Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies

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Although non-adherence is common across all branches of medicine, psychotic disorders pose additional challenges that increase its risk. Despite the importance of non-adherence, clinicians generally spend too little time on assessing and addressing adherence attitudes and behaviors. Importantly, how adherence is measured significantly impacts the findings, and the most frequently employed methods of asking patients or judging adherence indirectly based on efficacy or tolerability information have poor validity. Novel technologies are being developed that directly assess adherence and that can also be used to both provide real-time feedback to clinicians and serve as an intervention with patients. Several treatments are available that can positively impact adherence. Among psychosocial interventions, those combining multiple approaches and involving multiple domains seem to be most effective. Although long-acting injectable antipsychotics are theoretically a very powerful tool to assure adherence and signal non-adherence, recent results from randomized controlled trials failed to show superiority compared to oral antipsychotics. These data are in contrast to nationwide cohort studies and mirror-image studies, which arguably include more representative patients receiving long-acting antipsychotics in clinical practice. This disconnect suggests that traditional randomized controlled trials are not necessarily the best way to study interventions that are thought to work via reducing non-adherence. Clearly, non-adherence is likely to remain a major public health problem despite treatment advances. However, increasing knowledge about factors affecting adherence and leveraging novel technologies can enhance its early assessment and adequate management, particularly in patients with psychotic disorders.

Key words: Non-adherence, psychosis, schizophrenia, risk factors, assessment, interventions

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Adherence to treatment prescriptions is a critical aspect of health care (1); however, it is often given far less attention in routine clinical practice than necessary. Even though terms such as adherence or compliance are far from ideal in characterizing the interaction of clinicians, patients and medication-taking, they remain in widespread use. We need to develop better methods to de-stigmatize the challenges associated with taking medication as prescribed and create a better enabling environment of education, shared decision-making and responsibility in managing illness. All of this is predicated on the assumption that reaping the expected benefits of efficacious medications (and other treatments) depends upon taking them appropriately.

Medication-taking in the acute care setting is often facilitated by health care professionals, creating a sense of confidence among practitioners that adherence will continue in the post-acute setting. However, the management of many chronic diseases, such as psychotic disorders, suffers from enormous problems in medication adherence, leading to countless avoidable emergency room visits and days in the hospital, as well as suboptimal overall outcomes (2,3). It is estimated that 50% of patients suffering from chronic illness are not taking medication as prescribed after six months (4). The cost of non-adherence in the United States alone could be up to 300 billion dollars per year (5). Both physicians and patients have been shown to overestimate the amount of medication that a patient is taking (6), and physicians in general spend remarkably little time in addressing this issue, which is so critical to the success of their efforts (7,8).

Definitions and measurement strategies in this area vary considerably. In general, the simplest strategies for measuring adherence are likely to be inaccurate, and the most potentially informative strategies are invasive and/or expensive (1). Clearly, there are no specific predictors that are universally reliable and valid. A range of factors influence medication adherence and an individualized approach is important in order to intervene successfully.

In this review, we focus specifically on patients with psychosis, primarily schizophrenia. We discuss issues of definition and measurement, and review data about non-adherence among patients receiving naturalistic treatment for psychosis and those participating in clinical trials. We then discuss factors contributing to non-adherence and strategies to facilitate/enhance adherence.

DEFINITIONS AND MEASUREMENT

Ideally, patients should be taking all of their medications as prescribed. However, adherence is often considered to be "good", or patients are described as "adherent", if they are taking at least 70 or 80% of their medication. Some reports try to break adherence into multiple categories, including fully

adherent, partially adherent and non-adherent (9). However, in some cases, missing 20-30% of one's medication could have clinically significant consequences, while in other cases it might not. The type of medication, formulation, dosage and dosage frequency, along with individual characteristics, such as absorption and metabolism, phase of illness and vulnerability to disease recurrence or progression, will influence the impact of specific levels of non-adherence. Therefore, definitions will and should vary depending upon the context.

Although monitoring of adherence has always been an issue in health care, our ability to accurately determine the degree of adherence among our patients is limited. Methods available for monitoring adherence are generally divided into direct and indirect (1). Every method has its drawbacks and there is no universally accepted "gold standard", as summarized in Table 1.

