An analytical review on schizophrenia pharmaceutical treatment along with intelligent retrieval

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Abstract---Suicidal thoughts, higher use of resources like hospitalisation and related costs, and clinical deterioration may occur if schizophrenia patients fail to adhere to their drug regimens, according to a new study. We are analysing data from clinical trials of therapy that aim to boost the proportion of patients with schizophrenia who adhere to their medication. Nonadherence to therapy is a problem that affects both patients and healthcare providers. Behavioral treatment, long acting injectables (LAI), and antipsychotics based on methamphetamine LAI technology are a few examples. Only a small number of smartphone applications, such as medicine monitors and voice assistants, have been integrated with AI. The inclusion of clinically relevant samples in randomised, controlled, and blinded studies is necessary to measure not just adherence but...
also clinically important and long-lasting treatment outcomes for schizophrenia patients.

**Keywords**---Schizophrenia, Anti-psychotics, Drug related factors, Intelligent retrieval.

**Introduction**

A comprehensive treatment plan that includes antipsychotic medication is necessary since schizophrenia is a long-term and debilitating illness. (Baldessarini, 2013; Yan & Greene et al., 2018; Clifford & Crabb et al., 2020). Recent research indicated that quitting psychopharmacological treatment increased clinical decline rates by five times in patients with chronic psychosis (El Khoury & Pilon et al., 2020) a dozen times more likely to take their own life. (Forsman & Taipale et al., 2019). Patients who do not adhere to prescribed antipsychotic drug therapy face an increased risk of hospitalisation, a worsening of their general health and well-being, and an increase in healthcare costs (Nielsen & Jensen et al., 2015; Phan, 2016). In contrast, the long-term use of antipsychotics may lead to significant decreases in mortality and improved clinical results (Taipale & Tanskanen et al., 2020). Errors or noncompliance with antipsychotic drug regimens are rather common. Patients using oral formulations were found to have a prevalence that ranged from 20% to 89% (Barkhof & Meijer, 2012), 55 percent of the population (Phan, 2016). The source of the issue is a combination of patient characteristics, drug-related variables, and the kind of professional services supplied (Clifford & Crabb et al., 2020; Fleischhacker, 2013; Ostuzzi & Mazzi et al., 2018; Higashi K, Medic G et al., 2013).

Side effects, tolerance, and other medication-related difficulties might affect how well patients stick to their treatment plans. Treatment non-adherence in schizophrenia patients is strongly linked to other illness-related difficulties, such as poor health literacy and inconsistency in access to prescribed medicines, which are also linked to disorientation (Clifford & Crabb et al., 2020). Poor adherence to prescribed medication is also associated with severely symptomatic illness and co-occurring substance use disorders, resulting in a cycle of diminishing treatment effectiveness and clinical worsening. (Baldessarini, 2013; Czobor & Van Dorn et al., 2015).

After discontinuing antipsychotic medication, 40% of schizophrenia patients got an understanding of the need of continuing therapy after experiencing deterioration in their condition upon discontinuation (Tranulis & Goff et al., 2011). Concerns about stigma and ignorance about one's sickness may hamper one's willingness to receive treatment (Tranulis & Goff et al., 2011), as well as the unpleasant antipsychotic pharmaceutical side effects and the remission of these side effects following withdrawal of the medication (Baldessarini, 2013; Velligan & Weiden et al., 2009).

If clinicians in responsive and supportive clinical care systems have a good therapeutic relationship with their patients and their families are engaged, they may help them adhere to their treatment programmes (Sendt & Tracy et al., 2015). There are also a variety of technological approaches that may help patients stick to their medication regimen, including medication trackers, missed-dose alerts, activity check
lists and frequent phone calls from their doctor or pharmacist, all of which will be explored further on in this article (Barkhof & Meijer, 2012; Kreyenbuhl & Record et al., 2016). Early research assistance has been supported by a number of programmes, although these efforts have not been well explored (Clifford & Crabb et al., 2020; Fleischhacker, 2013; Ostuzzi & Mazzi et al., 2018; Higashi K, Medic G et al., 2013; Czobor & Van Dorn et al., 2015).

It is well accepted that early diagnosis and monitoring of drug non-adherence in schizophrenia patients is essential for long-term antipsychotic treatment. Non-adherence assessment in clinical practise, on the other hand, continues to be a problem that requires more research (Nielsen & Jensen et al., 2015; Kane & Kishimoto, 2013). For the sake of best therapeutic results, this review analyses new research on the variables that influence drug adherence in schizophrenia patients and assesses ways for boosting the adherence to prescription antipsychotic drugs.

1. Measuring Drug-Treatment Adherence In Schizophrenia

The outcomes of clinical study examining adherence may be influenced by the criteria and procedures employed to measure treatment nonadherence (Phan, 2016). A patient’s reluctance to take their medicine or a change in their medication dose may both result in treatment nonadherence (either purposeful or accidental). In clinical practise and experimental treatment research, it is critical to accurately assess nonadherence, particularly in disorders like schizophrenia that are notoriously difficult to treat (Nielsen & Jensen et al., 2015; Kane & Kishimoto, 2013). Many objective and subjective techniques have been offered and some have been tested (Bright, 2017). Direct observation of pill consumption, patient treatment diaries, periodic pill counting, and electronic monitoring tools are some of the methods that may be employed (therapeutic drug monitoring (TDM)). Patient questionnaires and symptom rating scales may be used to acquire information from patients regarding their medication use, and the latter can be used to assess the effectiveness of the treatment (Bright, 2017).

