staff who helped patients access our study are not directly involved in patient care, it cannot be ruled out that patients who are less adherent may be less cooperative in signing a consent form for a medication adherence study.

Argentina and Venezuela have very fragmented health systems with limited access for those individuals with limited resources. In Spain we have focused on a catchment area within the national health system, which offers free universal treatment, such that any individual who wants to receive voluntary treatment with psychiatric medications has access to it; there are no community outpatient laws and very limited LAI use since patients prefer oral medications. The most non-adherent patients from this catchment area probably are the ones who have not come for treatment for years. No data exists in our Spanish catchment area concerning how many schizophrenia patients do not come for treatment. Finland has a free universal health system similar to that of Spain and has a national database. A national cohort in Finland indicated that, on average, up to 30% of schizophrenia treatment years may not include antipsychotic treatment.[55] We are not aware of similar estimations in European countries for bipolar disorder or major depression.

Predicting Adherence: Variables Possibly Associated with Adherence

There is general agreement that adherence to psychiatric treatments is a really complex multidimensional phenomenon influenced by various factors that interact and lead to individual health behaviors.[56] In high-quality healthcare systems that guarantee universal full coverage for all citizens, treatment adherence is determined by the interplay of patient-related, disorder-related, and medication-related factors. Although research on treatment adherence is inherently biased due to numerous methodological limitations, significant findings that are consistently identified across studies likely reflect valid associations with relevant clinical implications.[57] Moreover, tolerability and efficacy of psychiatric drugs and, therefore, outcomes of mental disorders are not only determined by the medication's pharmacological profile but also through the interaction of additional factors, including the doctor–patient relationship and the patients' attitudes toward their illnesses and toward their prescribed medications.[58]

Although the literature does not provide consistent findings of which variables may predict adherence in psychiatric patients,[59] we have tried to summarize the findings in Table 2,[60–64] by including 5 systematic reviews and/or meta-analyses that have attempted to identify predictors of treatment adherence in psychiatric disorders. In order to review these predicting variables, we have classified them into four subsections: sociodemographic variables, clinical variables in mental disorders, medication variables, and self-reported health beliefs.

Sociodemographic Variables as Predictors of Adherence

The idea that sociodemographic variables are the sole determinants of adherence is discredited by evidence that a patient's level of adherence may vary widely over time but most sociodemographic variables are relatively stable.[65] Not surprisingly, Table 2 shows no consistent effects of sociodemographic variables on adherence. The only variable that changes remarkably over time is age, although one systematic review of adherence to antidepressants associated increased age with increased adherence, while another in schizophrenia and bipolar disorder reports the opposite.

Clinical Variables in Mental Disorders as Predictors of Adherence

Table 2 indicates that clinical variables produced conflicting and inconsistent findings with relatively weak associations. The most consistent findings are that 3/5 of the reviews indicate that substance use disorders and poor insight are associated with poor adherence. The problem with using substance use disorders as a predictor is that

Table 2 Systematic Reviews of Sociodemographic and Clinical Predictors of Adherence with Prescribed Psychiatric Treatment

Author	Samples and Methodology	Results (Only Significant Results are Described)
Rivero-Santana et al[60]	Systematic review of 32 observational studies of patients with depressive disorders using antidepressants. A quantitative synthesis was not performed because of the heterogeneity and lack of availability of the data reported.	↑ Adherence with: ↑ age, and White race ↓ Adherence with: medical comorbidities, substance abuse, and race (Hispanic patients or minority groups)
Sendt et al[61]	Systematic review of 13 observational studies of patients with schizophrenia using antipsychotics.	↑ Adherence with: ↑ positive attitude to medication, and ↑ insight into illness
Edgcomb and Zima[62]	Systematic review and meta-analysis of 28 studies of predictors of adherence to psychopharmacological treatment among children (<19 years old) with a primary psychotic disorder, bipolar disorder, depression, recent suicide attempt, or psychiatric hospitalization. Strength of association was measured by adjusted OR (CI).	↓ Adherence with: ↑ illness severity OR=0.44 (CI.32–0.62); p< 0.001 substance use OR=0.66 (CI 0.45–0.98); p=0.02 comorbid ADHD OR=0.61 (CI 0.41–0.91); p=0.008
Garcia et al[63]	Systematic review of 38 studies including patients with schizophrenia spectrum disorders and bipolar disorder.	↓ Adherence with: ↓ age ↓ level of education ↓ socioeconomic status ↓ insight ↑ cognitive impairment ↑ intensity of delusional symptoms ↑ suspiciousness ↓ therapeutic alliance ↑ barriers to care being a minority ethnicity having a substance abuse disorder
Czobor et al[64]	A patient-level meta-analysis of combined CATIE and EUFEST studies on schizophrenic patients. Strength of association was measured by adjusted OR (CI).	↓ Adherence with: substance use OR=2.01(CI 1.38–2.95); p=0.0003 insight OR=1.42 (CI 1.26–1.60); p=0.0001 hostility OR=1 0.37 (CI 1.16–1.62); p=0.0002

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CATIE, The Clinical Antipsychotic Trials of Intervention Effectiveness Study; CI, 95% confidence interval; EUFEST, The European First Episode Schizophrenia Study Trial; OR, odds ratio.

they vary enormously from country to country and from culture to culture but it appears reasonable that in those countries with substantial prevalence, active substance abuse is an important factor independent of lack of adherence in psychiatric patients. Once substance abuse has ceased, the treatment of the severe mental illness and medication adherence can become the focus.