Table 1 Methods for monitoring medication adherence and their drawbacks

Method	Drawbacks
Patient report	Unreliable (forgetting, hiding)
Patient self-assessment questionnaire	Unreliable (forgetting, hiding)
Patient diary	Unreliable (forgetting, hiding)
Informant report/questionnaire	Unreliable (lack of information, opinion)
Pill count	Somewhat unreliable, pills may not have been ingested
Clinical response/adverse effects	Unreliable, as presence/absence of efficacy and adverse effects is multiply determined
Assessment of physiologic response	Unreliable, as physiologic response is multiply determined
Blister pack	Somewhat unreliable, pills may not have been ingested
MEMS cap	Somewhat unreliable, pills may not have been ingested
Electronic pill trays	Somewhat unreliable, pills may not have been ingested
Pharmacy/prescription refill record	Somewhat unreliable, pills may not have been ingested
Observed ingestion	Highly resource intensive, can lead to conflicts
Measurement of drug in bodily fluid or blood	Only cross-sectional; improved adherence preceding a clinic visit ("white coat compliance")
Measurement of biomarker	Only cross-sectional; requites additive
Hair analysis	Requires long hair, requires a lot of strands, special lab needed
Ingestible event marker/digital health feedback system	Requires accepting a microelectronic chip in the pill and wearing a receiver on a patch on the torso; to date still expensive and not widely available

MEMS – medication event monitoring system

In some situations, patients can be observed swallowing their medication, and liquid preparations or rapidly dissolving formulations could facilitate the process. Measurement of drug concentration in blood or other bodily fluids can give useful information on adherence as well as on individual variability in absorption and metabolism. However, a random blood level may convey an only partial story, unless clinicians have done an observed ingestion and pharmacokinetic study to determine what the blood level "should be", if the patient were fully adherent. A biologic marker could be added to the drug as another method. These approaches could be considered expensive and burdensome to the patients and/or clinician. On the other hand, there are situations where blood level monitoring is a necessary part of treatment, such as with medications that have an established therapeutic window and/or common risk of toxicity (e.g., lithium).

Indirect methods of monitoring include asking the patient (the easiest and often most unreliable method). Measuring physiologic response associated with a particular drug or using clinical therapeutic response as a proxy for adherence are also strategies that are employed, but are fraught with potential problems. The clinical state can be influenced by many factors other than treatment and, for example, some patients with schizophrenia or bipolar disorder may remain asymptomatic for months or even years without medication.

A common method to assess adherence has been pill counts (i.e., counting the number of pills remaining in a medication bottle). However, it is easy for a patient to discard some pills or transfer them to another bottle. Unannounced home visits may get around this problem, but such efforts are clearly expensive and not always welcome. The use of electronic monitoring devices, such as medication event monitoring system (MEMS) pill bottle caps, is also common, but costly (10). The device records the date and time that the bottle was opened. However, this does not confirm that the patient has actually ingested the medication.

Electronic pill trays or boxes are also available, which can record the opening of the box and/or transmit a message to a third party when the box has not been opened (11). Such devices require an initial investment and are by no means foolproof. More recently, a novel technology, referred to as a digital health feedback system (12), has been developed that embeds an "ingestible event marker" in the tablet or capsule, which upon contact with gastric fluid electrolytes emits a unique signal, which is transmitted through bodily tissue to a small receiver worn in a patch on the torso. This device then transmits a signal to a cell phone indicating the time (and date) that the medication has been ingested. The ingestible chip is excreted in the feces and the signal that it emits is similar to that picked up by an electrocardiogram and is not transmitted outside of the person's body. The mobile phone stores the de-identified data and periodically transfers it to a password protected server

Table 2 Studies of non-adherence to medication in patients with major medical conditions (data from 14)

Medical condition	Number of studies	Non-/poor adherence
Diabetes mellitus	23	32.5%
Pulmonary diseases	41	31.2%
Infectious diseases	34	26.0%
End-stage renal disease	20	30.0%
Eye disorders	15	27.4%
Infectious diseases	34	26.0%
Obstetric and gynecological disorders	19	25.2%
Ear, nose, throat and mouth disorders	30	24.9%
Cardiovascular diseases	129	23.4%
Skin disorders	11	23.1%
Genitourinary and sexually transmitted diseases	17	23.0%
Cancer	65	20.9%
Gastrointestinal disorders	42	19.6%
Arthritis	22	18.8%
HIV/AIDS	8	11.7%

using secure encryptions. The adhesive monitor also captures physiologic metrics, including heart rate, body position, skin conductance, physical activity and sleep characteristics.

