

# Interventions to Improve Medication Adherence in People with Schizophrenia: A Systematic Review

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**Abstract:** Nonadherence to medications is very common in people with schizophrenia. Numerous methods have been implemented to improve medication adherence. The study aimed to determine what interventions have been used and to assess the effectiveness of these in improving medication adherence in people with schizophrenia. Two electronic databases (PubMed and Science Direct) and a manual search were used to locate RCT studies that examined interventions in medication adherence for schizophrenia, published between 2011 and 2022. The search was conducted using the terms (schizophrenia OR schizophrenic) AND (interventions OR adherence therapy) AND (medication adherence OR medication compliance). Sixteen studies were included, and relevant data were extracted and selected. Sixteen studies used interventions that involve family, health professionals (psychiatrists, psychologists, nurses, and pharmacists), SMS, and smart electronic reminders. Medication adherence was measured using medication refill records from hospital dispensing records or claim databases, electronic devices, plasma blood concentration, and participant self-reporting. Thirteen out of 15 studies showed significant improvements in adherence compared to routine care. The other three studies did not result in improved medication adherence. Interventions with diverse strategies delivered to individuals with schizophrenia showed the potential to reduce medication non-adherence in people with schizophrenia so that they can be utilized as an alternative to support treatment in people with schizophrenia in addition to antipsychotic medication. In future research strategies, it will be necessary to identify the main problems regarding nonadherence in people with schizophrenia individually and also identify the patient's perception of medication, illness, and behavior when taking medication in order to determine the next intervention that will be appropriate based on the patient's needs to improve adherence.

**Keywords:** adherence, schizophrenia, strategies, medication, interventions, systematic review

## Introduction

According to the 2017 Global Burden Disease report, 20 million people, or nearly 1% of the global population, suffer from schizophrenia.<sup>1</sup> Schizophrenia is a mental illness characterized by a wide range of symptoms. Positive symptoms (hallucinations, delusions, poor concentration), negative symptoms (apathy, lack of sense, poor or inadequate social functioning), and cognitive symptoms (disorganized thoughts, drowsiness, difficulty performing tasks, memory problems) symptoms are common in people with schizophrenia.<sup>2</sup> Current guidelines for schizophrenia care recommend antipsychotics as an essential part of long-term maintenance treatment for people with schizophrenia.<sup>3</sup> However, nonadherence to antipsychotic medication is more prevalent in people with schizophrenia, which may increase the risk of relapse, rehospitalization, suicide, and death.<sup>4-6</sup> Nonadherence to treatment has an impact on disease progression, leading to disease complications, disruption of physical and social functioning of the people with schizophrenia, and decreased quality of life.<sup>7</sup>

Nonadherence to antipsychotic treatments remains an enormous challenge for clinicians and pharmacists in treating people with schizophrenia.<sup>8,9</sup> Many factors contribute to partial and full nonadherence to medicines for schizophrenia, including poor insight,<sup>10</sup> a negative attitude towards medication,<sup>11</sup> chronicity of illness,<sup>12</sup> complicated treatment regimens, side effects of medications, cost of medication,<sup>13</sup> and poor social functioning. Furthermore, non-adherence among patients with schizophrenia and schizoaffective disorders has been associated with cognitive impairment, depression, substance abuse, inadequate or fragmentation of care, lack of family support,<sup>14</sup> cultural influences, and lower socioeconomic status.<sup>15</sup>

In the literature, “adherence” or “compliance” refers to the degree to which a person accepts advice from a healthcare professional or follows the instructions for their medicine.<sup>16</sup> According to the consensus definition, people with schizophrenia are considered adherent if they take more than 80% of their prescribed medication, have partial adherence if the person takes only 50% of the prescribed medication, and are nonadherent if they do not take the drug for 1 week.<sup>17</sup> Adherence to medication is a critical problem across all disease states but can be especially difficult for people with mental illness.