There have been contradictory findings in the use of objective measures to evaluate treatment adherence because correlations between multiple objective measures are not necessarily concordant and may be impacted by several clinical and technical variables (Velligan & Weiden et al., 2009; Velligan & Wang et al., 2007; Brain & Sameby et al., 2014). Adherence seems to be overestimated by subjective assessments (Velligan & Wang et al., 2007). Some researchers have expressed doubts about the validity or reliability of subjective measures (such as patient and clinician-rating scales) that are often employed in schizophrenia treatment adherence assessments. A number of subjective approaches have shown early indications of considerable validity, reliability, and sensitivity in these patients, however. Among them are the Episode-Specific Approach (ESA), the Brief Adherence Rating Scale (BARS), and the Medication Adherence Rating Scale (MARS) (Bright, 2017; Velligan & Wang et al., 2007).

Simple pill-counting is an objective metric (Brain & Sameby et al., 2014) Moreover, medication access is monitored electronically with the use of devices and reporting procedures. A Medication Event Monitoring System, a medicine bottle-cap with a microprocessor that records the incidence and time of each bottle opening, but not necessarily pill-taking, is one example of such techniques
(Brain & Sameby et al., 2014; Lee & Lee et al., 2019). Discarding medication and failing to record actual intake are some of the limitations of these systems (Kane & Kishimoto, 2013). Another problem is that patients, especially those with long-term mental health issues like schizophrenia, may not follow the prescribed treatment plan exactly as prescribed. In addition, some electronic monitoring technologies are pricey and may not be appropriate for many community settings (Velligan & Wang et al., 2007; Lee & Lee et al., 2019). These procedures are less costly and time consuming, but they may overstate patient adherence (Lee & Lee et al., 2019). For the purpose of proving that a patient has ingested medication, a blood test to measure circulating levels of the drug is a helpful tool. Intrusive and impacted by individual variability in pharmacokinetics and metabolism, as well as blood sampling time (Hiemke & Bergemann et al., 2018). A lack of knowledge with and training in treatment adherence evaluation tools has kept rating scales and other measurement-based techniques from being widely used in normal clinical psychiatric care (Kane & Correll, 2020).

Aiming to identify and assess treatment adherence evaluation methodologies, as well as treatments aiming at enhancing treatment adherence, we conducted this review. By kind of intervention evaluated, data are arranged according to the influence on treatment adherence among schizophrenia patient-subjects who meet standard criteria.

2. Drug-Related Risk Factors

Adherence problems with prescribed oral antipsychotic medication therapy may be exacerbated by inadequate perceived benefit, especially when contrasted to unpleasant side effects of specific drugs in individual patients, as well as high dosages or inappropriate complexity of drug combinations. Long-acting injectable formulations of effective antipsychotic drugs have been explored extensively to decrease some of these nonadherence causes.

3. Long-Acting Injected Antipsychotics

Antipsychotics with long-acting injectable (LAI) action are becoming more widely available, and this may help patients better adhere to their medication regimens. Fluphenazine and haloperidol’s decanoate esters were launched onto the market decades ago (Baldessarini, 2013), Several more SGAs have been added to the collection. Although these treatments are currently underutilised in many cultures, the costs associated with providing them, as well as the extra facilities and employees they need, may be high. LAI antipsychotics are used by about 15–28 percent of schizophrenia patients in the United States; only around 40 percent of European clinicians would use a LAI antipsychotic as the primary treatment in the United States, according to a study (Fiorillo & Barlati et al., 2020). Patients’ and society’s attitudes about and opinions of LAI pharmaceuticals, as well as concerns about possible severe side effects and the difficulty to rapidly stop treatment owing to the nature of LAI medicines, may all hamper their acceptance. SGA antipsychotics, in particular, have been shown to be hazardous to patients, despite this (Ostuzzi & Mazzi et al., 2018; Mohr & Knytl et al., 2017), Compared to orally delivered drugs, intravenous therapy may enhance treatment adherence and clinical outcomes in people with schizophrenia (Table 1). Retrospective or
"mirror-image" (within-subject comparisons done after and before the administration of LAI medicines) analysis and other assessments of clinical changes are used instead of prospective investigations, such as exploratory, randomised clinical trials. A number of factors were considered in these studies, such as the discontinuation rate, the number of expired prescription refills, the time elapsed between the time of the last refill and the actual discontinuation, and the percentage of days covered by a prescription, all of which were derived from databases (an estimate of the proportion of time with drug available, though not necessarily taken) (Yan & Greene et al., 2018; Gutiérrez-Casares & Cañas et al., 2010; Yoshimatsu & Elser et al., 2019).

It's hardly unexpected that patients on LAI had a greater percentage of adherence than those taking other oral antipsychotics (Table 1). Adherence to LAI antipsychotics varied from 68% to 81%, but oral antipsychotics were only adhered to by 24% to 52% of patients (Table 1). Predicted medication availability for LAI using first and second-generation antipsychotics was shown to have much lower discontinuation rates than oral formulations (Table 1). Prescription compliance with oral antipsychotics was tracked using MEMS, which counts the number of medication containers opened but does not record the number of pills consumed (Gutiérrez-Casares & Cañas et al., 2010). When coupled with a LAI antipsychotic, the adherence of patients with early psychosis to oral formulations was observed to increase (75 percent vs. 32 percent) (Titus-Lay & Ansara et al., 2018). Owing to the increasing frequency of visits to mental health facilities due to the administration of LAI antipsychotics, or the improved mental health afforded by injectable medicine, this relationship may be attributed.