The third more consistent clinical variable is that measures of increased severity within a disorder may decrease adherence; this appears to happen in patients with depression,[60] children[62] and patients with schizophrenia and bipolar disorder.[63] Interestingly, we could not find any systematic review that compared adherence across the three severe mental illnesses: schizophrenia, bipolar disorder and depression. The expert review in schizophrenia with a heavy emphasis on LAI antipsychotics to avoid non-adherence appears to imply that non-adherence may be a greater problem in schizophrenia, but we cannot find any study supporting this widely held belief. As indicated, the problem is that it is not easy to study adherence from a public health point of view unless one has access to a comprehensive national registry.

Medication Variables as Predictors of Adherence

The studies focused on a class of medication are contaminated by diagnoses, meaning that adherence to antidepressants tend to be studied in patients with depression while adherence to antipsychotics tend to be studied in patients with schizophrenia. As psychiatric patients tend

to have comorbidities and are prescribed many psychiatric medications beyond the specific medication for that diagnosis, it would be interesting to know whether patients with a main diagnosis tend to have varying adherence levels across medication classes or not. Patients with bipolar disorder frequently receive mood stabilizers and antipsychotics during maintenance treatment. It would be interesting to know whether the level of adherence and the predictors of adherence are the same or not, but we cannot find studies in the literature considering that approach.

Self-Reported Health Beliefs as Predictors of Adherence

Medication adherence in psychiatric patients may be influenced by health beliefs that are provided by the patients when they are asked. The self-reported health beliefs can refer to the patient or to a specific medication.

Self-Reported Health Beliefs Regarding the Patient

Health psychologists developed the health belief model (HBM)[66–68] to explain and predict health-related behaviors (Box 1). There are 3 self-reported health beliefs that may be relevant for medication adherence: first, the attitude towards medication in general, second, the health locus of control (HLOC), which refers to who is responsible for the management of a patient's disorders, and third, psychological reactance.

Box 1 HBM and Medication Adherence

HBM

- The HBM predicts health-related behaviors by focusing on the attitudes and beliefs of individuals.
- This model emerged in the 1950s as an application from the behavioral sciences to health problems and currently persists as the most widely recognized conceptual framework for explaining and predicting health-related behaviors by focusing on the attitudes and beliefs of individuals.[66–68]

DAI

- The original DAI-10 included 10 questions, each with true/false answers pertaining to various aspects of the patient's perceptions and experiences of psychiatric treatment.[73]
- DAI-10 scoring ranges from −10 to +10 with a total score >0 indicating a positive attitude toward psychiatric medications (pharmacophilia) and a total score <0 indicating a negative attitude toward psychiatric medications (pharmacophobia).
- A clinimetric version of the DAI[70] led us to include 8 items grouped into two subscales (positive and negative aspects of medications).

(*Continued*)

Box 1 (Continued).

HLOC

- HLOC reflects patients' beliefs about who or what is responsible for the management of their psychiatric disorder, influencing their health behaviors and consequently their mental health outcomes.[78] If patients believe that their own behaviors affect whether they stay healthy, become sick, or recover from an illness, they are said to have an "internal" HLOC orientation. On the other hand, beliefs attributing causation or control of illness to agents outside of the individual – other relevant people such as doctors or family members, the environment, fate, luck, or chance – are referred to as "external".[79]
- Traditionally, an internally oriented patient (ie, a patient believing that control of his/her health condition and health-related outcomes is contingent on his/her own behaviors and actions) has been considered more likely to engage in healthy behavior than an externally oriented patient (outside factors such as doctors, other people, or chance determine health outcomes).[80]
- The MHLC-C[77] is an 18-item general purpose, condition-specific locus of control self-report scale that can easily be adapted for use with any medical or health-related condition to assess individuals' beliefs on what influences their health. It is composed of four subscales:

  An internal locus of control subscale (internality).
- Three external locus of control scales (chance, doctors, and other powerful people).

Psychological reactance

- Psychological reactance can be considered the emotional reaction in direct contradiction to rules or regulations that threaten or suppress certain freedoms in behavior.[82]
- Psychological reactance theory is a commonly used framework for understanding health-care service users' resistance to persuasive health messages such as the need for adherence to prescribed treatment.[83]
- According to psychological reactance theory, freedom of behavior is an important, beneficial, and pervasive aspect of people's lives; when that freedom is threatened, they become motivated to restore it.[84,85]
- The Hong Psychological Reactance Scale[86] is a 14-item self-report questionnaire developed to assess individual differences in reactance proneness, that is, individuals' trait propensity to experience psychological reactance. Participants indicate the extent to which they endorsed each statement on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Abbreviations: DAI-10, Drug Attitude Inventory with 10 items; HBM, health belief model; HLOC, health locus of control.