Various strategies have been used to improve medication adherence in people with schizophrenia, including patient and family education,<sup>18</sup> motivational interviewing, cognitive and behavioral approaches, and other combinations of strategies.<sup>19,47</sup> A Several strategies could be considered complex interventions: these were multifaceted and involved case management and collaborative care interventions. Some previous studies have also described various interventions to improve compliance with schizophrenia and other mental disorders, such as bipolar disorders.<sup>20</sup> Other reviews evaluated the effectiveness of interventions only in certain populations in the country<sup>21</sup> or focused on specific methods.<sup>22,23</sup> This study differs from the previous another in that it focuses on people with schizophrenia receiving both inpatient and outpatient treatment, only uses oral antipsychotic medication, and focuses on adherence as the primary outcome.

Therefore, the objective of this review is to determine intervention methods that have been used in people with schizophrenia and to assess the effectiveness of these interventions in improving medication adherence in people with schizophrenia.

## Materials and Methods

### Search Strategy

We conducted a digital search of the PubMed database for studies that contained the following keywords: (schizophrenia\*) AND (intervention\* OR adherence therapy) AND (medication adherence OR medication compliance) and the Science Direct database that contained the keywords: (schizophrenia OR schizophrenic) AND (interventions OR adherence therapy) AND (medication adherence OR medication compliance). Furthermore, a hand search was conducted to identify additional relevant studies. To report the results of this systematic review, we use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.<sup>24</sup> The electronic search results were transferred to Mendeley; duplicates were automatically removed. Two authors (NC and SAK) used a three-step process to select relevant articles. First, titles and abstracts were screened independently to determine whether they met the eligibility criteria. Then, independently read the full text of the remaining articles to complete the final selection of relevant articles. Second, A.W.W reviewed all of the extracted data for the articles.

### Eligibility Criteria

We considered all possible designs for clinical trials, including single group trials, randomised control trials, control clinical trial, pilot, or feasibility study. Studies published in English between 2011 and 2022 were included. We excluded editorials, letters, practice recommendations, other guidelines, conference abstracts, conference reports, systematic reviews, and meta-analyses, as well as studies with an unclear procedure or intervention. Articles were included if they involved participants with a formal diagnosis of schizophrenia, schizoaffective or schizophreniform disorders, according to the criteria of the Diagnostic and Statistical Manual, DSM-V-TR<sup>25</sup> or International Statistical Classification of Disease, Tenth Revision (ICD-10),<sup>26</sup> and used oral antipsychotic medication in therapy. We excluded articles that

involved participants with a diagnosis of organic disorders, ICD-10 mental retardation, long-acting or depot antipsychotic medication use, homelessness, a suicide attempt, drug or substance abuse, and alcohol dependence.

### Risk of Bias Assessment

NC and SAK assessed the risk of bias in selected studies independently using a tool adapted from a Cochrane Collaborative tool for assessing the risk of bias in randomized trials. There were six criteria were used in this bias risk assessment: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants, personnel, and outcome assessment (information bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other bias (eg, confounding bias). Each criterion was rated as having a low risk of bias, being unclear (inadequate information for judgment), or having a high risk of bias.<sup>27</sup> Disagreements between N.C and S.A.K were resolved by consensus after discussion or by A.W.W when necessary. Details on the assessment of the risk of bias are presented in Figure 1.

## Results

### Study Selection

Figure 2. shows the PRISMA flow diagram for the literature search process. Initially, 708 studies were identified. After removing duplicates (n=8), we screened the articles according to eligibility criteria by reading the abstracts and titles. This resulted in 39 potential studies to be included. Of these, twenty-three were excluded; The reasons for excluding

	D1	D2	D3	D4	D5	D6	D7	Overall
Farooq et al, 2011	+	+	+	+	+	+	-	+
Valenstein et al, 2011	+	-	+	-	+	+	+	+
Montes et al, 2012	+	+	X	X	+	+	X	X
Velligan et al, 2013	+	+	+	-	+	+	+	+
Barkhof et al, 2013	+	+	-	-	+	-	X	+
Schulz et al, 2013	X	X	-	-	+	+	+	X
Chien et al, 2015	+	+	+	+	+	+	+	+
Chien et al, 2016	+	+	+	+	+	+	+	+
Ngoc et al, 2016	X	X	-	-	+	+	-	X
Mishra et al, 2017	X	-	-	-	-	+	-	X
Erteem & Duman, 2018	X	X	-	-	X	-	-	X
Shimada et al, 2018	+	X	+	-	+	+	+	+
Chien et al, 2019	+	+	+	+	+	+	+	+
Xu et al, 2019	+	+	+	-	+	+	+	+
Hamann et al, 2020	+	+	+	-	+	+	-	+
Cai et al, 2020	+	+	+	-	+	+	+	+