It is important to compare the effectiveness of LAI vs. oral antipsychotic drug therapy in order to improve treatment adherence. Compared to other medicines included in this analysis, clinical efficacy has been investigated in retrospective studies and in randomised controlled trials substantially more often. Clinical effectiveness differences between LAI and orally administered antipsychotics in mirror-image investigations were much greater than in prospective, randomised trials when the two were compared (Kishimoto & Hagi et al., 2018; Kishimoto & Nitta et al., 2013). 60% of randomised, comparative trials found that clinical exacerbations were prevented when LAI preparations were not significantly superior in preventing the overall incidence of illness-exacerbations (Mohr & Knytl et al., 2017; Gutiérrez-Casares & Cañas et al., 2010). Though LAI has been shown in certain randomised studies to offer stronger therapeutic benefits than oral antipsychotics (Alphs & Benson et al., 2015; Subotnik & Casaus et al., 2015).

Research comparing behaviour before and after an intervention (such as LAI antipsychotic treatment) has demonstrated greater outcomes than prospective, randomised trials, in contrast to retrospective or mirror image research. As a precaution against selection bias, researchers may exclude patients who have previously failed to adhere to treatment, such as those with substance abuse or co-occurring mental illness, from some RCTs. However well publicised the intervention may be, subjects' and researchers' expectations of a new intervention may distort mirror-image comparisons in favour of favourable outcomes.
Table 1. Adherence to treatment with long-acting injectable vs. oral antipsychotics

<table>
<thead>
<tr>
<th>Report</th>
<th>Design</th>
<th>Drugs (n)</th>
<th>Subjects (n)</th>
<th>Adherence Measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kishimoto et al. 2014 (34)</td>
<td>Metan</td>
<td>FGA-LAIs SGA-LAIs OAs</td>
<td>955 LAIs 1063 OAs</td>
<td>All-cause dc</td>
<td>dc: LAIs = OAs</td>
</tr>
<tr>
<td>Alphs et al. 2015 (35)</td>
<td>RCT</td>
<td>LAI-PAL OAs</td>
<td>226 LAI – PAL 218 OAs</td>
<td>MPR; dc rate (&amp; latency)</td>
<td>MPR: LAI&gt;OAs (40%/24%); dc rate: LAI&lt;OAs</td>
</tr>
<tr>
<td>Marcus et al. 2015 (36)</td>
<td>Retro</td>
<td>FGA-LAIs SGA-LAIs OAs</td>
<td>157 FGA LAIs 183 SGA LAIs 3428 OAs</td>
<td>PDC; Rx gap ≥60d</td>
<td>PDC: LAIs&gt;OAs; PDC: SGAs&gt;FGAs</td>
</tr>
<tr>
<td>Subotnik et al. 2015 (37)</td>
<td>RCT</td>
<td>RSP-LAI RSP-OA</td>
<td>27 RSP-LAI 30 RSP-OA</td>
<td>All-cause dc</td>
<td>RSP-LAI = RSP-OA</td>
</tr>
<tr>
<td>Pilon et al. 2017 (38)</td>
<td>Retro</td>
<td>SGA-LAIs OAs</td>
<td>3307 SGA-LAIs 21,355 OAs</td>
<td>PDC</td>
<td>PDC: LAIs&gt;OAs</td>
</tr>
<tr>
<td>Verdoux et al. 2017 (39)</td>
<td>Retro</td>
<td>FGA-LAIs SGA-LAIs OAs</td>
<td>104 FGA LAIs 184 SGA LAIs OAs</td>
<td>All-cause dc</td>
<td>dc rate: LAIs&lt;OAs</td>
</tr>
<tr>
<td>Vincent et al. 2017 (40)</td>
<td>Metan</td>
<td>LAI-PAL OAs</td>
<td>114 total</td>
<td>MPR</td>
<td>MPR: LAI&gt;OAs (81%/43%)</td>
</tr>
<tr>
<td>Greene et al. 2018 (41)</td>
<td>Retro</td>
<td>FGA-LAIs SGA-LAIs OAs</td>
<td>927 FGA LAIs 1934 SGA LAIs 2777 OAs</td>
<td>PDC or ≥60-day Rx-gap</td>
<td>Adherence LAIs=OAs by 5%; Discontinue: LAIs&lt;OAs by 20%</td>
</tr>
<tr>
<td>Kishimoto et al. 2018 (42)</td>
<td>Metan</td>
<td>FGA-LAIs SGA-LAIs OAs</td>
<td>562 FGA LAIs 3773 SGA LAIs 32,258 OAs</td>
<td>All-cause dc</td>
<td>dc: LAIs&gt;OAs</td>
</tr>
<tr>
<td>Shah et al. 2018 (43)</td>
<td>Retro</td>
<td>LAIs OAs</td>
<td>2302 LAIs 2302 OAs</td>
<td>PDC dc; dc rate</td>
<td>PDC: LAIs = OAs; dc rate: LAIs&lt;OAs</td>
</tr>
<tr>
<td>Suzuki et al. 2018 (44)</td>
<td>Obs</td>
<td>SGA-LAIs PP-OA</td>
<td>406 SGA-LAIs 432 PP-OA</td>
<td>All-cause dc &amp; Time to dc</td>
<td>dc rate: SGA-LAIs = PP-OA Dc latency: SGA-LAIs&gt;PP-OA</td>
</tr>
<tr>
<td>Titus-Lay et al. 2018 (45)</td>
<td>Retro</td>
<td>FGA-LAIs SGA-LAIs OAs</td>
<td>35 OAs 4 SGA LAIs</td>
<td>PDC; Lack of Rx-gap</td>
<td>Adherence: LAIs&gt;OAs (76%/32%)</td>
</tr>
<tr>
<td>Yan et al. 2018 (2)</td>
<td>Retro</td>
<td>APZ-LAI OAs</td>
<td>408 APZ-LAI 3361 OAs</td>
<td>PDC; d/c rate &amp; latency</td>
<td>PDC: LAI&gt;OAs; dc rate: LAI&lt;OAs</td>
</tr>
<tr>
<td>Song et al. 2019 (46)</td>
<td>Retro</td>
<td>SGA-LAIs OAs</td>
<td>6344 LAIs 7029 OAs</td>
<td>≥60-day Rx-gap</td>
<td>Persistence: SGA-LAIs&gt;OAs</td>
</tr>
<tr>
<td>Yoshimatsu et al. 2019 (47)</td>
<td>Obs</td>
<td>LAIs OAs</td>
<td>77</td>
<td>Rx duration</td>
<td>Adherence: LAIs&gt;OAs</td>
</tr>
</tbody>
</table>