Positive and negative attitudes toward medication in general are usually measured by the Drug Attitude Inventory-10

(DAI-10).[69] After a complex transformation[70] this led to the concepts of pharmacophobia, or fear of the use of pharmacological treatments, and pharmacophilia, or a positive attitude toward using or testing medications (Box 1). The association between more positive attitudes toward medication and higher adherence to prescribed treatments has been revealed in numerous studies in psychiatric patients.[71–76] Table 2 shows that one of the systematic reviews[61] of adherence in schizophrenia lists this association.

The HLOC dimension is measured by a scale called the Multidimensional HLOC.[77] In psychiatric patients, two HLOC dimensions are important: internal HLOC and doctor HLOC, in which either the patient or the doctor is responsible for the management of the disorders (Box 1).[78–80] Our research on this topic has shown that psychiatric outpatients have the conviction that their psychiatrists have greater influence on their mental health status even though they were, at the same time, aware of the efficacy of their own activities in coping with their mental disorder. Those psychiatric patients with low internal and external HLOC beliefs described greater adherence to treatment, while patients with high internal and external HLOC beliefs described lower adherence.[81]

Psychological reactance is defined precisely in Box 1,[82–86] but a simplified version is an emotional reaction toward rules perceived as a threat; it is typically measured using the Hong Psychological Reactance Scale.[86] In psychiatric outpatients, those who are more prone to reactance tend to show decreased adherence to prescribed treatment.[87,88]

To complete these three scales (DAI-10, Multidimensional HLOC and Hong Psychological Reactance Scale), which refer to the health beliefs of the patient, requires from 1 to 1.5 hours of the patient's time. Thus, we have developed the Patient Health Beliefs Questionnaire on Psychiatric Treatment[50] which summarizes the most important aspects and only requires 15 minutes. Patients are asked to rate, on a 6-point Likert scale (from 1, totally disagree, to 6, totally agree), the degree to which they agree or disagree with each statement. Higher scores on each subscale indicate a stronger belief. It includes major items from the 3 scales and has 5 subscales: 1) positive aspects of medication, 2) negative aspects of medication 3) psychological reactance, 4) internal HLOC, and 5) doctor HLOC.[50]

Health Beliefs Toward Specific Medications

Two key beliefs of patients have been found to have utility in explaining non-adherence to specific medications in psychiatric disorders: perceptions of personal need for treatment (necessity beliefs) and concerns about a range of potential adverse consequences (concern beliefs).[89] This Necessity-Concern Framework (NCF) asserts that patients implicitly weigh the costs against the benefits of taking a medication when deciding whether or not to adhere to it and that medication adherence will be greater the more a patient's beliefs in the necessity of the medication exceed his/her concerns.[90]

A meta-analytic review of the NCF to assess its utility in explaining nonadherence to prescribed medicines showed that higher adherence was associated with stronger perceptions of the necessity of treatment (OR = 1.74, 95% CI [1.57, 1.9], p=0.0001) and fewer concerns about treatment (OR = 0.504, 95% CI: [0.450, 0.564], p=0.0001); these relationships remained significant when data were stratified by study size, type of adherence measure used and country.[89]

The NCF can best be explored by using The Beliefs about Medicines Questionnaire (BMQ).[91] The BMQ-Specific scale includes 10 items on two subscales, each with five items assessing patients' beliefs about the medication they were prescribed for a specific illness in terms of necessity and concern about taking it. The degree of agreement with each statement is indicated on a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). Patients can be categorized into attitudinal groups based on their beliefs about their psychiatric medications.[92] The Necessity and Concerns scores can be split at the median to generate four attitudinal groups: Accepting (high necessity, low concern), Ambivalent (high necessity, high concern), Indifferent (low necessity, low concern), and Skeptical (low necessity, high concern).[93] In our studies, we have found that the NCF is better summarized by a dichotomous measure, the presence or absence of skepticism about that specific drug.

Although it has never been systematically studied, skepticism about a specific drug is probably partly explained by past experiences. According to Chang et al[94] decisions patients make about new prescriptions are dependent on pre-existing beliefs and expectations rather than based on objective interpretations of health information. Dolovich et al[95] proposed that past experiences with medications and relationships with health-care providers influenced patients' expectations of their medications. Horne et al[91] showed that patients' pre-existing beliefs about treatment influence their evaluation of the new prescriptions and their adherence. There is need for studies exploring the

relationship between past and present experiences with specific medications and skepticism about them.