D1: Random sequence generation  
 D2: Allocation concealment  
 D3: Blinding of participants and personnel  
 D4: Blinding of outcome assessment  
 D5: Incomplete outcome data  
 D6: Selective reporting  
 D7: Other sources of bias

X High  
 - Unclear  
 + Low

Figure 1 Summary of quality assessment of studies.

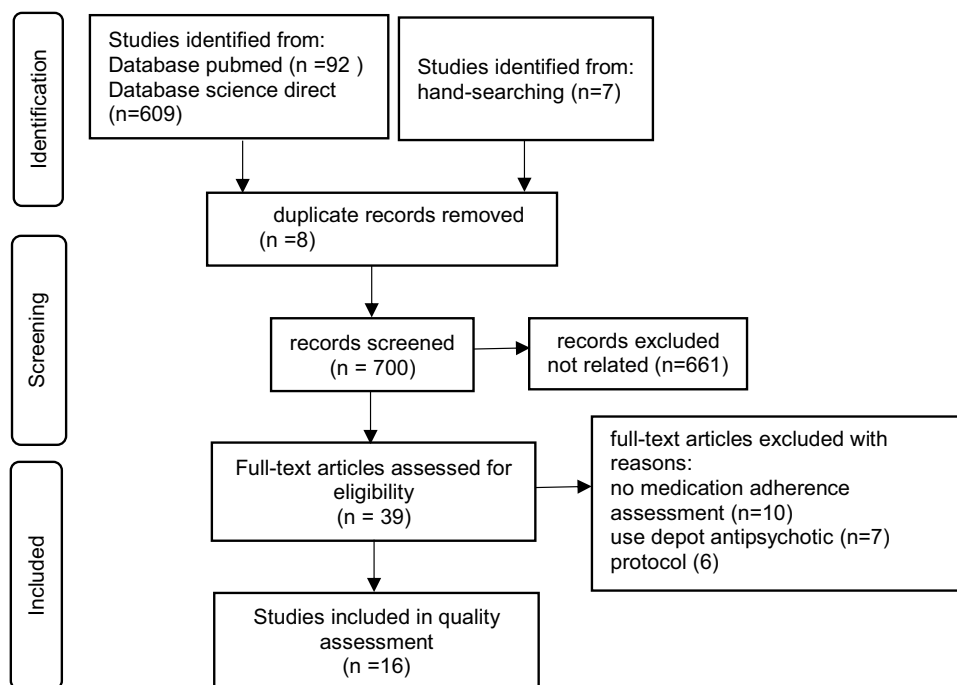


Figure 2 PRISMA diagram of this review.

studies were: no medication adherence assessment (n=10), using depot antipsychotic (n = 7), and protocol (n = 6). Sixteen studies met the inclusion criteria for this review.

## Characteristics of Included Study

All sixteen studies included in this review were randomized controlled trials. Eleven studies were at low risk of bias and five studies were at high risk of bias. The main characteristics of the included studies are presented in Table 1. The oldest studies were published in 2011<sup>28,29</sup> and the most recent study was published in 2020.<sup>30,31</sup> Fifteen studies used a randomized controlled trial design with two arms,<sup>28–42</sup> and one study used a randomized controlled trial design with three arms.<sup>43</sup> The studies were conducted in the United States,<sup>29,43</sup> several countries in East, West and South Asia such as China,<sup>31,36</sup> HongKong,<sup>35,40,41</sup> Japan,<sup>34</sup> Turkey,<sup>33</sup> Pakistan,<sup>28</sup> India,<sup>32</sup> and Vietnam,<sup>42</sup> as well as European countries such as Spain,<sup>37</sup> the Netherlands,<sup>38</sup> and Germany.<sup>30,39</sup>