A major premise underlying this type of approach is that a large proportion of non-adherence, particularly among people with psychiatric/cognitive disorders, is not due to a willful, conscious refusal to take medication, and that any technology which can aid and empower patients and caregivers to play a more informed role in their own health care will offer a way to enhance adherence. Accurate, readily accessible data on patterns of patient medication-taking can facilitate that process. In addition, linking data on adherence patterns to relevant physiologic and behavioral measures, such as sleep and activity, can allow for even greater information sharing regarding health status, treatment targets and specific medication effects.

A pilot study in 28 patients with schizophrenia and bipolar disorder has found this approach to be feasible and acceptable to patients (12). We cite this as an example of a monitoring technique that can also serve as an "intervention" platform to facilitate adherence. In addition, it is likely that further technological innovations will enhance and extend such opportunities.

Prescription refills can also be used as a measure of adherence. Although initially such data were only available in "closed" systems, such as the Department of Veterans Affairs Health Care System, health management organizations, or single service payment systems (e.g., Medicaid/Medicare), broader attempts have been implemented (13). Here too, data are potentially flawed, since filling a prescription by no means insures that the medication was ingested. However, absence of prescription refills is a strong indication of non-adherence. It is particularly important to look at prescription refills over time in order to produce a metric, such as the medicine prescription refill ratio.

EPIDEMIOLOGY

According to a meta-analysis that focused on non-psychiatrist physician prescriptions (including exercise, diet, vaccination etc., as well as medication taking) (14), the average study-defined adherence was highest in HIV disease (88.3%, 95% CI: 78.9-95.2%, 8 studies), followed by arthritis (81.2%, 95% CI: 71.9-89.0%, 22 studies), gastrointestinal disorders (80.4%, 95% CI: 73.9-86.2%, 42 studies) and cancer (79.1%, 95% CI: 75.9-84.2%, 65 studies). The average adherence in other physical diseases ranged between 74 and 77%, including skin disorders (76.9%, 95% CI: 66.5-85.9%, 11 studies); cardiovascular diseases (76.6%, 95% CI: 73.4-79.8%, 129 studies), and infectious diseases (74.0, 95% CI: 67.5-80.0%, 34 studies). Patients with pulmonary diseases (68.8%, 95% CI: 58.5-75.8%, 41 studies) and diabetes mellitus (67.5%, 95% CI: 58.5-75.8%, 23 studies) had the lowest adherence (14) (Table 2).

Most studies in psychotic patients reported high frequencies of non-/poor adherence (Table 3). A study based on Medicaid beneficiaries in San Diego County, California (N=2,801) assessed patients' adherence by utilizing pharmacy records between 1998 and 2000. Using cumulative possession ratio for defining adherence, 24% of all schizophrenia patients were non-adherent (ratio=0.00-0.49), 16% were partially adherent (ratio=0.50-0.79), and 19% were excess fillers (ratio >1.10) (19). Based on Veterans Affairs pharmacy data for patients who received antipsychotic medication between 1998 and 1999 (N=63,214), poor adherence (defined as medication possession ratio <0.8) was seen in 40% of patients (20). Another study (22) also used Veterans Affairs data from the fiscal year 2000-2003 (N=34,128) and the same non-adherence definition, finding that poor adherence was seen in 36.0-37.1% of patients (mean medication possession ratio in patients with poor adherence during the study years: 0.42-0.47). Interestingly, the authors found that adherence fluctuated over time in some patients. Altogether, 61% of patients had adherence difficulties at some point over the 4-year period, and approximately 18% had consistently poor adherence, 43% were inconsistently adherent, and 39% had consistently good adherence (22).

Table 3 Studies of non-adherence to medication in patients with psychotic disorders