Our Studies on Medication Adherence and on Antipsychotic Pharmacokinetics

The first author started almost 10 years ago conducting studies of medication adherence, particularly in relatively stable psychiatric patients, which led to a collaboration with the second author in the last 4 years. The second author has spent 25 years conducting pharmacokinetics studies of psychiatric drugs, particularly antipsychotics, which recently led him to explore the pharmacological complexity of non-adherence.

Predictors of Medication Adherence in Our Studies of Relatively Stable Psychiatric Outpatients

Table 3 describes our 3 largest non-overlapping studies[44,80,96] of these predictors.

Sociodemographic Variables as Predictors of Adherence

Table 3 demonstrates that our research on the role of sociodemographic variables in medication adherence has led to inconsistent results. Among them, only age and level of education appeared to be frequently related to treatment adherence. While older age increases adherence, lower educational level decreases adherence. Our experience gained from the studies shown in Table 3 suggests that some of the effects of different levels of education or gender probably just reflect different levels of self-reported health beliefs based on gender, education or age.

Clinical Variables as Predictors of Adherence

Table 3 shows that our research on the role of clinical variables in medication adherence has found that these variables are rarely significant. Only one study in depressive patients showed adherence decreasing as clinical severity increased. On the other hand, it is very likely that our stable patients do not include active substance users who are treated using other resources specific for substance users; therefore, medication adherence in our studies was not contaminated by obvious active substance use. We plan to study whether the effects of self-reported health beliefs on adherence vary based on the main diagnosis: schizophrenia, bipolar disorder and major depression.

Medication Variables as Predictors of Adherence

Table 3 demonstrates that our research on the role of medication variables in medication adherence has found that these variables are rarely significant. Only one study in depressive patients showed adherence decreasing as adverse effects increased. Neither the class of psychiatric drug nor duration of use had been a significant predictor of adherence behavior, but our studies had been limited by never exploring in a large sample whether or not drug variables may become significant within diagnostic groups.

Self-Reported Health Beliefs as Predictors of Adherence

The studies shown in the last row of Table 3 suggest that pharmacophobia in general and skepticism about a specific drug may be the best predictors of poor adherence, but one has to take into account that some countries may have very low levels of pharmacophobia, probably causing skepticism to become more important in that country. Future studies will need to consider whether the combination of psychological reactance and HLOC may be more relevant in specific psychiatric disorders.

Pharmacokinetic Studies and Adherence in Psychiatric Patients

The second author has spent 25 years[97] conducting pharmacokinetic studies by using what psychiatrists call blood levels and pharmacologists call therapeutic drug monitoring (TDM) in order to establish which genetic,[98] environmental[99] and personal variables[100] govern the relationship between dosages and serum concentrations of each psychiatric drug. Most of his studies have observed inpatients taking medications under close supervision, so he has been able to assume that most patients were consistently adherent.[101]

Clozapine has a very peculiar place in psychiatry because it is a very effective drug in treatment-resistant schizophrenia. In spite of its complex toxicological profile, when properly used it decreases the mortality of patients with treatment-resistant schizophrenia.[102] The next 3 subsections include a summary of the second author's studies on clozapine non-adherence in reference to clinical relevance, half-life and TDM.

Clozapine Non-Adherence and Clinical Relevance

The pharmacological effects of antipsychotic non-adherence vary from acute treatment to relapse prevention during maintenance treatment. Sudden antipsychotic discontinuation during the acute treatment phase

Table 3 Our Studies in Medication Adherence of Psychiatric Medication in Outpatients That Analyzed Sociodemographic (Gender, Age and Educational Level) Variables, Clinical Variables (Psychiatric Diagnosis), Medication Variables (Class, Treatment Duration, Polypharmacy), and Self-Reported Health Beliefs