## Types of Intervention and Personnel Who Delivered the Intervention

The Supervised Treatment in Outpatients for Schizophrenia (STOPS) program employs a drug supervisor who is appointed by the patient's family or close relatives. The drug supervisor is responsible for administering drugs from health facilities to patients in the correct dose and supervising treatment and recording patient medication adherence. STOPS, used an educational intervention for caregivers (key care supervisors) to administer and supervise the medication provided free of charge as part of a treatment program.<sup>28</sup>

In five studies, motivational interviews were used as an intervention, while normal treatment (TAU) and routine care were used as controls.<sup>33,35,38,40,41</sup> Motivational interviewing (MI) is a client-centered consultation method, supported by a series of phases, that is, engaging, focusing, evoking, and planning. Patients participate in discussions with therapists about their concerns and problems with medication. The overall objective is to increase the patient's personal motivation to change.

One study applied adherence therapy intervention.<sup>39</sup> Adherence therapy (AT) is a treatment-based, patient-centered that aims to reduce psychiatric symptoms in patients by increasing treatment adherence. The four cornerstones of AT are keeping the patient engaged and minimizing resistance to change, providing the patient with the information required by

**Table 1** Summary Characteristics of Included Studies

Location (Author, date)	Intervention Description	People Who Deliver the Intervention	Participants Involved (Intervention/Control)	Study Design
Pakistan (Farooq et al, 2011) <sup>28</sup>	Participants received usual care plus STOPS in the intervention group or usual care in the control group. In the STOPS, participants each had a key care supervisor, who is a family member, living with people with schizophrenia for at least six months and providing support for the treatment, ie, being responsible for administering drugs from health facilities to patients in the correct dose, supervising treatment, and recording patient medication adherence. The key care supervisor was educated on the nature of the illness, common misconceptions about treatment, and the importance of medication adherence, as well as basic skills in how to administer and supervise the medication.	Patients' family members	Total participants: 95 Outpatients with diagnoses of schizophrenia or schizoaffective disorder hospital psychiatry department. Mean age: (STOPS 29 years; SD 8.1/TAU 30 years; SD 8.3) Range 17–60 years Gender: (STOPS 85.5% male; 14.5% female/TAU 85.5% male; 15.5% female)	Randomized controlled trial, two arms
United States (Valenstein et al, 2011) <sup>29</sup>	Participants received usual care plus Meds-Help in the intervention group or usual care in the control group. Meds-Help consists of a unit of use packaging (including all medications), medication education sessions, reminders, and notification for patients if they failed to fill antipsychotic prescriptions within 7–10 days of fill date.	Pharmacist in Meds-Help team	Total participants: 118 Outpatients with diagnoses of schizophrenia, schizoaffective, or bipolar disorder. Mean age: Meds Help 49.6 years; SD 11.0/UC 50.2 years; SD 11.7 Range unknown Gender: (all participants 97% male; 3% female)	A randomized controlled trial, two arms
Spain (Montes et al, 2012) <sup>37</sup>	For three months, participants in the intervention group received daily SMS reminders to take their medication on their cell phones, whereas participants in the control group did not receive SMS.		Total participants: 251 Outpatients with schizophrenia diagnosis at psychiatric centers. Mean age (SMS 38.6 years; SD 10.2/Control 40.6 years; SD 11.5) Range 18–65 years Gender: (SMS 65% male/Control 67.5% male)	A prospective, open, randomized controlled trial, two arms
United States (Velligan et al, 2013) <sup>43</sup>	Participants were divided into three groups (Med-eMonitor, PharmCAT, and TAU). Participants received Med-eMonitor as a device (an electronic intervention) that provides prescribing information, including an alarm to take medication. Participants received assessments of neurocognitive function, behavior, adaptive functioning, and the environment. Interventions in Pharm-CAT were individualized and specifically targeted to adherence. participants received Pharm-CAT intervention once a week for 30 to 45 minutes. TAU: As usual, treatment consists of medication and psychiatric appointments routinely.	Therapists	Total participants: 142 Outpatients with the diagnosis of schizophrenia or schizoaffective disorder at a community mental health center. Mean age: (MM 43 years; SD 10.15/Pharm CAT 43 years; SD 11.04/TAU 42 years; s.d. 9.27) Range 18–60 years Gender: (MM 55.32% male; Pharm CAT 52.08% male/TAU 52.82% male)	In a randomized trial, three arms

(Continued)

Table I (Continued).