Psychotic population	Number of patients	Study type	Measurement method	Non-/poor adherence
Schizophrenia, Norway (15)	280	Naturalistic	Serum concentration	58.4%
Schizophrenia, USA (16)	876	Naturalistic	Self-report	48.4%
Schizophrenia, meta-analysis across 39 studies (17)	40-423 per study	Mixed	Mixed	40.5%
Schizophrenia, Nigeria (18)	313	Naturalistic	Self-report	40.3%
Schizophrenia, Medicaid beneficiaries (19)	2801	Naturalistic	Pharmacy records	40%
Schizophrenia, USA (20)	63,214	Naturalistic	Pharmacy records	40%
Schizophrenia, first episode, 1 year (21)	400	RCT	Discontinuation against medical advice	37.1% (Kaplan-Meier estimate); 28.8% (raw)
Schizophrenia, USA (22)	34,128	Naturalistic	Pharmacy records	36.0-37.1%
Schizophrenia, France (23)	291	Naturalistic	Self-report	30.0%
Psychotic disorders, meta-analysis across 86 studies (24)	23,796; 20-2257 per study	Mixed	Mixed	25.8%
Psychosis, Australia (25)	1825	Naturalistic	Self-report	11.8%
Schizophrenia, first episode, 1 year (26)	498	RCT	Informant and observer report scale	11.6%
Schizophrenia, first episode, 1 year (27)	151	RCT	Dropout from the study due to non-compliance (self-report)	11.3%
Schizophrenia, chronic, within 2 months of exacerbation (28)	300	RCT	Dropout from the study due to non-adherence	8.0%
Schizophrenia, chronic, stable, 1 year (29)	365	RCT	Dropout from the study due to poor compliance	4.1%
Schizophrenia, chronic, stable, 2 years (30)	337	RCT	Dropout from the study due to non-compliance	3.7%
Schizophrenia, chronic, after acute relapse, 1 year (31)	1294	RCT	Dropout from the study due to non-compliance	3.0%
Schizophrenia, first episode, >2 years (32)	555	RCT	Dropout from the study due to non-compliance	2.3%

RCT – randomized controlled trial

Lacro et al (17) reviewed the studies published between 1980 and 2000 which identified risk factors for medication non-adherence in patients with schizophrenia. They included data from 15 cross-sectional, 14 prospective and 10 retrospective studies, with a mean number of 110±80 patients per study (median=80, range=40-423). Across these studies, the unweighted mean non-adherence frequency was 40.5% (median=40%, range=4-72%). Analyzing only the ten studies in which trained personnel measured adherence and in which adherence was defined as "regularly taking medication as prescribed", the weighted mean adherence frequency was 41.2% (median=39%, range=20.0-55.6%). When only the five studies that defined adherence as "taking medications as prescribed at least 75% of the time" were analyzed, the weighted mean adherence frequency was 49.5% (median=47.0%, range=37.7-55.6%) (17). Nosé et al (24) systematically reviewed studies that reported non-adherence with medication and scheduled appointments in community settings. In the 86 studies included (71% prospective, 29% cross-sectional) from the US (44%), Europe (36%) and other areas (20%), involving 23,796 patients (253.8±440.4 per study, median=103, range=20-2257), the overall weighted mean non-adherence by study definition was 25.8% (95% CI: 22.5-29.1%).

Non- or poor adherence in more recent studies was reported to be 48.4% (USA, nationwide, N=876, self-report) (16), 11.8% (Australia, N=1825, self-report) (25), 40.3% (Nigeria, N=313, self-report) (18), 30% (France, N=291, self-report) (23) and 58.4% (Norway, N=280, serum concentration) (15) (Table 3). Thus, non-adherence figures vary widely, presumably reflecting differences in the targeted population, definitions and measurement methods. However, of note, studies using more firm measurement methodology, such as pill count, electronic monitoring, and blood drug level, tend to indicate higher non-adherence (14,15,23,33). In addition, the duration of follow-up certainly also influences the observed frequencies of non-adherence.

Unlike naturalistic studies, controlled trial settings allow us to assess patients'

Table 4 Factors associated with non-adherence

Patient characteristics
Sex, age, race
Education
Socio-economic status
Knowledge
Perceived need for treatment (insight)
Motivation
Beliefs about treatment risks and benefits
Past experiences/"transference"
Past history of adherence
Self-stigma
Illness characteristics
Illness duration (first episode, chronic)
Illness phase (acute, maintenance, etc.)
Symptom type and severity (e.g., negative symptoms, depression, demoralization)
Cognitive function
Lack of insight
Substance use
Comorbidities
Degree of refractoriness
Potential for relatively asymptomatic intervals or "spontaneous remission"
Medication characteristics
Efficacy (consider different domains)
Effectiveness
Adverse effects (of relevance for the patient)
Delivery systems/formulation
Dosage frequency
Cost/access
Provider/system/treatment characteristics
Therapeutic alliance
Frequency and nature of contact with clinicians

