A SYSTEMATIC REVIEW ON PHARMACEUTICAL TREATMENT OF SCHIZOPHRENIA AND INTELLIGENCE RETRIEVAL

Saumya Das*[1], Madhvi Singh[1], Avijit Mazumder[1], Deepika Pathak[1], Navneet Khurana[2], Prathibha Pandey[3]

[1]Noida Institute of Engineering and Technology, (Pharmacy Institute) Knowledge Park-II,

Greater Noida, UP 201306, India

[2] Lovely Professional University, Phagwara, Punjab, India

[3]Department of Biotechnology, Noida Institute of Engineering and Technology, Knowledge Park-II, Greater Noida, UP 201306, India

Corresponding Author Email: awasthi.saumya22@gmail.com

ABSTRACT

According to a recent study, schizophrenia patients who fail to comply with their medication regimens may have thoughts of suicide, increased resource utilization, such as hospitalization and associated expenditures, and clinical deterioration. This study will conduct a comprehensive review of therapies aimed at promoting treatment adherence among schizophrenia patients, with an emphasis on the evidence gained from their testing. Numerous therapies have concentrated on the drug, patient, and clinical service-related elements of treatment nonadherence. Several examples include LAI pharmaceutical formulations, behavioral therapy, and technology-assisted methamphetamine. LAI antipsychotics and behavioral strategies for integrating medication use into daily routines with electronic monitoring have been carefully examined. Although it is rare to see artificial intelligence (AI) implemented into mobile applications such as medicine tracking systems and voice assistants, the results of these experiments have been mixed at best. Patients with schizophrenia, who are notoriously difficult to treat, require randomized, controlled, blinded trials employing clinically relevant samples to evaluate not just adherence, but also clinically meaningful and lasting treatment outcomes.

INTRODUCTION

Since schizophrenia is a chronic and disabling condition, a complete treatment strategy that involves antipsychotic medication is required [1–3]. A recent study found that discontinuing such psychopharmacological therapy increased clinical deterioration rates by five times in persistently

psychotic individuals [4] and raised suicide risk by more than a dozen times [5]. Noncompliance with antipsychotic drug therapy prescribed by a doctor is linked to an increased risk of hospitalization, deterioration of overall health and wellbeing, and higher healthcare costs. It is also linked to a possible loss of responsiveness to restarted therapy if the patient does not adhere to therapy [6,7]. On the other hand, prolonged long-term antipsychotic medication has been linked with a significant reduction in overall mortality and clinical improvement [8]. Antipsychotic medication errors or nonadherence are quite prevalent. Its prevalence has been estimated to vary from 20% to 89 percent among patients treated with oral formulations [9], with a median incidence of 55% [7]. The underlying cause of this issue is complicated and multifaceted, comprising I drug-related variables, (ii) patient characteristics, and (iii) the form of professional services given [3,10–12]. Adherence to therapy is influenced by medication-related variables such as formulation, dose, and complexity of drug regimens, as well as side effects and tolerability. Forgetfulness, disorientation, psychosis, co-occurring depression, and other illness-related variables, as well as poverty, illiteracy, and inconsistent access to prescribed medications, have all been linked with impaired treatment adherence in schizophrenia patients [3]. Severely symptomatic disease and co-occurring drug usage issues are also related to poor adherence to recommended therapy, resulting in a loop of decreasing treatment efficacy and clinical deterioration [1,13]. Although poor adherence to antipsychotics in the past is often related to future deterioration, one research indicated that 40% of schizophrenia patients received insight into the critical need for continuous therapy after suffering worsening of the disease after discontinuing medication [14]. As a result, a lack of awareness of one's illness and worries about stigma might impede acceptance of treatment [14], as does exposure to unpleasant side effects of antipsychotic medications and their resolution upon discontinuation of the medication [1,15]. On the other hand, a good therapeutic alliance with clinicians within responsive and supportive clinical care systems that give social support and encouragement, as well as family engagement, may all contribute to treatment adherence [16]. Additionally, as discussed below, technical interventions aimed at promoting adherence, such as pill organizers and reminders such as missed-dose alarms, activity checklists, and the regular clinician or pharmacy-based telephone calls, may all assist in integrating medicine-taking into a daily routine [9,17]. Numerous initiatives have facilitated early study support but have not been properly studied adequately [3,10–13]. Early detection and monitoring of medication non-adherence are commonly regarded as critical for maintaining long-term antipsychotic therapy in schizophrenia patients. Nonetheless, estimating non-adherence practically and accurately remains a challenge in clinical practice and is a subject of ongoing study [6,18]. Due to the critical nature of treatment adherence in achieving optimal clinical outcomes in the treatment of schizophrenia, this overview discusses recent research on factors affecting drug adherence and evaluates methods for increasing adherence to prescribed antipsychotic medications in patients diagnosed with schizophrenia.