Location (Author, date)	Intervention Description	People Who Deliver the Intervention	Participants Involved (Intervention/Control)	Study Design
The Netherlands (Barkhof et al, 2013) <sup>38</sup>	Participants received MI intervention to improve medication adherence, whereas participants in the control group received HE with an individual lecture method that contained general health topics.	Therapists (psychologists, a psychiatrist, and community mental health nurses)	Total participants: 96 Inpatients and Outpatients with diagnosis of schizophrenia or schizoaffective disorder in mental health care institutions Mean age: (MI 35.9 years; SD 10.3/HE 34.7 years; SD 1.4) Range 18–65 years Gender: (MI 78% male/HE 81% male)	A randomized controlled trial, two arms
Germany (Schulz et al, 2013) <sup>39</sup>	In the intervention group, participants received AT as an add-on to TAU. Inpatients receive AT as a course over eight one-on-one sessions, each with a different focus, that include assessment, structured medication problem solving, exploring patients' ambivalence towards medication, testing patient beliefs in medication, and assisting patients in achieving their life goals. For the control group, participants received TAU that followed national guidelines for the treatment of schizophrenia that were provided by psychiatrists and nurses based on individualized medication, psychotherapy, and occupational therapy.	Therapists (mental health nurses)	Total participants: 123 Inpatients with the schizophrenic disorder in psychiatric services. Mean age: (AT 35 years; SD 10/TAU 36 years SD 9) Range ≥ 18 years Gender: (AT 60% male/TAU 56% male)	A parallel-group randomized controlled trial, two arms
Hong Kong (Chien et al, 2015) <sup>40</sup>	Participants (9–10 participants under each of the six nurse therapists) received a biweekly MI-based AT program that consists of cognitive, motivational, insight-inducing, and behavioral training. For the control group, participants received TAU (routine outpatient and community mental health services).	Therapists (Community psychiatric nurses)	Total participants: 110 Outpatients with a primary diagnosis of schizophrenia spectrum disorders at the Community Psychiatric Nursing Service. Mean age: (MI 29.21 years SD 9.64/TAU 28.13 years SD 8.96) Range 18–60 years Gender: (AT 50.88% male; 49.12% female/TAU 52.63% male; 47.37% female)	A parallel-group randomized controlled trial, two arms
Hong Kong (Chien et al, 2016) <sup>41</sup>	Participants received the MI-based AT program as an addition to routine care, which consisted of three phases and adopting a few strategies based on Chinese cultural tenets. The AT was aimed to engage participants in addressing their needs and concerns regarding medication adherence, leading them to set goals and action for change in adherence. For the control group, participants received TAU (routine psychiatric care).	Therapists (Community psychiatric nurses)	Total participants: 128 Outpatients with schizophrenia and its subtypes such as schizoaffective and schizophreniform disorders at the Community Psychiatric Nursing Service Mean age: (AT-based MI 29.13 years SD 9.87/TAU 28.23 years SD 9.23) Range 18–64 years Gender: (AT 52.24% male; 47.76% female/TAU 53.73% male; 46.27% female)	A randomized controlled trial, two arms