Provider/system/treatment characteristics (*continued*)
Duration of treatment (past and expected)
Complexity of administration
Accessibility and cohesion of services
Access to care
Continuity of care
Reimbursement
Ability to monitor adherence
Provision of psychoeducation
Availability of trained psychosocial treatment specialists
Evaluation of obstacles to adherence
Access to alternative formulations (e.g., long-acting injectable antipsychotics)
Complexity of administration
Family/caregiver characteristics
Nature of relationship
Perceived need for treatment (insight)
Beliefs about treatment risks and benefits
Knowledge, beliefs, attribution
Involvement in psychoeducation
Involvement in adherence monitoring
Stigma
Environmental characteristics
Physical environment
Level of supervision
Orderliness
Safety and privacy
Stigma
Extrafamilial support system
Other resource characteristics
Financial
Transportation

adherence in a prospective manner, often with more accurate methods, such as pill counts or blood levels. In addition, since the characteristics of patients (including socio-demographic, diagnostic and biological variables) are known in detail, it is easier to examine potential predictors for non-adherence. However, there is likely to be a selection bias, in that patients recruited in trials are required to undergo consenting procedures, and are therefore likely to be more adherent and to have better cognitive function. Moreover, participation in a controlled trial alters the ecology of treatment delivery and experience. Patients in clinical trials are also prone to receive more and different types of attention than those in routine care, from measures of adherence to reminders to attend clinical/research assessment sessions, or the provision of free medication (1,34,35). Furthermore, adherence is often measured only among patients who continued in the trial, while patients who are non-adherent might be more likely to drop out of the study. Indeed, patients who drop out from the study because of non-adherence are often reported as "withdrew consent" or "patient decision", and the underlying reasons are rarely examined in detail. Thus, for several reasons, it is fair to assume that adherence is much higher in clinical trials than in routine care.

In recent long-term maintenance studies in patients with schizophrenia, the dropout due to non-adherence was as low as 2.3% (N=555, first episode psychosis patients, ≥2 year duration) (32), 3% (N=1294, chronic patients after acute relapse, 1 year duration) (31), 3.7% (N=337, stable patients, oral treatment arm, 2 year duration) (30), 4.1% (N=365, stable chronic illness, 1 year duration) (29), 8% (N=300, unstable patients within 2 months of exacerbation, oral treatment arm, 1 year duration) (28), 11.3% (N=151, first-episode patients, 1 year duration) (27), and 11.6% (N=498, first-episode patients, 1 year duration) (26) (Table 3). However, these figures do not include broader non-adherence.

A randomized controlled trial in first episode psychosis (N=400) reported the number of patients who discontinued treatment against medical advice prior to completing 1 year of treatment (21). The authors regarded these patients as "non-adherent" (raw data: 28.8%, Kaplan-Meier estimate: 37.1%), and this approach might better reflect the occurrence of non-adherence in a more general fashion. In this study, poor treatment response ($p<0.001$) and low medication adherence ($p=0.02$) were independent predictors of discontinuation against medical advice, and ongoing substance abuse, ongoing depression, and treatment response failure significantly predicted poor medication adherence ($p<0.01$) (21).

FACTORS CONTRIBUTING TO NON-ADHERENCE

There are many factors associated with potential non-adherence (17,36), summarized in Table 4. Physicians

usually spend an inadequate amount of time assessing these factors, and patients do not generally communicate their intentions regarding medication-taking to clinicians. There is not a non-adherent personality type, and there is no standardized, universally valid and reliable approach to predicting adherence behavior. Race, sex and socio-economic status are not consistent predictors of poor adherence (1). It is also important to recognize that non-adherence is not necessarily irrational or misguided behavior. Non-adherence is highly influenced by patient knowledge, attitudes towards their illness and the medication, as well as past experiences with their illness and its treatment. In particular, the perceived risks and benefits of the treatment and of the illness (i.e., "illness insight") play a major role in adherence behaviors. Furthermore, lack of support systems and fragmented health care contribute to non-adherence.

In the case of individuals with psychotic disorders, there are a number of unique challenges. Lack of insight or lack of awareness of the illness itself (17,21) is a particular challenge in schizophrenia. In addition, the cognitive impairment frequently seen in psychotic disorders and present to some degree in a majority of individuals with schizophrenia is another important factor (37-39). Although adverse effects of medication are often assumed by clinicians to be a major predictor of non-adherence, the results of patient surveys vary, and some specific adverse effects have more impact than others. In addition, no doubt some patients discontinue medication because of adverse effects that they might not even identify as such. Akinesia, for example, might not be identified by the patient as an adverse effect of medication, as might also be the case with akathisia. Even clinicians can fail to recognize or misdiagnose these phenomena (40).

Although clinicians might underestimate its impact, inadequate response to treatment, even as early as two weeks after initiation of pharmacotherapy (41), is one of the most frequent reasons for discontinuing clinical trials. The complexity of the prescribed regimen has also been shown to influence adherence (17). Although clinicians and pharmaceutical companies are aware of the need to simplify regimens, this remains a problem for many patients.