MEASURING DRUG-TREATMENT ADHERENCE IN SCHIZOPHRENIA

The definition of treatment nonadherence, and methods used for its assessment, can affect results of clinical research aimed at evaluating adherence [7]. Treatment nonadherence involves a variety of patient behaviors, ranging from treatment refusal to irregular use or altered dosing (underuse or

overuse), either intentional or unintentional. Accurate assessment of nonadherence is challenging but essential in clinical practice as well as for experimental therapeutics research, particularly with such difficult-to-treat disorders like schizophrenia [6,18]. Several objective and subjective methods of doing so have been proposed and partially evaluated [20]. Objective methods include directly observing patients ingesting pills, patient treatment diaries, periodic pill-counting, and electronic monitoring techniques, as well as assaying concentrations of drugs or their metabolites in body fluids (therapeutic drug monitoring [TDM]). Subjective methods include asking patients to rate their medicine-taking, use of self-report or clinician questionnaires, and assessing treatment response by clinical examination of symptomatic status and use of symptom rating scales [20]. Although objective measures are preferable for assessing treatment adherence, their use has yielded inconsistent results in that correlations between different objective measures are not always concordant, and can be influenced by many clinical and technical factors [15,21,22]. Subjective measures typically appear to be biased toward overestimating adherence [21]. A recent systematic review found that subjective measures (patient and clinician-rating scales) are widely used to assess treatment adherence in schizophrenia patients but questioned their validity and reliability. Nevertheless, at least three largely subjective methods have demonstrated preliminary evidence of substantial validity, reliability, and sensitivity in such patients. They include the Episode-Specific Approach (ESA), the Brief Adherence Rating Scale (BARS), and the Medication Adherence Rating Scale (MARS) [20,21]. Among objective measures, simple pill-counting [22] as well as electronic monitoring with devices and reporting mechanisms for keeping track of medicine-access. Such methods include a *Medication Event Monitoring System*, a medicine bottle-cap with a microprocessor that records the occurrence and timing of each bottle opening, but not necessarily pill-taking [22,23]. Limitations of such methods include confounding by discarding of medicine, and failure to document actual ingestion [18]. In addition, patients, particularly those with chronic psychotic illness, may not follow the required instructions faithfully. Also, some electronic monitoring methods are relatively costly and may not be suitable for many community settings [21,23]. Pill- counts, and self-reports are simpler, inexpensive methods but, again, can overestimate adherence [23]. Assays of circulating drug concentrations are useful to document that some drug-ingestion has occurred. However, they can be considered somewhat intrusive and are affected by individual differences in drug metabolism and pharmacokinetics, and the timing of blood sampling [24]. Generally, the use of rating scales and other measurement-based approaches in routine clinical psychiatry care remains limited due to time constraints and lack of familiarity or training with assessment tools that are adequately validated to support the assessment of treatment adherence [25]. In the present overview, we sought to define and evaluate techniques used to evaluate treatment adherence as an outcome measure, as well as interventions aimed at improving treatment adherence. The findings are organized by the type of intervention tested for its effects on treatment adherence among patient-subjects diagnosed with schizophrenia by standard criteria.

DRUG-RELATED RISK FACTORS

Drug-related factors that contribute to poor or erratic adherence to prescribed oral antipsychotic drug treatment include insufficient perceived benefit, particularly compared to unpleasant adverse effects of some medicines in individual patients, as well as the use of excessive doses or

unwarranted complexity of drug combinations and dosing schedules. A widely studied approach to limiting some of these sources of nonadherence has been to rely on the use of long-acting injected preparations of effective antipsychotic medicines.