Vietnam (Ngoc, Weiss & Trung, 2016) <sup>42</sup>	FSPP is a program that involves patients and their families as participants and consists of three sessions that take place in the hospital. Participants provide information about schizophrenia and treatment, facilitate family discussions about problems and challenges of being a schizophrenic family member, and teach patients how to reintegrate into the community and live a normal life.	Patients' family members	Total participants: 59 Inpatients with schizophrenia at a psychiatric hospital. Mean age: (FSPP 24.87 years SD 5.11/Control 23.69 SD 4.37) Range 18–30 years Gender: (FSPP 48.6% male/Control 51.4% male)	A randomized controlled trial, two arms
India (Mishra et al, 2017) <sup>32</sup>	Participants in the intervention group received counseling by a pharmacist and education via Patient Information Leaflets (PILs), called collaborative care intervention, as an addition to the usual care by a psychiatrist.	Psychiatrist and pharmacist	Total participants: 23 Outpatients with schizophrenia Mean age: unknown Range 18 - ≥ 60 years Gender: (Collaborative care, 26.09% male; 30.43 female/UC 8.70% male; 34.78% female)	A prospective randomized controlled trial, two arms
Turkey (Erteem & Duman, 2018) <sup>33</sup>	Participants received MI in the intervention group. Participants were individually interviewed by a researcher in the psychosis unit, and the purpose of each interview was to determine the resistance of the patients to change, understand the symptoms of the disease, identify the factors related to non-adherence, evaluate the benefits and side effects of the treatment subjectively, and encourage the self-efficacy of a patient in maintaining the treatment.	Researcher (a Ph.D. student in the psychiatric nursing department)	Total participants: 40 Outpatients at a university hospital Psychiatric clinic. Mean age: (MI 43.20 years SD 10.54/Control 40.05 years SD 10.87) Range 18–64 years Gender: (MI 70% male; 30% female/Control 50% male; 50% female)	A randomized controlled trial, two arms
Japan (Shimada et al, 2018) <sup>34</sup>	Participants were divided into an intervention group (group OT plus IOT) and control group (group OT). Participants received IOT which consists of MI, self-monitoring, individualized visits, handicraft activities, individualized psychoeducation, and discharge planning.	Occupational therapists and other hospital staff	Total participants: 129 Inpatients at a psychiatric hospital. Mean age: (IOT+GOT 41.39 years SD 11.04/ GOT 43.39 years SD 9.97) Range 20–65 years Gender: (IOT+GOT 50% male; 50% female/ GOT 48.53% male; 51.47% female)	A multicenter, randomized controlled trial, two arms
HongKong (Chien et al, 2019) <sup>35</sup>	Participants received AT based on MI over 3 months focused on principles of expressing empathy, developing discrepancies between client's beliefs and evidence, supporting self-efficacy, avoiding argumentation, and rolling with resistance to behavioral change.  For the control group, participants received routine care consisting of monthly home visits, mental health assessment, administration of medications, and brief education by community psychiatric nursing services and psychiatric consultations by a psychiatrist	Therapists (community psychiatric nurses)	Total participants: 128 Outpatients at the Community Psychiatric Nursing Service Mean age: (MI 28.87 years SD 9.54/Routine Care 29.53 years SD 9.96) Range 18–65 years Gender: (AT 55.22% male; 44.78% female/ Routine Care 53.73% male; 46.27% female)	A randomized controlled trial, two arms

(Continued)

Table I (Continued).

Location (Author, date)	Intervention Description	People Who Deliver the Intervention	Participants Involved (Intervention/Control)	Study Design
China (Xu et al, 2019) <sup>36</sup>	Participants were given 686 program plus LEAN, a program that included the recruitment of a lay health supporter and text messages for medication reminders, health education, monitoring of early signs of relapse, and facilitated linkage to primary healthcare. For the control group, participants received the 686 program, a program that provides support and monitors medication for people with schizophrenia by home visit.	Patients' family members (Lay health supporters)	Total participants: 271 Outpatients in a community-based mental health program. Mean age: (LEAN 46.5 years SD 12.65/686 program 45.5 years SD 12.72) Range unknown Gender: (LEAN 55.4% female/686 program, 55.4% female)	A randomized controlled trial, two arms
Germany (Hamann et al, 2020) <sup>30</sup>	Participants provided an individual consultations with group training in SDM-PLUS based on MI and negotiation approaches	Health care staff (consultants, residents, nurses, psychologists, and social workers)	Total participants: 322 Inpatients at a psychiatric hospital. Mean age: (SDM-PLUS 42.1 years SD 12.9/ Control 41.4 years SD 13.6) Range 18–65 years Gender: (intervention 52% female; 48% male/ Control 47% female; 53% male)	Cluster randomized controlled trial, two arms
China (Cai et al, 2020) <sup>31</sup>	The LEAN program, was extended from the previous LEAN program by Xu et al, (2019).	Patients' family members (lay health supporters)	Total participants: 244 Outpatients in a community-based mental health program. Mean age: (LEAN 46.5 years SD 12.65/686 program 45.5 years SD 12.72) Range unknown Gender: (LEAN 55.4% female/686 program, 55.4% female)	A randomized controlled trial, two arms