D, days; dc, discontinuance; AAs, antipsychotic drugs first generation antipsychotic FGA; injectable antipsychotic LAI; long-term antipsychotic treatment Medication Event Monitoring System (MEMS) - Meta-analysis, or simply
"meta" oral antipsychotic OA; observational study Obs; MPR: Medication Possession Ratio Pharmacist-Filled Prescription Days (PDC) Prospective RCTs using paliperidone are called RCTs with prospective randomization. SGA is a second-generation antipsychotic; RSP is for risperidone; Rx stands for prescription. It is worth noting that 16/21 research (76.2 percent) showed evidence of greater treatment adherence with the use of LAI antipsychotics: 12/14 (85.7 percent) of observational or retrospective studies, and 4/7 (57.1 percent) of RCT or meta-analyses (x2 = 2.10, p = 0.15).

4. Countering Other Drug-Related Factors

Lack of apparent therapeutic benefit, side effects, previous poor experiences with comparable therapies, and the complexity of the medication regimen (many medicines and doses/day) all tend to have a detrimental impact on treatment adherence with antipsychotic drugs (Phan, 2016; Sendt et al., 2015; Kane et al., 2013). For example, we were unable to locate trials evaluating particular strategies to improve compliance with such prevalent clinical criteria. In spite of this, good clinical practise calls for a low dose administered just a few times each day (1). In addition, patients should be warned of possible side effects, and they should be monitored and intervened on a regular basis in order to reduce the negative consequences (Phan, 2016; Baldessarini, 2013). Despite the fact that antipsychotic combos may be effective in certain cases (49), In contrast to optimal monotherapy, such polytherapy has seldom been fully tested for safety and effectiveness. Discomfort and side effects are increased, as is the expense, and treatment compliance is harmed when many medications are used (Phan, 2016; Baldessarini, 2013). Clozapine is the only antipsychotic medicine that has not been shown to lower the risk of mental hospitalisation in comparison to other antipsychotics, according to an extensive meta-analysis evaluating the effects of single vs. multiple antipsychotic regimens (Tiihonen et al., 2019). That research, however, did not examine treatment adherence in relation to treatment complexity explicitly.

5. Lack Of Insight

Schizophrenia treatment adherence is affected by a patient’s ongoing psychotic symptoms, insight, attitude toward drugs, and capacity to reflect on prior experiences. Nonadherence was shown to be connected with patient perceptions of elements such as the denial of mental disease in a recent qualitative investigation, particularly early in the course of psychotic illness (Clifford et al., 2020). The researchers in the same study also discovered that improved treatment adherence was linked to the capacity to remember previous unpleasant symptoms that were present before therapy and their improvement with treatment (Clifford et al., 2020). In a meta-analysis of 1154 individuals from two major clinical studies, it was shown that co-occurring drug addiction was likewise linked to poor treatment adherence among patients with schizophrenia, leading to the same results (Czobor et al., 2015). Studies have shown that being able to recognise that you have a medical condition is linked to better adherence (Velligan et al., 2009; Tessier et al., 2017). Symptom severity, neurocognitive performance, perceived stigma, and other characteristics linked with psychotic disease are likely to influence insight (Baldessarini, 2013; Nielsen et al., 2015)
Increasing self-awareness, self-reflection, and a positive outlook toward therapy are all goals in studies of various psychological therapies. A wide range of findings have been obtained (Table 2) (Anderson et al., 2017; Staring et al., 2010; Barkhof et al., 2013; Schulz et al., 2013; Chien et al., 2015; von Bormann et al., 2015; Abdel et al., 2016; Chien et al., 2016; Yanagida et al., 2017; Cetin et al., 2018; Ertem & Duman, 2019; Chien et al., 2019; Tatu & Demir, 2020; Yildiz & Aylaz, 2021) see the next section for further information.