LONG-ACTING INJECTED ANTIPSYCHOTICS

A growing list of *long-acting injectable* (*LAI*) antipsychotics appears to be a potentially effective option for improving treatment adherence. Such preparations were introduced as the decanoate esters of fluphenazine and haloperidol several decades ago [1], and now include several modern SGAs [26]. However, these drugs remain largely underutilized in many cultures, and they can be relatively expensive, including costs of extra facilities and staff as well as the drugs themselves. In the US, only 15%–28% of schizophrenia patients receive LAI antipsychotics, and only about 40% of European clinicians would consider an LAI antipsychotic as an initial treatment for psychotic illness [26]. Moreover, social attitudes and patient perceptions, and fears about the use of LAI medicines, as well as the continued presence of subjectively distressing adverse effects and concerns about the risk of severe adverse effects with treatment that cannot be discontinued rapidly, all can limit their acceptance. Nevertheless, there is growing evidence that the use of LAI antipsychotics, especially SGAs [11,27], can improve treatment adherence and may also improve clinical responses in schizophrenia patients, based on comparisons with orally administered medicines (Table 1). Most of the available research on this topic has involved retrospective or 'mirror-image' (within-subject comparisons during vs. before use of LAI drugs) analyses of treatment adherence, and variable assessment of clinical changes, rather than prospective, randomized trials, especially involving subjects with established poor treatment adherence. Estimates of treatment adherence in such studies have involved database-derived indices, including discontinuation rate (gap in the availability of medicine based on prescription refills, e.g., for >60 days), counts of lapsed prescription refills per time, latency to discontinuation, the proportion of days covered (putative medicine-availability) by prescriptions (putative medicine-availability), the average duration of prescription refill cycles, and medication possession ratio (MPR) of drugs (an estimate of the proportion of time with drug available, though not necessarily taken) [2,28–47]. Unsurprisingly, most studies report significantly higher adherence with LAI than with orally administered antipsychotics of various types (Table 1). Reported adherence rates with LAI antipsychotics were 68%–81%, compared to only 24%–52% with orally administered antipsychotics (Table 1). Similarly, discontinuation rates and MPR-based estimates of medicine availability were significantly more favorable for LAI compared to oral formulations of various first – and second-generation antipsychotics (Table 1). One finding of superior adherence with LAI vs. oral antipsychotics evaluated adherence with oral medication by use of the Medication Event Monitoring System (MEMS) which records timing and counts of medicine container openings, but not actual pill-taking [28]. Interestingly, in another study, adherence with oral formulations was found to increase when merely combined with an LAI antipsychotic in subjects with early psychosis (75% vs. 32%) [45]. This association might reflect the increased frequency of contacts between patients and clinicians and nurses associated with the administration of LAI antipsychotics during more regularly timed visits to mental health facilities, or with improved mental health provided by the injected medicine. An important consideration regarding LAI vs. oral antipsychotic drug treatment is relative effectiveness regarding clinical outcomes, as it is for all interventions aimed at enhancing treatment adherence. A growing number of retrospective studies, as well as randomized controlled comparison trials, have been reported, with far more tests of clinical effectiveness than with

other interventions considered in this report. Generally, differences in clinical effectiveness between LAI and orally administered antipsychotics have been much larger in mirror-image studies than in prospective, randomized trials [42,48]. Of note, in a total of 21 randomized, prospective comparison trials, we found the sparing of major clinical exacerbations in schizophrenia patients to be quite variable among trials (I2 score = 63%), and, surprisingly, that prevention of illness-exacerbations, overall, was not significantly superior with LAI preparations (OR = 0.830 [CI: 0.642–1.07]; z-score = 1.42, p= 0.155) [27,28]. Nevertheless, some randomized trials have found substantially greater clinical benefits with LAI over oral antipsychotic treatment [35,37].

The basis of observed differences in relatively favorable outcomes of retrospective or mirror-image studies (behavior before vs. during an intervention such as treatment with an LAI antipsychotic) than in prospective, randomized trials is not clear. Some RCTs aimed primarily at testing treatment effectiveness rather than treatment adherence may be subject to selection bias involving exclusion of participants with a history of poor treatment adherence or other factors that may tend to compromise treatment responsiveness, such as substance abuse and other co-occurring psychiatric illnesses. In addition, mirror-image comparisons may be biased toward favorable outcomes by expectations of a novel intervention by both subjects and investigators when the intervention is known, and perhaps, especially if study participants are selected for past treatment nonadherence.

Table 1. Adherence to treatment with long-acting injectable vs. oral antipsychotics

Report	Design	Drugs (n)	Subjects(n)	Adherence Measure	Outcome
Kishimoto et al. 2014 [34]	Metan	FGA-LAIs SGA-LAIs OAs	955 LAIs 1063 OAs	All-cause dc	dc: LAIs = OAs
Alphs et al. 2015 [35]	RCT	LAI-PAL OAs	226 LAI – PAL 218 OAs	MPR; dc rate (& latency)	MPR: LAI>OAs (40%/24%); dc rate: LAI<OAs
Marcus et al. 2015 [36]	Retro	FGA-LAIs SGA-LAIs OAs	157 FGA LAIs 183 SGA LAIs 3428 OAs	PDC; Rx gap ≥60d	PDC: LAIs>OAs; PDC: SGAs>FGAs
Subotnik et al. 2015 [37]	RCT	RSP-LAI RSP-OA	27 RSP-LAI 30 RSP-OA	All-cause dc	RSP-LAI = RSP-OA
Pilon et al. 2017 [38]	Retro	SGA-LAIs OAs	3307 SGA-LAIs 21,355-OAs	PDC	PDC: LAIs>OAs
Verdoux et al. 2017 [39]	Retro	FGA-LAIs SGA-LAIs OAs	104 FGA LAIs 184 SGA LAIs OAs	All-cause dc	dc rate: LAIs<OAs
Vincent et al. 2017 [40]	Metan	LAI-PAL OAs	114 total	MPR	MPR: LAI>OAs (81%/43%)