the patient about medications and side effects, and generating discrepancies in the patients' beliefs about treatment.<sup>44</sup> The patients in the intervention group received eight sessions of AT in addition to TAU.<sup>39</sup> Adherence therapy is based on the concept that patient beliefs have an impact on medication adherence.<sup>16,45,46</sup>

Montes et al<sup>37</sup> used an SMS reminder strategy. Patients received SMS reminders every day for more than 3 months to take their antipsychotic medication. The intervention group was compared with the control group who received standard therapy.<sup>37</sup> Velligan et al,<sup>43</sup> used PharmCAT and Med-eMonitor (MM) interventions for patients. PharmCAT is a component of the Full-CAT program, which consists of a series of intervention strategies aimed at compensating for the cognitive impairment associated with schizophrenia and improving adaptive functioning, but the interventions are only aimed at patient compliance issues. A Med-eMonitor (MM) is a smart pill container or electronic device in the home of a patient that helps remind patients to take medication, provides warnings in the case of the wrong medication, records side effects experienced by patients, and follows up if the patient does not adhere via telephone.

Meds-Help is a pharmacy-based intervention. The intervention is in the form of prescribing treatment packages followed by education and medication counseling by pharmacists for people with schizophrenia.<sup>29</sup> Similarly, collaborative care<sup>32</sup> is a pharmacy-based intervention. Mishra et al,<sup>32</sup> used collaborative care with pharmacists and psychiatrists working together as a team to improve patient drug compliance and patient clinical outcomes.

The Family Schizophrenia Psychoeducation Program (FSPP) is a program offered to people with schizophrenia and their families to provide comprehensive information on schizophrenia through direct discussions with psychiatrists, psychologists, and nurses in a hospital with the ultimate goal of improving medication adherence and improving the quality of life of patients with schizophrenia.<sup>42</sup>

Individualized occupational therapy (IOT) strategies are tailored to enhance cognitive functioning and prompt adaptive behaviors to maximize functional outcomes for patients with schizophrenia. It consists of a combination of effective psychosocial treatment programs, including motivational interviewing, self-monitoring, individualized visits, handicraft activities, individualized psychoeducation, and discharge planning.<sup>34</sup>

An intervention called LEAN (Lay Health supporters, E-platform, Award, and integration) involved the recruitment of lay health supporters; an electronic platform with mobile texting/SMS for medication reminders, health, education, and monitoring; the awarding of token gifts for positive behavioral improvement; and integration of texting with the health system.<sup>31,36</sup> In this review, two studies were using the LEAN strategy. The first study conducted by Xu et al, used a 2-arm randomized controlled trial design, while the study conducted by Cai et al, was a randomized controlled trial of a step-by-step wait list design, which is a follow-up implementation of LEAN from previous trials.