6. Psychosocial Interventions

Several psychosocial therapies have been studied in recent decades to see whether they affect treatment adherence in people with schizophrenia. Patients in hospitals and those who are ambulatory may benefit from motivational interviewing, adherence treatment, and other types of psychoeducation (Table 2) (Anderson et al., 2017; Staring et al., 2010; Barkhof et al., 2013; Schulz et al., 2013; Chien et al., 2015; von Bormann et al., 2015; Abdel et al., 2016; Chien et al., 2016; Yanagida et al., 2017; Cetin et al., 2018; Ertem & Duman, 2019; Chien et al., 2019; Tatu & Demir, 2020; Yildiz & Aylaz, 2021). Patient-centered, directed motivational interviewing aims to explore and resolve patient ambivalence regarding diagnosis and treatment in order to increase their drive to improve (Song et al., 2019). It was initially intended for patients who were struggling with substance misuse. Small, controlled trials with mixed results have been conducted on persons with psychotic diseases that have been customised to their needs (Table 2) (Barkof et al., 2013; Schulz et al., 2013; Chien et al., 2015; von Bormann et al., 2015; Abdel et al., 2016; Chien et al., 2016; Yanagida et al., 2017; Cetin et al., 2018; Ertem & Duman, 2019). Patients and clinicians may work together in adherence therapy to come up with treatment options that are more meaningful and enjoyable for them. It is based on the ideas of motivational interviewing and cognitive behavioral therapy (CBT) (Chien et al., 2019). Antipsychotic therapy has a variety of strategies, including cooperative problem-solving, sharing knowledge, and examining ambivalence (Chien et al., 2019). Some controlled studies of adherence therapy have shown variable results, however extended treatment over 12–18 months resulted in better treatment adherence outcomes (Table 2) (Anderson et al., 2017; Staring et al., 2010; Schulz et al., 2013; ; von Bormann et al., 2015; Chien et al., 2016; Tatu & Demir, 2020). Assessment of outcomes was improved by using Adherence Rating (ARS) and Medication Adherence Rating (MARS) measures rather than a larger 30-item Drug Attitude Inventory (DAI-30) (Table 2).

Patients and their families may be educated on the causes, symptoms, treatment, and prognosis of certain mental diseases via organized educational programs. It seeks to help patients acknowledge and accept that they have a disease, encourage motivation to better the condition, and boost self-esteem through enhancing patients' and their families' understanding and treatment of the illness (Tatu & Demir, 2020). At least four studies of varied types have tested these therapies in the recent past (Abdel et al., 2016; Yanagida et al., 2017; Cetin et al., 2018; Ertem & Duman, 2019; Chien et al., 2019; Tatu & Demir, 2020; Yildiz & Aylaz, 2021; Gray et al., 2016; Montes et al., 2010). Following a group or individual psychoeducational program was shown to enhance medication adherence in all these investigations; however, the longevity of these effects is unknown since follow-up evaluations lasted only 1–12 weeks (Table 2).
Table 2. Psychosocial interventions on treatment adherence among schizophrenia patients

<table>
<thead>
<tr>
<th>Report</th>
<th>Method</th>
<th>Design</th>
<th>Setting</th>
<th>Subjects (n)</th>
<th>Sessions &amp; Months</th>
<th>Final Months</th>
<th>Adherence Measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. 2010 (51)</td>
<td>AT</td>
<td>RCT</td>
<td>OPD</td>
<td>12 AT 14 TAU</td>
<td>8 2.0</td>
<td>2.0</td>
<td>PETiT</td>
<td>AT = TAU</td>
</tr>
<tr>
<td>Staring et al. 2010 (52)</td>
<td>AT</td>
<td>RCT</td>
<td>OPD</td>
<td>53 AT 52 TAU</td>
<td>— 6.0</td>
<td>12</td>
<td>Interview</td>
<td>AT&gt;TAU</td>
</tr>
<tr>
<td>Barkhof et al. 2013 (53)</td>
<td>MI</td>
<td>RCT</td>
<td>OPD (nonadherent)</td>
<td>55 MI 59 TAU</td>
<td>8 6.5</td>
<td>12</td>
<td>MAQ DAI</td>
<td>MI = TAU</td>
</tr>
<tr>
<td>Schulz et al. 2013 (54)</td>
<td>AT</td>
<td>RCT</td>
<td>OPD (newly dc)</td>
<td>80 AT 57 TAU</td>
<td>8 —</td>
<td>3.0</td>
<td>CDR MARS DAI-30</td>
<td>AT = TAU</td>
</tr>
<tr>
<td>Chien et al. 2015 (55)</td>
<td>AT</td>
<td>RCT</td>
<td>OPD</td>
<td>57 AT 57 TAU</td>
<td>8 4.0</td>
<td>6.0</td>
<td>ARS</td>
<td>AT&gt;TAU</td>
</tr>
<tr>
<td>Von Bormann et al. 2015 (56)</td>
<td>AT</td>
<td>RCT</td>
<td>OPD (newly dc)</td>
<td>38 AT 32 TAU</td>
<td>8 —</td>
<td>6.5</td>
<td>DAI-30</td>
<td>AT = TAU</td>
</tr>
<tr>
<td>Abdel Aziz et al. 2016 (57)</td>
<td>IP</td>
<td>QE</td>
<td>Inpatient</td>
<td>82 IP</td>
<td>5 1.5</td>
<td>—</td>
<td>Pill-count</td>
<td>IP&gt;TAU</td>
</tr>
<tr>
<td>Yanagida et al. 2017 (59)</td>
<td>GP</td>
<td>Open</td>
<td>Hospitalized</td>
<td>70 GP</td>
<td>6 —</td>
<td>0.25</td>
<td>DAI-10 score improved</td>
<td></td>
</tr>
<tr>
<td>Cetin &amp; Aylaz 2018 (61)</td>
<td>MGP</td>
<td>RCT</td>
<td>OPD</td>
<td>55 MGP 80 TAU</td>
<td>8 1.0</td>
<td>1.0</td>
<td>MARS</td>
<td>MGP&gt;TAU</td>
</tr>
<tr>
<td>Ertem et al. 2018 (61)</td>
<td>MI</td>
<td>RCT</td>
<td>OPD</td>
<td>20 MI 20 TAU</td>
<td>6 —</td>
<td>6.0</td>
<td>MAS</td>
<td>MI&gt;TAU</td>
</tr>
</tbody>
</table>
7. Behavioral Interventions