Patients might also suffer from lack of information as to what to expect from treatment in terms of the risk of specific side effects, time course of response, or degree of impact that a treatment might have in specific domains. The nature and extent of psychoeducation coupled with an optimum therapeutic alliance has been found to be an important predictor of adherence behavior (17,38). Shared decision-making is a concept which incorporates these elements (42).

Cost and overall access remain obstacles in many cases, and the transition from inpatient to outpatient care or the transfer from one provider/payer to another can impact both access and cost to the patient. These problems might be included under the rubric of inadequate discharge planning or inadequate clinical follow-up (17,21,43).

Stigma has also been associated with non-adherence in schizophrenia (44). Although progress has been made in altering perceptions about this illness, the public at large remains poorly informed and stigma remains a major problem.

A particular problem among early phase patients and those who have had a generally good response to treatment is the belief that treatment is no longer necessary. The treatment of asymptomatic disease is always a challenge, but in psychotic disorders this is a particular problem. In addition, among patients in stable remission from symptoms, the time course of relapse is such that medication discontinuation might not result in an exacerbation or relapse for many months (or even years) and this can contribute further to a false sense of security that treatment is no longer necessary.

Some clinicians continue to suggest that those patients who discontinue medication and relapse as a result will be more convinced about the need for continuous treatment. Robinson et al (39) reported on a group of first episode patients who had experienced a relapse due to drug discontinuation, but then went on to discontinue medication yet again after recovering from the prior relapse. A history of significant extrapyramidal side effects during the index admission as well as poorer cognitive function and social educational background were significant predictors of medication discontinuation in this context (39).

It is also important to recognize that adherence can vary across the multiple medications that a patient might be taking. Decisions regarding each medication might be influenced by different factors, such as the awareness of what each specific drug is intended to do. As indicated in Table 4, there are also characteristics of the medication that should be considered. Patients' perception/experience of medication efficacy is an important element. However, in a complex disease such as schizophrenia, medication might be efficacious in one domain (e.g., positive symptoms), but much less so in another domain (e.g., negative symptoms and/or cognitive dysfunction). Patients need to understand what degree of improvement and in which domains they should expect.

Similarly, adverse effects vary from medication to medication and will also be influenced by the phase of illness, with drug-naïve or early phase patients being more sensitive to many side effects. The formulations that are available (e.g., liquid, fast dissolving, long-acting injectable), as well as the number of doses required per day, are also important factors in influencing adherence.

Provider/system characteristics are also to be considered. They include the amount of time devoted to assessing factors that might influence adherence, providing psychoeducation (to both patients and families if appropriate), and creating an atmosphere of shared decision-making and therapeutic alliance. Frequency and continuity of care and the ability of clinicians to monitor adherence using the various

methods discussed previously are also important.

The availability of case managers, health coaches and/or peer counselors can also be valuable in facilitating adherence. Another potentially influential domain is family/caregiver characteristics. The extent to which these parties are involved in helping to manage the illness and the amount of psychoeducation that they have received is also important. Clinicians should attempt to understand and take into consideration their knowledge, beliefs and attitudes as well as the nature of their relationship with the patient and their potential role in facilitating and monitoring medication taking.

THE ROLE OF INTERVENTIONS TO IMPROVE OR MAINTAIN ADHERENCE

Traditionally, psychoeducation has been the main strategy to improve adherence, but new psychosocial approaches have been suggested. Needless to say, optimizing the pharmacotherapy is a critical step towards better adherence. Moreover, new technology may enable us to enhance it further. These psychosocial, pharmacological and technological approaches should supplement each other to maximize their potential effect.

Psychosocial interventions

Various psychosocial interventions have been proposed and studied. Over 50 randomized controlled trials have been reported to date (45). Some examined a specific intervention as monotherapy, some examined the combination of two or more types of interventions (46). The target of the interventions varies and includes the individual, group, family, or community (such as assertive community treatment, ACT) (47). It is difficult to draw clear lines between interventions and to categorize them in specific groups, but the key components include psychoeducation, cognitive-behavioral therapy (CBT), and motivational interviewing.