Author	Sample and Methodology	Results (Only Significant Results are Described)
De las Cuevas et al[88]	145 consecutive psychiatric outpatients with depression. Adherence measured by MMAS-4. To predict adherence level, a direct method of discriminant analysis was carried out. SCs of the canonical discriminant function were presented.	**Sociodemographic, Clinical and Medication Variables** ↑ Adherence with: ↑ level of education (SC=−.43) ↓ Adherence with: ↑ severity of depression (SC=0.51), and ↑ severity of adverse effects (SC=0.50)
		Self-reported Health Beliefs ↑ Adherence with: ↑ positive attitude towards medication (SC=−.47), ↓ BMQ-Harm (SC=0.51). and ↓ BMQ-Concern (SC=0.51)
De las Cuevas et al[96]	967 consecutive psychiatric outpatients, all diagnoses. Adherence measured by MMAS-8. Strength of association was measured by partial correlations (r). Unfortunately, the effect of age after control by self-report measures was not calculated.	**Sociodemographic, Clinical and Medication Variables** ↑ Adherence with ↑ age (r= 0.19; p< 0.001)
		Self-reported Health Beliefs ↑ Adherence with: ↓ Internal HLOC (r= −.14; p< 0.001), ↑ Doctor HLOC (r= 0.19; p< 0.001), and ↓ psychological reactance (r= −.20; p< 0.001).
De las Cuevas et al[44]	1291 psychiatric outpatients from Spain, Argentina and Venezuela. Adherence measured by the Sidorkiewicz tool. Strength of association measured by adjusted OR. Multivariate analyses (logistic regression and chi-squared automatic interaction detector segmentation) showed that only pharmacophobia[a] in general and skepticism[b] about specific medications were associated with non-adherence. Pharmacophobia was the major factor associated with nonadherence, but when pharmacophobia was rare (Argentina), skepticism was the most important variable associated with non-adherence. Sociodemographic and clinical variables lost their significance after correcting for skepticism and pharmacophobia.	**Sociodemographic, Clinical and Medication Variables** ↑ Adherence with females: in Venezuela OR=1.90 (CI 1.15–3.14); p= 0.012 in Argentina OR=1.45 (CI 1.04–2.01); p= 0.003 ↑ Adherence with ↑ age: Spain OR =1.01 (CI 1.00–1.02); p= 0.002 Argentina OR=1.02 (CI 1.01–1.03; p= 0.001 Venezuela OR=1.03 (1.01–1.04; p= 0.01
		Self-reported Health Beliefs ↓ Adherence with pharmacophobia: Spain OR =1.5 (1.2–2.0); p= 0.003 Argentina OR=2.2 (CI 1.3–3.7); p=0.005 Venezuela OR=2.6 (CI 1.4–4.8); p= 0.002 ↓ Adherence with skepticism: Spain OR =1.56 (CI 1.18–2.06); p=0.002 Argentina OR=4.4 (CI 3.1–6.2); p=0.001 Groups with highest non-adherence in total sample (3 countries): • 40% in skeptical patients • 44% in skeptical and pharmacophobic patients • 44% in pharmacophobic patients

Notes: [a]Pharmacophobia was measured by the Drug Attitude Inventory-10 items; it represents the fear of taking drugs or medicines. Pharmacophobia refers to an attitude toward medications in general while skepticism refers to an attitude toward a specific psychiatric medication. [b]Skepticism about a specific medication was defined using the Beliefs about Medicines Questionnaire-Specific Scale; it means a patient had high concern about adverse reactions and low belief in the necessity of taking that medication.
Abbreviations: CI, 95% confidence interval; HLOC, health locus of control; MMAS-4, Morisky Medication Adherence Scale, 4 items; MMAS-8, Morisky Medication Adherence Scale, 8 items; OR, odds ratio; SC, standardized coefficient.

probably causes rapid relapse as most antipsychotics are completely eliminated from the body in one week. It is quite more complicated to predict the effects of sudden antipsychotic discontinuation once the patient is stable under treatment maintenance, since some patients may relapse but others may not or take many months to relapse.

Patients with treatment-resistant schizophrenia are ideal candidates for studying the effect of non-adherence since most of them need continuous antipsychotic treatment to avoid harm to self or others. Moreover, clozapine is frequently used for both acute and maintenance treatments in these patients, making it perhaps the ideal drug for a study of antipsychotic non-adherence. In fact,

clozapine has a peculiar pharmacodynamic[103] and pharmacokinetic profile,[104] and when patients who are consistently taking it decide to stop suddenly, this non-adherence can manifest with serious clozapine withdrawal syndromes including cholinergic rebound,[105] worsening of psychosis and motor symptoms,[106] or appearance of never-manifested symptoms such as catatonia.[107]

Clozapine Non-Adherence and Half-Life

The relationship between non-adherence and decreased clozapine TDM levels is governed by the concept of half-life. Pharmacokinetic textbooks[108] usually state that five half-lives are required to 1) reach steady state after starting a dose and, 2) to eliminate 95% of the serum drug concentrations once steady state has been reached and the drug is stopped. The literature on how to establish clozapine half-life in the average clozapine patient and in a specific clozapine patient is not straightforward.

Pharmacokinetic clozapine studies usually have been conducted using single dosing,[109] but this design is not a good representation of clozapine half-life in the clinical environment after repeated dosing. The clozapine package insert in the US[110] proposes that after repeated dosing average clozapine half-life is 12 hours. This relatively short half-life is not compatible with the possibility of single-day administration.[102] As the matter of fact, by using drug discontinuation in the clinical environment, the second author obtained a half-life of 17 hours in one patient and 34 hours in another.[104] Clozapine is lipophilic and deposits in the fat tissue[111] which explains the dramatic increase in clozapine half-life after repeated dosing.[109]

In the clinical environment, the problem is the half-life that governs clozapine elimination after discontinuation is not average clozapine half-life, but rather the individual's clozapine half-life, which varies according to the metabolic characteristics of each patient. Pharmacogenetic science was developed by first establishing that some patients had very high concentrations when given an average dosage; they were called poor metabolizers (PMs). Conversely, other patients had non-detectable concentrations with average doses; they were called ultrarapid metabolizers (UMs).[112]