To help individuals with schizophrenia take their medication on a daily basis when previous psychosocial therapies had had uneven or inconclusive outcomes, numerous individually designed behavioural techniques were devised (Clifford et al., 2020; Kreyenbuhl et al., 2016; Gray et al., 2016). There are a number of treatments that may be used in conjunction with these tactics, including reminders from pharmacies, financial or other reinforcements, computerised monitoring and apps for mobile phones (Table 3) (Kreyenbuhl et al., 2016; Montes et al., 2010; Granholm et al., 2012; Montes et al., 2012; Velligan et al., 2013; Beebe et al., 2014; Beebe et al., 2016; Dahan et al., 2016; Beebe et al., 2017; Kidd et al., 2018; Xu et al., 2019; Uslu & Buldukoglu, 2020). A professional therapist visits the patient’s house every week for 30 to 45 minutes for PharmCAT, whereas Cognitive Adaptation Training (CAT) employs visual aids such as signs, labels, and checklists to help patients remember to take their medication. Efficacy of these techniques has been investigated in at least two controlled trials in the recent past (Beebe et al., 2014), with promising results that may last for some time (Table 3).

When a pharmacy for schizophrenia patients used an electronic medication monitor that alerted treatment personnel if a patient was taking the incorrect drug or at the wrong time, medication adherence increased significantly above randomised treatment as usual (TAU) (Beebe et al., 2014). Adherence was raised by as much as 92 percent with the use of both in-person and electronic interventions (Beebe et al., 2014). At the end of the four-month follow-up period, distributing a handbook to the patient’s family members to urge their general support of the patient’s treatment had no effect on adherence (Uslu & Buldukoglu, 2020).

Pharmacists may help patients manage their medication by providing them with individually packaged medicines and sending them reminders to renew their prescriptions. They can also notify their prescribing doctors when a patient hasn’t filled a prescription on time. Because it included individuals with diagnoses other than schizophrenia, the approach was tested in a randomised controlled study that isn't included in Table 3 (Valenstein et al., 2011). At a 12-month follow-up, it
found indications of much higher treatment adherence than in routine clinical care.

Even with LAI antipsychotics, there is a chance of non-compliance due to the frequency of clinic visits necessary for injections. Two controlled studies have assessed the use of financial incentives to promote treatment adherence using LAI antipsychotics rather than orally given medicines. In both cases, the increased incentives resulted in much more adherence than without them (Priebe et al., 2016; Priebe et al., 2013).

Several randomised controlled studies assessed the treatment adherence of patients receiving or not receiving telephone-based therapy. Unstructured weekly phone calls from nurses to 847 outpatients with schizophrenia were shown to improve treatment compliance and attitudes regarding medication. There was a 97% increase in investigator-rated treatment compliance over TAU after the intervention across at least four months (Kreyenbuhl et al., 2016). Using the MARS questionnaire, 140 outpatients with schizophrenia failed to show a meaningful improvement after two months of treatment (Beebe et al., 2016).

Telephone Strategy-Problem Solving (TIPS) is another manual-guided telephone-based intervention that includes nurses trained to manage a range of community living challenges that are considered to impair treatment adherence (Beebe et al., 2014; Beebe et al., 2017). It was put through its paces in three randomised studies (Table 3). Using pill counts over a three-month period, a small study including 28 patients with psychotic disorders revealed no significant differences in adherence (78 percent–85 percent) among those who received TIPS phone calls on a weekly vs. daily basis (Beebe et al., 2014). Over the course of six months, 105 outpatients with schizophrenia participated in a study that found no improvement in pill count adherence, but substantial increases in the percentage of participants with blood medication concentrations regarded to be within a therapeutic range (Beebe et al., 2017). An additional controlled experiment with 46 outpatients with schizophrenia found that TIPS led to improved MARS compliance scores after two months of therapy (Beebe et al., 2014).

The efficacy of a treatment named LEAN was investigated in a big clinical trial. Medicine reminders, health education and monitoring may be provided through nonprofessional help or mobile messaging. Outpatients with schizophrenia were studied in rural China by researchers (Xu et al., 2019). Adherence to LEAN was much higher than TAU after six months of therapy.