Psychoeducation aims to teach patients or families to better understand the illness, appropriate medications and potential side effects. It targets individuals or patient groups, sometime families, and involves counseling sessions, and/or use of written/audiovisual materials. It has been the mainstay of strategies to improve adherence for years; however, the results of studies do not appear to be consistently positive. Studies examined psychoeducation without adjunctive components, such as behavioral intervention or family involvement, and showed that it was not efficacious in improving adherence (45-48). Nevertheless, psychoeducation provided together with family involvement seems to have better efficacy than when given to patients alone (48), and psychoeducation becomes more efficacious when other strategies are combined, such as environmental or behavioral interventions (45). A recent meta-analysis (44 trials, N=5142) included randomized controlled trials examining all didactic interventions of psychoeducation, such as programs addressing the illness from a multidimensional viewpoint, including familial, social, biological and pharmacological perspectives (but excluding interventions with elements of behavioral training, such as social skills or life skills training). In this meta-analysis, the incidence of non-adherence was lower in the psychoeducation group (49).

CBT is a psychotherapeutic approach that challenges patients' cognitive processes and maladaptive behaviors through goal-oriented, explicit procedures. In CBT, adherence is conceptualized as a coping behavior based on an individual's perception of the illness and his/her beliefs about medications (46). CBT therapists help patients identify and modify negative automatic thoughts about medications and use guided discovery to strengthen patients' beliefs that taking medication is associated with staying well and achieving goals (36,50).

Motivational interviewing is a semi-directive, client-centered counseling style used to enhance behavior change by helping clients to explore and resolve ambivalence (51). This technique, which was originally developed for treating addiction, has been applied to a broad range of patients in order to assess their level of motivation to adopt medication-adherent behaviors. In motivational interviewing, the clinician tailors the intervention to the patient's current level of motivation. Clinicians try to better understand patient's perspective through expressing empathy, supporting self-efficacy in an unwavering manner, highlighting discrepancies between the patient's current health behaviors and core values, and working with resistance. Patients may then be better able to identify their own solutions to potential barriers to medication adherence. The process includes five phases, consisting of pre-contemplation, contemplation, preparation, action and maintenance (52).

Various interventions combining the components mentioned above have been developed, and their efficacy in improving adherence has been examined. Compliance (adherence) therapy is a form of CBT which incorporates motivational interviewing and psychoeducation to help patients understand the connection between relapse and medication non-adherence (53). Some studies have shown the efficacy of compliance therapy to improve insight, treatment acceptance, and adherence (54-56), but others have not (57,58). Other psychological interventions with positive results include adherence-coping-education (ACE) (59), interpersonal and social rhythm therapy (60), and cognitive adaptation training (CAT) (36). CAT is a strategy that uses individually tailored environmental supports such as signs, checklists and electronic devices to cue adaptive behaviors in the patient's home environment and help compensate for cognitive deficits. CAT significantly improved adherence and reduced relapse compared to treatment as

usual in patients with schizophrenia (36). Such environmental support, needless to say, can help patients to be adherent to the medication, but programmatic interventions, such as ACT and intense case management (ICM), are also reported to be effective. For example, meta-analyses which examined ACT and ICM showed that each intervention was more efficacious in retaining patients in contact with services and preventing hospitalization than standard community care (61,62).

Thus, studies have examined various interventions that are sometimes similar, or that combine multiple approaches. Results are mixed, but interventions specifically designed to improve adherence with a more intensive and focused approach, and interventions combining several strategies, such as CBT, family and community based approaches, have shown more consistently favorable results (45).

Pharmacologic interventions

Drug treatment should always be carried out trying to balance efficacy and adverse effects. Clinicians have to optimize the recommendations by taking into consideration the treatment history, response, comorbidity, side effects, etc. Side effects should be avoided as much as possible by drug choice or dose adjustment, but adding another class of medication, such as anticholinergics for extrapyramidal side effects, can also be an option. Most importantly, patients should be given sufficient information about the medication and be part of the decision making process (63).

Pharmacological strategies which may enhance adherence include switching, dose adjustment, treating side effects, simplifying the treatment regimen, and the use of long-acting injections. Simplifying the medication regimen can be helpful especially for patients with cognitive impairment. A study examined this issue and found that decrease in dosing frequency helped patients to be more adherent. Using a US Veterans Administration data base, Pfeiffer et al (64) examined the medication possession ratio among patients with schizophrenia. Patients who had a decrease in dosing frequency (N=1,370) had a small but significant increase in mean ratio compared with patients (N=2,740) without a dosing frequency change ($p<0.001$). However, patients who were already in simple and stable regimens did not seem to benefit from further simplification. There were no significant differences between those receiving once-daily dosing and those receiving more than once-daily dosing (64).