Thus, according to pharmacokinetic science PMs are characterized by having extremely long half-lives and very high concentration-to-dose (C/D) ratios. On the other hand, UMs are characterized by having extremely short half-lives and very low C/D ratios. The application of this principle to clozapine is facilitated because in therapeutic doses clozapine follows linear kinetics, which means the relationship between concentrations and doses is stable; the clozapine C/D ratio is a constant in a specific individual unless it is modified by an environmental variable.[112] Complexity ensues, however, because: 1) estrogens are inhibitors of clozapine metabolism, meaning that females have higher clozapine C/D ratios; 2) smoking is an inducer of clozapine metabolism, meaning that non-smokers have higher C/D ratios; and 3) Asians have lower clozapine metabolism, meaning that Asians have higher clozapine C/D ratios. In summary, to classify a clozapine patient as PM or UM one has to define ranges after stratifying for gender, smoking and ethnicity.[112]

Clozapine Non-Adherence and TDM

The second author has reviewed thousands of clozapine TDMs in hundreds of inpatients under standard conditions and, regarding establishing non-adherence, he can provide a basic scientific principle and some recommendations. The basic principle is that any clozapine TDM, to be easily interpreted, has to be steady state: the clozapine dosage must not have been changed for at least 1 week (>5 half-lives) and must have been drawn early in the morning before taking any clozapine dosage (at least 12 hours after the last dosage).

Recommendations on interpreting non-adherence vary among the following: 1) inpatient with many repeated clozapine TDMs, 2) outpatient with repeated clozapine TDMs and 3) outpatient with no prior clozapine TDM.

When the second author studies inpatients who are supervised by nurses during clozapine intake and live under controlled conditions including a stable smoking routine, he always calculates a mean C/D ratio in that specific patient based on at least 3–4 TDMs. Non-adherence should be suspected when a clozapine C/D ratio decreases more than half than the mean C/D ratio of prior TDMs from that specific patient and there is no alternative explanation (discontinuation of an inhibitor or addition of an inducer).[113]

If the patient is outpatient and even when multiple clozapine TDMs are available, the unresolved issue is how many of the collected measures are contaminated by non-adherence. Thus, one needs to review all changes in medications, caffeine intake, smoking or infections, and use common sense to eliminate values that appear suspicious. Then, use remaining values to calculate the mean C/D ratio which may represent clozapine metabolism in that patient and which can be used for future comparisons.

If there are no prior measures, it is extremely difficult to establish non-adherence. In that case, the second author compares the clozapine C/D ratio with those he has found among clozapine UMs, according to their definitions after stratification by gender, smoking status and ancestry.[112] As a general principle, any very low clozapine C/D ratio compatible with being a UM in the absence of inducers (eg, carbamazepine or valproate) is likely to be explained by non-adherence.[114]

In summary, despite 25 years of research on clozapine TDM, the second author cannot provide any simple advice on how to use clozapine TDM to identify non-adherent patients. Furthermore, as will be discussed in the section on future studies, the use of TDM to predict the effects of or to identify non-adherence for other psychiatric drugs appears much more complicated. In a published editorial, the first and second authors acknowledged that the distinction between non-adherent patients and UMs is more an art than a science.[115] Furthermore, they agree that if they were provided all the money and technology currently available they do not have enough knowledge to use TDM of 80 different psychiatric drugs to reliably determine non-adherence in their three-country study that included 1372 patients taking 2454 psychiatric medications.

Future Studies

We are planning future studies in psychiatric patients on predictors of medication adherence and the use of TDM to explore non-adherence.

Future Studies on Predictors of Medication Adherence

We are planning future psychiatric studies in outpatients focused on insight and studies in inpatients.

Future Studies of Insight in Outpatients

Our outpatient studies of adherence to medication in psychiatric patients have not explored the role of the complex topic called "insight" which may include patients' recognition of having a psychiatric disorder and awareness that treatment could be helpful. There is general agreement that insight into mental illness is a multi-dimensional complex construct that can be impaired in many, if not all, mental disorders.[116] The scientific literature indicates a strong link between impaired insight and nonadherence to psychiatric medication.[117,118] For this reason, in order to increase the validity of the adherence tool when we first published it, we proposed the incorporation of a new Insight subscale into the questionnaire.[50] The insight literature frequently focus in schizophrenia and includes 3 relevant components: 1) awareness of having an illness, 2) attribution of one's symptoms to the illness and 3) acknowledgment of a need for treatment. The second component (attribution of one's symptoms to the illness) was not included in our insight subscale because varies from schizophrenia to other psychiatric disorder. On the other hand, we included the need to see a psychiatrist (rather than the family doctor) as an attempt to assess one step further toward insight into mental illness. In our ongoing studies, patients are being asked to rate, on a 6-point Likert scale, the degree to which they agree or disagree with each statement, from strongly disagree to strongly agree. In summary, the principles governing the design of this subscale are that insight: 1) is relevant for all psychiatric disorders, 2) is measured as a continuum, and 3) involve 3 components (awareness of having an illness, acknowledgment of a need for treatment and the need to see a psychiatrist).