Greene et al. 2018 [41]	Retro	FGA-LAIs SGA-LAIs OAs	927 FGA-LAIs 1934 SGA-LAIs 2777 OAs	PDC or ≥60-day Rx-gap	Adherence LAIs>OAs by 5%; Discontinue: LAIs<OAs by 20%
Kishimoto et al. 2018 [42]	Metan	FGA-LAIs SGA-LAIs OAs	562 FGA LAIs 3773 SGA LAIs 32,258 OAs	All-cause dc	dc: LAIs<OAs
Shah et al. 2018 [43]	Retro	LAIs OAs	2302 LAIs 2302 OAs	PDC dc; dc rate	PDC: LAIs = OAs; dc rate: LAIs<OAs
Suzuki et al. 2018 [44]	Obs	SGA-LAIs PP-OA	406 SGA-LAIs 432 PP-OA	All-cause dc & time to dc	dc rate: SGA-LAIs = PP-OA Dc latency: SGA-LAIs>PP-OA
Titus-Lay et al. 2018 [45]	Retro	FGA-LAIs SGA-LAIs OAs	35 OAs 4 SGA LAIs	PDC; Lack of Rx-gap	Adherence: LAIs>OAs (76%/32%)
Yan et al. 2018 [2]	Retro	APZ-LAI OAs	408 APZ-LAI 3361 OAs	PDC; d/c rate & latency	PDC: LAI>OAs dc rate: LAI<OAs
Song et al. 2019 [46]	Retro	SGA-LAIs OAs	6344 LAIs 7029 OAs	≥60-day Rx-gap	Persistence: SGA-LAIs>OAs
Yoshimatsu et al. 2019 [47]	Obs	LAIs OAs	77	Rx duration	Adherence: LAIs>OAs

AAs, antipsychotic drugs; d, days; dc, discontinuation; FGA, a first-generation antipsychotic; LAI, a long-acting injectable antipsychotic; MEMS: Medication Event Monitoring System; Metan, meta-analysis; MPR: Medication Possession Ratio; OA, an oral antipsychotic; Obs, observational study; PDC, percentage of days covered by filled prescriptions; Pros, prospective; PP, paliperidone; RCT, prospective, randomized controlled trial; Retro, retrospective; RSP, risperidone; Rx, prescription; SGA, second-generation antipsychotic. Note that 16/21 studies (76.2%) found evidence of better treatment adherence with use of LAI antipsychotics: 12/14 (85.7%) of observational or retrospective studies, 4/7 (57.1%) of RCTs or meta-analyses ($x2 = 2.10$, $p= 0.15$).

COUNTERING OTHER DRUG-RELATED FACTORS

Among antipsychotic drug-related factors that contribute to treatment nonadherence, lack of perceived clinical benefit, adverse effects, past negative experiences with similar treatments, and complexity of drug regimen (multiple drugs and doses/day) all appear to degrade treatment adherence [7,16,18]. We were unable to identify studies that evaluated specific interventions aimed at increasing adherence by modifying such commonly clinically encountered factors. Nevertheless, the sound clinical practice includes moderate dosing with as few drugs given as few times a day as possible [1]. Moreover, patients should be informed about potential adverse effects, and they require ongoing monitoring and intervention to minimize the impact of unpleasant effects [1,7]. Although combinations of antipsychotics might be beneficial in some circumstances [49], such polytherapy has rarely been adequately evaluated for safety and efficacy in direct comparison to optimized monotherapy. Moreover, the use of multiple

medicines can produce confusion about dosing, increase the risk of adverse effects, costs, and further compromise treatment adherence [1,7]. A recent meta-analysis comparing effects of regimens with single vs. multiple antipsychotic drugs found that combination treatments were associated with reduced risk of psychiatric hospitalization compared to monotherapies, with the single exception of the use of clozapine alone [49]. However, that study did not specifically evaluate treatment adherence concerning treatment complexity.

LACK OF INSIGHT

Ongoing symptoms of psychotic illness, insight, attitude toward medicines, and ability to reflect on previous experiences can affect treatment adherence in schizophrenia patients. In a recent qualitative study aimed at identifying patient-perceived factors associated with nonadherence, denial of having a mental illness was a prevalent finding, especially early in the course of psychotic illness [3]. The same study also found that ability to recall earlier distressing symptoms present before treatment, and their improvement with treatment was associated with better treatment adherence [3]. Similar conclusions arose from a meta-analysis of factors associated with treatment adherence in 1154 patients included in two large clinical trials, with the additional finding that co-occurring substance abuse also was associated with poor treatment adherence among schizophrenia patients [13]. Insight into having an illness also was linked consistently to better adherence in other studies [15,50]. Insight itself is a complex phenomenon likely to be related to symptom-severity, neurocognitive functioning, perceived stigma, and other factors associated with psychotic illness [1 6]. Studies of several types of psychosocial interventions have included the aim of increasing insight, self-reflection, and a positive attitude toward treatment. Their results have been heterogeneous (Table 2) [51–64] as is reviewed in the next section.