The development of long-acting injectable (LAI) medication was intended to facilitate the benefits of pharmacological treatment by reducing the all-too-likely variability in ingestion. Major guidelines (36,65-68) recommend the use of LAIs when non-adherence is an issue. LAIs offer not only "guaranteed" medication delivery, but also other potential advantages, such as immediate awareness of non-adherence, no abrupt decline in blood level after a missed injection, freedom from daily medication and reducing concerns about medication adherence as a source of family conflict or tension (69).

Thus, LAIs are intended to facilitate adherence and thereby reduce relapse rates. However, the results from recent, large, randomized controlled trials have been discouraging. Rosenheck et al (70) conducted a federally funded trial and reported that risperidone-LAI was not significantly superior in preventing hospitalization compared to clinicians' choice oral antipsychotics. Similarly, in a study comparing risperidone-LAI with any oral antipsychotic, Schooler et al (71) did not find a significant difference between the two treatment groups. A recent meta-analysis based on 21 randomized controlled studies (including the two studies mentioned above) found that LAIs were not significantly superior to oral antipsychotics (N = 4,950, risk ratio=0.93, 95% CI: 0.80-1.08, p=0.35), both in primary analyses and across multiple secondary analyses (35).

However, the results from randomized controlled trials are in strong contrast to some naturalistic studies. For example, Tiihonen et al (72) reported in a nationwide Finnish cohort that the risk of rehospitalization with LAIs was one-third that of oral antipsychotics. Moreover, most LAIs showed significant superiority compared to each oral counterpart regarding all-cause discontinuation.

Mirror-image studies, which compare the periods pre- and post-LAI introduction within subjects, are another way to examine the efficacy of LAIs. In a recent meta-analysis based on 25 mirror-image studies (N=5,940), Kishimoto et al (73) reported that LAIs showed strong superiority over oral medication in preventing hospitalization (16 studies, N=4,066, risk ratio= 0.43, 95% CI: 0.35-0.53, $p<0.001$) and decreasing the number of hospitalizations (15 studies, 6,396 person/years, rate ratio=0.38, 95% CI: 0.28-0.51, $p < 0.001$).

Given such a discrepancy of the results between randomized controlled trials, nationwide cohort studies and mirror-image studies, a question arises as to what is the best way to assess LAI effectiveness in comparison to oral medication. As mentioned before, participants in clinical trials might over-represent patients with better adherence to treatment, lower illness severity, and better cognitive capabilities. Perhaps most importantly, participation in a clinical trial can have a substantial impact on adherence. At the same time, non-randomized, open, naturalistic or mirror-image studies can have their own limitations, such as selection bias, expectation bias, and time effect. Therefore, we need to be thoughtful about how to best use evidence from multiple types of trial design as well as measurement of adherence and non-adherence related outcomes. Generalizability of study results should be a major goal. Studies with a design which is different from randomized controlled trials may more accurately represent the patient population that is most likely to be

prescribed LAIs in clinical practice, i.e., patients with adherence issues.

CONCLUSIONS

Non-adherence is frequent across all domains of medicine. However, patients with psychotic disorders pose additional challenges that increase the risk for and frequency of non-adherence. Although of great importance for treatment outcomes, clinicians generally spend too little time on discussing and addressing adherence attitudes and behaviors. Importantly, the method of adherence measurement significantly impacts the results, and the most frequently employed methods of asking patients or judging adherence indirectly, based on efficacy or tolerability information, have poor validity. Novel technologies are being developed that directly assess adherence and can both provide real-time feedback to clinicians and be used as an intervention with patients.

A number of treatment strategies have already been developed and tested that can positively impact adherence. Among psychosocial interventions, those combining multiple approaches and involving multiple domains seem to yield the best outcomes. Although LAIs are theoretically a very powerful tool to assure adherence and signal non-adherence, recent results from randomized controlled trials have failed to show superiority of LAIs compared to oral antipsychotics. These data are in contrast to nationwide cohort studies and mirror-image studies, which involved real-world patients prescribed LAIs in clinical practice. This disconnect suggests that traditional randomized controlled trials may not necessarily be the best way to study interventions that are thought to work via reducing non-adherence. Rather, we should consider large, simple randomized trials that enroll populations representative of patients who would be eligible for LAI treatment in clinical settings, and that change the ecology of the treatment delivery and patient contact as little as possible compared to usual care conditions.

Clearly, non-adherence is a major public health problem that is likely to continue despite treatment advances. However, more clinical and research emphasis should be put on finding better solutions for the identification and management of treatment non-adherence, particularly in patients with psychotic disorders.

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