For schizophrenia patients, MATS (Mobile Assessment and Treatment for Schizophrenia) was intended as an additional mobile phone-based cognitive-behavioral intervention to improve treatment adherence, socialising, and notably to reduce auditory hallucinations. 42 out of the 55 participants who began it and completed it in a scientific experiment were randomly selected. Self-report text messages show that patients who are able to live independently and complete the 12-week treatment programme have significantly improved adherence (Granholm et al., 2012).
Using 60 hospitalised schizophrenia patients, a randomised, controlled study examined the effectiveness of a personalised intervention aimed at increasing adherence to antipsychotic medication therapy. An average of six sessions of psychoeducation, motivational interviewing, and cognitive behavioural therapy (CBT) were used in the intervention to help patients achieve and maintain treatment adherence. TAU had considerably worse adherence and attitudes toward medicine at the conclusion of therapy, but there was no evaluation of long-term retention of the impact (Dahan et al., 2016).

Research designs, intensity and length of treatments, and adherence measurements limit meaningful comparisons of the reported behavioural therapies. Patients’ desire and capacity to comply with such therapies may also change over time based on their impressions of how they affect their privacy and independence. An individual strategy to balancing patient choices and the continued efforts of their doctors to prevent drop-out risk or treatment rejection is necessary.

Table 3. Quantitative comparisons of the several reported behavioral interventions

<table>
<thead>
<tr>
<th>Report</th>
<th>Intervention Type</th>
<th>Study design</th>
<th>Setting</th>
<th>Subjects (n) &amp; Interventions</th>
<th>Adherence Measure</th>
<th>intervention (mos)</th>
<th>Follow-up (mos)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montes et al., 2010 (66)</td>
<td>Weekly TI vs TAU</td>
<td>RCT</td>
<td>OPD</td>
<td>409 TI 438 TAU</td>
<td>Interview</td>
<td>3.0</td>
<td>4.0</td>
<td>TI&gt;TAU (96.7%, 91.2%)</td>
</tr>
<tr>
<td>Granholm et al., 2012 (67)</td>
<td>MATS +payments</td>
<td>Open</td>
<td>OPD</td>
<td>42 MATS</td>
<td>Self-report</td>
<td>3.0</td>
<td>3.0</td>
<td>Adherence not improved</td>
</tr>
<tr>
<td>Montes et al., 2012 (68)</td>
<td>Daily TM vs TAU</td>
<td>RCT</td>
<td>OPD</td>
<td>100 TM 154 TAU</td>
<td>MAQ</td>
<td>3.0</td>
<td>6.0</td>
<td>TM&gt;TAU</td>
</tr>
<tr>
<td>Velligan et al., 2013 (69)</td>
<td>PharmCAT vs eMM vs TAU</td>
<td>RCT</td>
<td>OPD</td>
<td>47 PharmCAT 48 eMM 47 TAU</td>
<td>Pill-count eMM</td>
<td>9.0</td>
<td>9.0</td>
<td>Both&gt;TAU (90.5%, 72%)</td>
</tr>
<tr>
<td>Beebe et al. 2014 (70)</td>
<td>Weekly TIPS ± Daily text</td>
<td>RCT</td>
<td>OPD</td>
<td>10 TIPS 10 texts 8 both</td>
<td>Pill-count</td>
<td>3.0</td>
<td>3.0</td>
<td>All similar</td>
</tr>
<tr>
<td>Beebe et al. 2016 (71)</td>
<td>TI</td>
<td>RCT</td>
<td>OPD</td>
<td>140 Total</td>
<td>MARS</td>
<td>3.0</td>
<td>3.0</td>
<td>TI = TAU</td>
</tr>
<tr>
<td>Dahan et al., 2016 (72)</td>
<td>TMI</td>
<td>RCT</td>
<td>Hospital 30 TMI 30 TAU</td>
<td>VAS DAI-10</td>
<td>1.0</td>
<td>1.0</td>
<td>TM&gt;TAU</td>
<td></td>
</tr>
<tr>
<td>Beebe et al. 2017 (73)</td>
<td>Weekly TIPS</td>
<td>RCT</td>
<td>OPD</td>
<td>105 Total</td>
<td>Pill-count Drug assay</td>
<td>6.0</td>
<td>6.0</td>
<td>Pill count: TIPS = TAU Assays: TIPS&gt;TAU (54.7%, 32.7%)</td>
</tr>
<tr>
<td>Kidd et al. 2018 (74)</td>
<td>CATC vs. Support</td>
<td>RCT</td>
<td>OPD</td>
<td>10 CATC 10</td>
<td>BARS</td>
<td>4.0</td>
<td>4.0</td>
<td>No difference</td>
</tr>
</tbody>
</table>
8. Substance Abuse And Illness-Severity

Co-occurring substance use in schizophrenia patients has been frequently associated to poor treatment adherence and clinical outcomes (Clifford et al., 2020; Czobor et al., 2015; Sendt et al., 2015; Bright, 2017). Direct testing of particular therapies aiming at enhancing treatment adherence in schizophrenia patients with drug addiction is uncommon despite the relevance of this link. 55 individuals with schizophrenia and drug addiction were studied using a CBT-based, skill-training approach. When looking at the 34 participants who finished the therapy (62 percent), adherence was considerably higher at the three-month follow up, but there was no control group to compare it with (Shaner et al., 2003). Study participants with schizophrenia who used illicit substances or alcohol were shown to have poor treatment adherence if their psychotic symptoms did not improve and their tolerance of antipsychotic side effects was lower than expected (Clifford et al., 2020).