PSYCHOSOCIAL INTERVENTIONS

In recent decades, several psychosocial interventions have been evaluated for effects on treatment adherence among schizophrenia patients. These include motivational interviewing, adherence therapy, and psychoeducation for both hospitalized and ambulatory patients (Table 2) [51–64]. Motivational interviewing is a patient-centered, directive method aimed at enhancing motivation to change by exploring and resolving ambivalence about both diagnosis and treatment [46]. It was originally designed for patients with alcohol and drug abuse. Adapted for patients with psychotic disorders, it has been tested in two small, controlled trials with mixed results (Table 2) [53,61]. Adherence therapy is a brief intervention based on principles arising from both motivational interviewing and CBT, seeking to facilitate collaborative decision-making between patients and clinicians, in a process intended to make decisions about the treatment more meaningful and engaging to patients [55]. Its techniques include shared problem-solving regarding treatment, exchanging information, exploring ambivalence, and evaluating beliefs about the pros and cons of antipsychotic treatment [55]. Several controlled trials of adherence therapy have reported inconsistent effects on treatment adherence, although relatively favorable improvements in adherence were found with longer treatment over 12–18 months (Table 2) [51,52,54–56,58,62]. Outcomes varied with methods of assessment, including greater benefits as

measured with the relatively specific Adherence Rating (ARS) and Medication Adherence Rating (MARS) scales than with the broader, 30-item Drug Attitude Inventory (DAI-30) (Table 2).

Psychoeducation involves structured educational programs that consider the etiology, symptoms, treatment, and prognosis of particular psychiatric disorders with patients and families and can be applied individually or in groups. It aims to help patients to realize and accept having an illness, foster motivation to improve the situation and increase self-esteem by strengthening- ing understanding and management of the illness by patients and their families [63]. Such interventions have been evaluated recently in at least four trials of various designs [57,59–66]. All of these studies reported improved medication adherence to follow- ing a program of a group or individual psychoeducation, but the persistence of the benefits is uncertain as follow-up assessments were for only 1–12 weeks.

Report	**Method**	**Design**	**Setting**	**Subjects (n)**	**Sessions & Months**	**Final Months**	**Adherence Measure**	**Outcome**
Anderson et al. 2010 [51]	AT	RCT	OPD	12 AT 14 TAU	8 2.0	2.0	PETiT	AT = TAU
Staring et al. 2010 [52]	AT	RCT	OPD	53 AT 52 TAU	—— 6.0	12	Interview	AT>TAU
Barkhof et al. 2013 [53]	MI	RCT	OPD (nonadherent)	55 MI 59 TAU	8 6.5	12	MAQ DAI	MI = TAU
Schulz et al. 2013 [54]	AT	RCT	OPD (newly dc)	80 AT 57 TAU	8 ——	3.0	CDR MARS DAI-30	AT = TAU
Chien et al. 2015 [55]	AT	RCT	OPD	57 AT 57 TAU	8 4.0	6.0	ARS	AT>TAU
Von Bormann et al. 2015 [56]	AT	RCT	OPD (newly dc)	38 AT 32 TAU	8 ——	6.5	DAI-30	AT = TAU
Abdel Aziz et	IP	QE	Inpatients	82 IP	5	1.5	Pill-count	IP>TAU

al.								
2016 [57]			to dc	39 TAU	—–		Rx diary	
Chien et al. 2016 [58]	AT	RCT	OPD	67 AT 67 TAU	6 3.0	18.0	ARS	AT>TAU
Yanagida et al. 2017 [59]	GP	Open	Hospitalized	70 GP	6 —–	0.25	DAI-10	DAI-10 score improved
Cetin & Aylaz 2018 [60]	MGP	RCT	OPD	55 MGP 80 TAU	8 1.0	1.0	MARS	MGP>TAU
Ertem et al. 2018 [61]	MI	RCT	OPD	20 MI 20 TAU	6 —–	6.0	MAS	MI>TAU
Chien et al. 2019 [62]	AT+MI	RCT	OPD (nonadherent)	67 AT+MI 67 TAU	6 3.0	12	ARS	AT+MI> TAU
Tatu et al. 2020 [63]	GP	QE	OPD	24 GP 21 TAU	8 —–	3.0	MARS	GP>TAU
Yildiz et al. 2020 [64]	ACT+ MI	QE	OPD	36 MI+ACT 51 TAU	8 —–	2.0	Interview	Motivation: ACT+MT >TAU