Future Studies in Acute Inpatients

As we have seen, self-report measures of health beliefs play a valuable role in predicting adherence, but their validity depends upon the individuals' willingness and ability to accurately report their experiences. Patients in an acute phase of a mental illness, particularly although not exclusively psychotic disorders, usually present a deteriorated perception of reality and are often characterized by a lack of awareness and poor insight. Nevertheless, according to Bell et al[119] self-report psychological testing instruments may be valid even when patients lack awareness of their illness, awareness of the need for treatment, or awareness of the consequences of their illness. During hospitalization in a psychiatric ward, medication-taking behavior is closely supervised by medical personnel and medication adherence approaches 100%, but after hospital discharge treatment adherence tends to decrease over time.[20]

With this set of limitations, future studies of acute psychiatric inpatients may have no options other than exploring adherence once the patients are stable and ready to be discharged. As a matter of fact, predischarge planning programs are considered important in assisting patients to take charge of their illness, become partners in the treatment process, reduce the likelihood of readmission[120] and at the same time become educated concerning medications and encouraged toward medication adherence.[121] It is possible that this predischarge moment would be an opportune time

to study the self-reported dimensions in order to predict future adherence in outpatient settings. As far as we know, there are no studies of these self-report measures at the time of discharge.

Future Studies of TDM and Non-Adherence

We are planning further studies on clozapine TDM and non-adherence. Then, we comment on the greater complexity involved in studying the relationship between non-adherence and TDM of other antipsychotic or other psychiatric drugs.

Future Studies of Clozapine TDM and Non-Adherence

We have started to explore non-adherence in clozapine outpatients through the use of large databases of repeated samples by collaborating with some of the leaders in outpatient TDM.[122] Regarding the use of single clozapine TDM to establish non-adherence, the first step is to further extend the criteria of low clozapine C/D ratios after stratification by gender and smoking from Asians[114] to Caucasians. In a second step, we think that there is potential for using the metabolite norclozapine,[123] which appears to have a longer half-life than clozapine.

Future Studies of TDM Based on Other Antipsychotics and Non-Adherence

These are interesting times to use TDM to establish non-adherence in antipsychotics other than clozapine since the literature is starting to 1) acknowledge its relevance, 2) pay attention to a TDM guideline, and 3) include interest on the part of commercial companies. On the other hand, we comment on the complexity of moving forward in this area.

Many authors[33,124] are starting to acknowledge that many of the schizophrenia patients considered treatment-resistant by their psychiatrists are merely non-adherent. It is very clear that when a patient is taking doses that are therapeutic in an average patient and has no detectable serum concentrations using a well-validated method, the patient is obviously non-compliant. It is much more complicated when the serum concentrations are low. A major step occurred in 2004,[125] when a group of experts published the first TDM guideline providing lower and upper therapeutic ranges for many psychiatric drugs. In 2018,[126] the third version of this guideline was published and this version has received much more attention to the point that a modified section of the antipsychotic TDM guideline was published in a journal targeting clinicians.[127] In summary, most psychiatrists would agree that when a patient has a serum concentration below the therapeutic range for this antipsychotic, the dosage should be increased and another TDM obtained before considering the patient treatment-resistant to that antipsychotic. On the other hand, it is much more complicated to establish how to diagnose non-adherence based on subtherapeutic concentrations of a specific antipsychotic, since it may be explained by pharmacokinetic confounders.

To diagnose a low C/D ratio as compatible with non-adherence there is need for a thorough understanding of the pharmacokinetic variables influencing drug clearance and the C/D ratio of each specific antipsychotic. After clozapine, oral risperidone and oral paliperidone are the antipsychotics of which we are most knowledgeable,[101] but the literature on C/D ratios show some discrepancies between some European labs and the US and other European labs for oral risperidone[128] and between Korean and non-Korean studies of oral paliperidone.[129] The literature on C/D ratios of LAI risperidone[128] and paliperidone[130] is limited by little data and lack of knowledge of the half-life of the different formulations.[131] The use of olanzapine and quetiapine C/D ratios in clinical practice is just starting.[132] Most other second-generation antipsychotic TDM science is too underdeveloped to firmly establish therapeutic ranges.[126]

Until recently, antipsychotic TDM held no interest for pharmaceutical companies and was only studied by independent investigators with limited funding, who frequently used naturalistic designs from TDM outpatient databases that offered limited access to clinical information. More recently, some commercial companies[133] began introducing new commercial TDM methods that can provide same-day data even to outpatient facilities. Such a system has been marketed first for clozapine.[134] Both the interest of commercial companies in this area and the development of new TDM technologies are excellent pieces of news, but increase the risk of promoting non-validated practices such as using antipsychotic concentrations in urine to detect non-adherence.[135] Renal drug elimination of any antipsychotic and its metabolites is an extremely complex and poorly understood topic.