Adherence to antipsychotic therapy has a shaky relationship with demographics and the number of years spent unwell with psychosis (Sendt et al., 2015). Treatment adherence was improved by behavioural treatments for psychotic illness patients in remote regions that facilitated access to more aggressive psychiatric care (Xu et al., 2019). Symptom intensity has been consistently linked to lower treatment adherence, but neurocognitive deficits have been inconsistently linked to lower treatment adherence (16). Antipsychotic medication usage was related with higher treatment adherence when patients had favourable views about the medication and a good perception of its benefits (Sendt et al., 2015).

To improve treatment compliance and patient satisfaction with their care, it is possible to use Shared Decision-Making procedures for anti-psychotic medication (Bright, 2017). Patients are involved in their own care by being given clear information and being listened to in order to get to a mutually agreed-upon course of action (Hiemke et al., 2017). Evidence of greater patient satisfaction and increased treatment adherence have been found via the use of this technique, although more extensive follow-up and more precise outcome measurements are required to test these first impressions (Hiemke et al., 2017).

9. Therapeutic Support And Healthcare Settings

Few studies have looked at how patients’ living, or treatment settings impact their adherence to therapy. Treatment compliance in individuals with schizophrenia may be predicted by a strong therapeutic connection between the patient and the prescribing doctor (Clifford et al., 2020; Phan, 2016; Tessier et al., 2017). Nevertheless, therapies aiming at improving treatment adherence and focusing on
the therapeutic connection are still being explored. Patient-clinician therapy interactions might benefit from collaborative decision-making, but this has to be studied further to see if it has any effect on treatment adherence or clinical outcomes (Hiemke et al., 2017). For those who are seriously mentally ill, family support or participation in treatment planning has been linked to increased treatment compliance (Sendt et al., 2015; Uslu & Buldukoglu, 2020). Adherence rates in schizophrenia patients are currently unaffected by particular treatments for family members or carers (Uslu & Buldukoglu, 2020).

Patients with schizophrenia may benefit from improved treatment approaches and greater access to community mental health services. Due to the limited and difficult access to healthcare services in rural areas and among the low-income population in both, these standards have been judged particularly important (Xu et al., 2019; Farooq et al., 2011). Large samples of schizophrenia patients have shown increased treatment compliance and clinical results as a result of the use of ACT models (Valenstein et al., 2011). With frequent home visits or even phone consultations with trained nurses promoting medication adherence, schizophrenia patients benefit from behavioural techniques (Table 3). Treatment adherence and clinical results have improved in remote locations with limited access to mental health care facilities that use electronic monitoring of patient treatment and progress in conjunction with caregiver training to oversee medication delivery (Xu et al., 2019; Farooq et al., 2011).

10. Artificial Intelligence/Intelligent Retrieval And Digital Tracking

AiCure, an AI platform, has been used to keep track of and encourage treatment compliance in people with schizophrenia who use mobile phones (Bain et al., 2017). Patients with schizophrenia who were on an experimental, supplementary, orally delivered medicine were given the technique as part of an exploratory study (Bain et al., 2017). AiCure uses face recognition technology to verify the administration of medication and creates encrypted data for each dosage event to be monitored immediately or later and perhaps intervene for six months, with the treatment adherence validated by assays of plasma drug concentrations. In one experiment, schizophrenia patients with poor treatment adherence were either AiCure or mDOT. AiCure had an average cumulative adherence rate of 90% and mDOT had an average cumulative adherence rate of 72% (a non-significant difference) (Bain et al., 2017).

The Food and Drug Administration has authorised a new formulation of SGA aripiprazole that includes a microsensor (Fowler et al., 2019). With this device, physicians may electronically monitor medicine consumption and other parameters, such as activity levels and patient self-ratings of mood, thanks to a skin patch sensor (Fowler et al., 2019). In three uncontrolled, open-label, two-month studies including seriously mentally ill participants, the technique has undergone preliminary testing for compliance with aripiprazole (Fowler et al., 2019; Kopelowicz et al., 2017; Peters-Strickland et al., 2016). One study found that 74 percent of participants were able to appropriately utilise the therapy monitoring and were happy with it (Peters-Strickland et al., 2016). For this revolutionary technology's therapeutic usefulness to be fully evaluated in terms of
treatment adherence and long-term results, more testing with appropriate controls and long-term outcomes is required (Kane et al., 2020).

11. Conclusion

Failure of antipsychotic treatment in schizophrenia patients may lead to suicide, an increase in the need for professional services, and an increase in the cost to society. Patient features and professional services can contribute to poor adherence to medication treatment. If a patient ignores treatment guidelines for an extended period of time, both his or her health and financial well-being may suffer. Patients' adherence to medication has been studied in clinical studies using a wide range of drugs and techniques. In addition to LAIs, which have been demonstrated to improve treatment adherence and clinical outcomes, there are a slew of other possible treatments. It is well known that LAI medications may improve adherence, but they are not widely used because of their rigid dosing schedules and lack of attraction to patients. Products manufactured by LAI, Los Angeles International Pharmaceuticals. A long-term follow-up study of patients who have previously failed oral medication is thus required to compare oral to LAI antipsychotics and to evaluate the two types of treatments. Even while psychological and behavioral treatments have been shown to be beneficial via educational interventions, encouragement, and tighter professional supervision, their testing has been based on results of often questionable reliability and limited exposure. Therapeutic compliance is increasingly being improved by the use of technology. Mobile or other monitoring systems employing cell phones may also be used to keep tabs on patients' medication use and clinical progress. Traditional treatment strategies such as medication management, therapy, and technology-based procedures have no advantage over any of these other approaches in terms of either clinical or economic outcomes.

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