BEHAVIORAL INTERVENTIONS

Given the inconsistent or inconclusive results of the preceding psychosocial interventions, several individually tailored behavioral strategies have been developed to foster the incorporation of medicine-taking into the daily routines of schizophrenia patients [3,17,65]. These interventions include the use of environmental supports, such as pharmacy-based or telephone reminders, financial or other reinforcements, electronic monitors, and mobile phone applications (Table 3) [17,66–76]. One of these, Cognitive Adaptation Training (CAT), uses environmental supports such as signs, labels, specially designed pill- containers, and checklists; a related method, PharmCAT (Pharmacological Cognitive Adaptation Training), targets adherence with personalized approaches maintained in weekly 30– to 45-min home visits from a specially

trained therapist. These techniques have been evaluated in at least two controlled trials in recent years [70], with favorable findings of uncertain duration (Table 3). Pharmacy for schizophrenia patients resulted in significantly increased adherence to medication, compared to running-domized treatment-as-usual (TAU), or to use of an electronic medication monitor (eMM) that prompts scheduled self-medication and warns when the wrong medication is taken or at the wrong time and alerts treatment staff of such lapses [70]. Both of these in-person (PharmCAT) and electronic (eMM) interventions increased adherence by as much as 92%, as measured with an electronic monitor [70]. Conversely, the use of these methods without clinician support did not yield increased adherence at four-month follow-up compared with giving a manual to family caregivers aimed at encouraging their general support of the patient's treatment [76].

Another pharmacy-based intervention, Meds-Help, consists of individualized, unit-dose packaging of medicine, an educational session, reminders to refill prescriptions mailed to patients, and notification of prescribing clinicians when patients failed to fill a prescription on time. This method was evaluated in a controlled trial not included in Table 3 as it enrolled patients diagnosed with disorders other than schizophrenia [77]. It found evidence of significantly increased treatment adherence at 12-month follow-up compared to standard clinical care. Even LAI antipsychotics can have imperfect adherence since regularly scheduled visits to a clinic are required for injections. Financial incentives to increase treatment adherence with LAI antipsychotics rather than orally administered drugs have been evaluated in two controlled trials (also not included in Table 3 as some participants were diagnosed with bipolar disorders). Both found significantly greater adherence than without the added incentives [78,79]. Several RCTs evaluated treatment adherence in patients given telephone-based interventions or not in addition to TAU. In one, unstructured weekly telephone reminders by nurses targeting treatment adherence and attitudes toward medicines were evaluated in a trial involving 847 schizophrenia outpatients. The intervention resulted in a highly significant, 97% increase in investigator-rated treatment adherence compared to TAU, sustained for at least 4 months [66]. Another trial involving 140 schizophrenia outpatients failed to find a significant effect at 2 months, based on self-reports with the MARS questionnaire [71]. Another manual-guided telephone-based intervention, Telephone Intervention-Problem Solving (TIPS), involves nurses trained to resolve a variety of difficulties in community living believed to affect treatment adherence [70,73]. This method was tested in three controlled trials (Table 3). A small trial involved 28 psychotic disorder outpatients randomized to receive weekly vs. daily TIPS telephone calls and found no significant differences in adherence (78%–85%) as evaluated with pill counts over 3 months [70]. Another trial with 105 schizophrenia outpatients also did not yield increased adherence based on pill counts but did find significantly increased proportions of subjects with serum drug concentrations considered to be within a therapeutic range over 6 months [73]. In a third controlled trial involving 46 schizophrenia outpatients, TIPS resulted in increased MARS ratings of adherence after 2 months of treatment [70].

A large, controlled trial evaluated the effectiveness of an intervention called LEAN (Lay health-supporter, E-platform, Award, and integration). It involves nonprofessional supporters and mobile texting for medication reminders, health education, and monitoring. It was tested in rural China with 271 schizophrenia outpatients [75]. After 6 months of treatment, pill- count-assessed

adherence was significantly increased with LEAN compared to TAU. An additional mobile phone-based cognitive-behavioral intervention, called MATS (Mobile Assessment and Treatment for Schizophrenia), was developed to improve treatment adherence, socialization, and specifically to reduce auditory hallucinations in schizophrenia patients. In a controlled trial, among 42 participants (of 55 entered) who completed 12 weeks of treatment, adherence measured by self-report text messages, improved significantly, but only among those able to live independently and to complete the intervention [67]. An individualized intervention focusing on adherence to antipsychotic drug treatment was evaluated in a randomized, controlled trial involving 60 hospitalized schizophrenia patients. The intervention employed individualized evaluation of challenges in achieving and maintaining treatment adherence, selection of an effective and tolerated antipsychotic drug, psychoeducation, motivational interviewing, and CBT in an average of six sessions. At the end of the treatment, adherence and attitudes toward medication were significantly improved compared to TAU, but long-term retention of the effect was not assessed [72]. Meaningful and quantitative comparisons of the several reported behavioral interventions are precluded by the dissimilar study designs, intensity, and duration of interventions, and measures of adherence employed. Moreover, acceptance of such interventions is likely to vary among individual patients, corresponding to their views of the interventions as interfering with their privacy and autonomy, and cooperation may fluctuate over time. Such considerations suggest that an individualized approach is required to balance patient preferences, along with ongoing efforts of their clinicians to reduce drop-out risk or treatment refusal.