Future Studies of TDM Based on Other Psychiatric Drugs and Non-Adherence

Antidepressant TDM is reviewed by the expert guideline,[126] but there is little information on second-generation antidepressants and some of them, such as paroxetine and fluoxetine, definitively inhibit their own metabolism, making the interpretation of their C/D ratios

very complicated. Their C/D ratios do not follow linear kinetics,[136] and the C/D ratio is not constant in an individual patient since it varies with the dosage.

TDM of mood stabilizers is reviewed by the expert guideline.[126] Most psychiatrists agree that lithium TDM is well established, but it is more complicated for those mood stabilizers which are also antiepileptic drugs and have complicated pharmacokinetics.[136] Carbamazepine does not follow linear kinetics due to auto-induction.[132] Valproate TDM is severely neglected and very complicated since the total serum valproate concentrations do not follow linear kinetics due to protein displacement[137] and its auto-induction has received almost no attention.[138]

Most TDM experts will probably agree that we are very far from being able to use serum TDM to diagnose non-adherence in patients taking antidepressants or mood stabilizers. Most patients with non-detectable serum concentrations taking therapeutic dosages are likely to be non-adherent. On the other hand, it is a very humbling experience to remember that the concept of UM was introduced in medicine when a group of Swedish psychiatrists observed 2 families with several members taking tricyclic antidepressants (TCAs). They found repeated non-detectable serum concentrations in spite of reassurance by the patients and families that the patients were taking the TCAs. A gene study of the metabolic enzyme explained that these 2 families have multiple active copies of the gene, leading to the first description of the genetic UMs.[139]

Our conclusion after 25 years of conducting pharmacokinetic studies in psychiatric drugs is that we have limited understanding of how to use blood levels to predict the effects of non-adherence or to establish it. The next 25 years should bring much better understanding if systematic studies are conducted in the real clinical environment.

Expert Opinion on the Complexity of Studying Medication Adherence in Psychiatry

The last two subsections provide our expert opinion on the complexity of adherence due to its dynamic profile and on personalized approaches.

Complexity of Adherence Studies: Adherence Changes Over Time

According to the Common-Sense Theoretical Model of Illness, adherence is a dynamic process that changes over time based on the feedback mechanism between health threats (symptom identification) and appraisal of the coping behavior (taking medications).[140] Since the social and environmental contexts of psychiatric patients may change over time, their experiences with and perceptions of their psychiatric disorders and prescribed treatments may also change. These experiences and perceptions can challenge and modify previous beliefs about illness and medications, and therefore their adherence to medicines may change.[141] The changes in adherence add complexity to the study of large samples with a cross-sectional design. Any longitudinal study of a non-adherent patient may be made impossible by the lack of collaboration of the most non-adherent patients.

The Need for a Personalized Approach When Studying Adherence

The term personalized medicine or the narrower term personalized prescription may mean different things to different professionals.[140] A psychologist may propose that it means using individualized treatment based on the individual psychological characteristics of the patient. A pharmacologist may propose that it means using individualized treatment based on the individual pharmacological characteristics of the patient. Both versions are discussed as our final message on medication adherence in psychiatric patients.

Personalization Based on Psychology with Potential for Improving Non-Adherence

We hope that once we integrate the insight subscale into our Patient's Health Belief Questionnaire on Psychiatric Treatment[50] and also consider skepticism about some specific drugs, this assessment will provide a comprehensive way of measuring self-reported health beliefs as a predictor of non-adherence and, more importantly, develop personalized interventions based on the patient's reasons for non-adherence. On the other hand, we acknowledge that personalized prescription by using psychological measures from self-report is in its early stages.

Personalization Based on Pharmacology for Preventing Non-Adherence

In our studies, patients frequently explain their non-adherence as skepticism about some specific drugs. We have no definitive proof, but our experience suggests that many cases may be due to lack of consideration of

a personalized approach to prescriptions by their psychiatrists. Many patients do not tolerate or respond to average doses and need lower or higher doses, so they may not tolerate an average dose of a specific psychiatric drug very well. We hope as the science of personalized prescription advances and pharmacogenetics and TDM are used to personalize dosing and drug selection,[100] the number of patients with this negative experience may be reduced. On the other hand, we acknowledge that personalized prescription by using pharmacological principles is also in its early stages of implementation. We do not recommend current commercial pharmacogenetic tests since they are not validated.[98]

To conclude our review of the literature and of our studies, as we have previously recognized, our studies have limitations that may bias our opinions. On the issue of the prediction of adherence in psychiatric patients, our reflections are limited by not having taken into consideration the patient's insight, not having expanded our studies to acute patients admitted to psychiatric wards, and the fact that those related to active substance abuse were not obviously active in our outpatient samples. Finally, we acknowledge we are only starting to understand the pharmacological principles behind the clinical relevance of non-adherence which may be different for different drugs and how TDM can be used in psychiatry to establish their non-adherence or predict its consequences.

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