Report	**Intervention Type**	**Study design**	**Setting**	**Subjects (n) & Interventions**	**Adherence Measure**	**intervention (mos)**	**Follow-up (mos)**	**Outcome**
Montes et al., 2010 [66]	Weekly TI vs TAU	RCT	OPD	409 TI 438 TAU	Interview	3.0	4.0	TI>TAU (96.7%, 91.2%)
Granholm et al., 2012 [67]	MATS +payments	Open	OPD	42 MATS	Self-report	3.0	3.0	Adherence not improved
Montes et al., 2012 [68]	Daily TM vs TAU	RCT	OPD	100 TM 154 TAU	MAQ	3.0	6.0	TM>TAU

Velligan et al., 2013 [69]	PharmCAT vs eMM vs TAU	RCT	OPD	47 PharmCAT 48 eMM 47 TAU	Pill-count eMM	9.0	9.0	Both>TAU (90.5%,72%)
Beebe et al. 2014 [70]	Weekly TIPS ± Daily text	RCT	OPD	10 TIPS 10 text 8 both	Pill-count	3.0	3.0	All similar
Beebe et al. 2016 [71]	TI	RCT	OPD	140 Total	MARS	3.0	3.0	TI = TAU
Dahan et al., 2016 [72]	TMI	RCT	Hospital	30 TMI 30 TAU	VAS DAI-10	1.0	1.0	TM>TAU
Beebe et al. 2017 [73]	Weekly TIPS	RCT	OPD	105 Total	Pill-count Drug assay	6.0	6.0	Pill count: TIPS = TAU Assays: TIPS>TAU (54.7%, 32.7%)
Kidd et al. 2018 [74]	CATC vs. Support	RCT	OPD	10 CATC 10 Support	BARS	4.0	4.0	No difference
Xu et al. 2019 [75]	LEAN	RCT	OPD	271 Total	Pill-count	6.0	6.0	LEAN>TAU
Uslu et al. 2020 [76]	Weekly TIPS vs. TAU	RCT	OPD	22 TIPS 24 TAU	MARS	2.0	2.0	TIPS>TAU

SUBSTANCE ABUSE AND ILLNESS-SEVERITY

Among patient-related factors, co-occurring substance abuse has been found consistently to predict poor treatment adherence and to compromise clinical outcomes in schizophrenia patients

[3,13,16,20]. Despite the importance of this association, direct testing of specific interventions aimed at improving treatment adherence in schizophrenia patients with substance abuse remains rare. One CBT-based, skill-training approach was tested in 55 patients with schizophrenia and substance abuse. Among the 34 subjects (62%) who completed the treatment, adherence was significantly increased at three-month follow-up based on within-subject, mirror comparison, but without a control group [80]. Another qualitative study of factors influencing treatment adherence in schizophrenia patients found that the use of illicit drugs or alcohol was strongly associated with inadequate improvement of psychotic symptoms and inferior tolerability of adverse effects of antipsychotic drugs – both associated with poor treatment adherence [3]. Demographic variables and years of psychotic illness have shown an inconsistent association with adherence to antipsychotic treatment [16]. However, behavioral interventions for psychotic disorder patients in rural areas aimed at facilitating access to more assertive psychiatric care showed beneficial effects on treatment adherence [75]. Greater symptom severity also has been found consistently to be associated with inferior treatment adherence, whereas relationships of neurocognitive impairments with treatment adherence have been inconsistent [16]. Nevertheless, positive patient attitudes toward antipsychotic medicines and perceived benefits of their use were tentatively associated with better treatment adherence [16]. Shared Decision-Making approaches to antipsychotic treatment may have a positive effect on treatment adherence and to satisfaction of severely mentally ill patients with their care [20]. This approach includes patients in decisions about their treatment by providing clear information and listening to their preferences and concerns to reach shared decisions [24]. The method has yielded some evidence of improved satisfaction among patients with severe mental illnesses, and suggestions that treatment adherence is improved, although longer follow-up with larger samples and more specific outcome measures is needed to test these preliminary impressions adequately [24]

THERAPEUTIC SUPPORT AND HEALTHCARE SETTINGS

Factors affecting treatment adherence about the environments in which patients live or where they are treated remain little investigated. Nevertheless, a secure therapeutic alliance between patient and prescribing clinician has long been recognized as a predictor of treatment adherence, including with schizophrenia patients [3,7,50]. Nevertheless, interventions specifically targeting the therapeutic relationship and aimed at increasing treatment adherence remain to be developed. In particular, shared decision-making probably can improve therapeutic relationships from both patient and clinician perspectives, but it requires further study to establish particular benefits to treatment adherence and clinical outcome [24]. In addition, family support or involvement in the treatment planning for the severely mentally ill has been associated with better treatment adherence [16,76]. However, specific interventions for family members or caregivers, so far, have not shown significant improvements in adherence rates in schizophrenia patients [76].

It is also plausible to expect that greater access to community mental health services and improved models of care would support treatment adherence in schizophrenia patients. Such factors have been considered particularly important in rural areas and with low-income rural or urban populations, for whom healthcare resources are often limited and not readily accessible [75,81]. The use of Assertive Community Treatment (ACT) models has improved treatment

adherence and clinical outcomes in large samples of schizophrenia patients [77]. Also, behavioral approaches involving frequent home visits or even telephone discussions with trained nurses have increased access to clinical care when needed and found to increase treatment adherence in schizophrenia patients (Table 3). Similarly, enhancing the services of community mental health centers with electronic monitoring of the treatment and progress of individual patients, combined with training of caregivers to supervise drug administration have increased treatment adherence and improved clinical outcomes in rural areas with limited mental healthcare resources [75,81].

ARTIFICIAL INTELLIGENCE AND DIGITAL TRACKING

A novel artificial intelligence (AI) platform for use on mobile devices, called AiCure, has been used to measure and pro-mote treatment adherence in schizophrenia patients [87]. The method was tested in an exploratory trial involving an investigational, adjunctive, orally administered drug aimed at improving cognitive impairments in schizophrenia patients [87]. AiCure visually confirms ingestion of medicine with facial recognition technology and generates encrypted data for each drug dosing event for immediate or later monitoring and possible intervention. In one trial, schizophrenia subjects who showed poor treatment adherence (fewer than 70%) were offered AiCure (n = 75) or mDOT (modified Directly Observed Treatment; n = 53) for 6 months, with treatment adherence backed with assays of plasma drug concentrations. The average cumulative rate of adherence was 90% with AiCure and 72% with mDOT (a non-significant difference), but rates of treatment nonadherence before the intervention were not reported [87]. A novel preparation of the SGA aripiprazole embedded with a microsensor recently received FDA-approved for clinical use [88]. This system includes a sensor in a skin- patch to support electronic monitoring by clinicians of drug intake and other measures, including activity levels and self-ratings of mood [88]. The method has received preliminary testing for adherence with aripiprazole by severely mentally ill subjects in three uncontrolled, open-label, two-month trials [88–90]. In one, most participants seemed to be satisfied with, and able to correctly use the treatment monitoring, with an estimate of adherence of 74% [90]. Again, the clinical value of this innovative technology requires further critical assessment with adequate controls and long-term outcomes regarding treatment adherence and clinical status [91].

Conclusions

Antipsychotic medication failure by patients being treated for psychotic disorders such as schizophrenia can have severe adverse consequences, including increased morbidity and dysfunction, a higher suicide risk, a greater demand for clinical services, including in-patient hospitalization, and a higher cost to society in the long run. Multiple variables linked to medication and dose features, patient characteristics, and clinical services contribute to suboptimal adherence to pharmacological therapy. Prolonged noncompliance with therapy may have serious effects in terms of both the patient's health and financial well-being. Some of the many treatments and interventions aimed at improving patient adherence have at least been tested in the clinical setting. Anti-psychotic medications in long-acting injectable (LAI)

formulations, which ideally should overcome treatment nonadherence and boost clinical response, are among the many options. Because of their efficacy in boosting adherence, LAI medicines have been widely accepted in many locations and cultures, although they are often underutilized because of their strict dose schedule and lack of acceptability. Further studies with participants matched for prior nonadherence to oral medicine and randomized to therapy with an oral antipsychotic or LAI antipsychotic and long-term follow-up are needed to establish their capacity to also enhance clinical outcomes in schizophrenia. Several psychological and behavioral therapies are effective based on educational interventions, encouragement, and tighter clinical follow-up, although their testing has been based on outcome measures of often unclear reliability and generally short exposures. The use of technology to improve treatment adherence is on the rise. Mobile and other monitoring approaches are among the methods that may be used, as well as the use of cell phones to keep in touch with patients and keep track of their medication intake and clinical progress. Clinically and financially, it has not been shown that monitoring medication use, psychological therapies, or technology-based interventions are superior to standard therapeutic interventions.

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