SDM-PLUS is an intervention with an approach to increase patient motivation through special communication techniques provided by trained health workers so that patients are allowed to be directly involved in discussions with health workers regarding their treatment.<sup>30</sup>

The involvement of the healthcare professional providing the intervention can be seen in all the studies included in this review. Interventions in the form of motivational interview techniques,<sup>33,35,38,40,41</sup> adherence therapy,<sup>39</sup> IOT,<sup>34</sup> and SDM-PLUS<sup>30</sup> were provided by therapists (psychologists, psychiatrists, or mental health nurses), while the STOPS (Supervised Treatment in Outpatients for Schizophrenia),<sup>28</sup> FSPP (Family Schizophrenia Psychoeducation Program),<sup>42</sup> and LEAN (Lay Health supporters, E-platform, Award and iNtegration)<sup>31,36</sup> programs were delivered by family members. Two interventions involved pharmacists, which were Meds Help<sup>29</sup> and Collaborative Care.<sup>32</sup>

## Participants Characteristic

The total number of participants in each study ranged from 23 to 322 participants. Based on the characteristics of participants in thirteen studies, data on the age of participants ranged from 14–65 years, while the remaining three studies were unknown.<sup>29,31,36</sup> The mean age of the participants in fifteen studies ranged from 16.2 to 50.2 years, but in Mishra et al<sup>32</sup> studies it was not stated. In all studies, the majority of the participants involved were male (range between 50% and 97%). Five studies involved only male participants<sup>37–39,42,43</sup> and two studies only female participants,<sup>31,36</sup> the rest included both male and female participants.<sup>25–27,32–35,40,41</sup>

Inpatients and outpatients with schizophrenia or related psychoses, such as schizoaffective disorder, who were receiving treatment in a hospital or community service department, were enrolled in the 16 studies included in this

systematic review. Farooq et al,<sup>28</sup> Valenstein et al<sup>29</sup> Cai et al,<sup>31</sup> Montes et al,<sup>37</sup> Chien et al,<sup>35,40,41</sup> Mishra et al,<sup>32</sup> Ertem and Duman,<sup>33</sup> and Xu et al<sup>36</sup> included out-patients. Hamann et al,<sup>30</sup> Velligan et al,<sup>43</sup> Schulz et al,<sup>39</sup> Ngoc et al,<sup>42</sup> and Shimada et al,<sup>34</sup> included inpatients and only one study included inpatients and outpatients.<sup>38</sup>

## Medication Adherence Measurements

Three approaches were used to measure adherence in sixteen studies, including: (1) participants' response to a questionnaire via researcher interview or participants' self-reporting, (2) electronic compilation of participants' dosing history, and (3) analysis of medication refill record from hospital dispensing record or claim database. Self-report measures were the Medication Adherence Questionnaire (MAQ),<sup>37,38</sup> Drug Attitude Inventory (DAI),<sup>31,36–39</sup> Medication Adherence Rating Scale (MARS),<sup>30,39</sup> Morisky Medication Adherence Scale (MMAS),<sup>34</sup> Adherence Rating Scale (ARS and BARS).<sup>31,35,36,40,41</sup> Other studies used self-ratings by patients or relatives or healthworkers,<sup>28,42</sup> pill count,<sup>31,36,43</sup> and blood plasma level.<sup>39</sup> Adherence rates were reported as mean or median percentages or percentages of complete doses taken, or assessment tool scores.

Three studies<sup>29,37,38</sup> used the MAQ questionnaire. The MAQ is also known as the 4-item Morisky Medication Scale (MMAS-4) and Morisky Scale.<sup>48</sup> The MAQ is a self-assessment questionnaire consisting of four questions with yes-or-no answers. When the answer indicates a negative adherence issue, a score of 1 is recorded.<sup>49</sup> The total score ranges from 0 (good adherence) to 4 (poor adherence).<sup>49</sup> In Barkhof et al,<sup>38</sup> measurements of adherence using MAQ were carried out at the beginning of participant recruitment, post-treatment, and six months of follow-up, but in Montes et al,<sup>37</sup> measurements of adherence were carried out at the beginning of participant recruitment, 3 months after the intervention, and 3 months after the intervention was stopped. The total MAQ score in the intervention group was compared with the control group.<sup>37,38</sup>

The MMAS-8 is an updated version of the previous Morisky scale, consisting of 8 items with dichotomous answers "Yes or No". The total score ranged from 0 to 8, with higher scores indicating better adherence to prescribed medication. In a study by Shimada et al,<sup>34</sup> assessments were conducted by trained evaluators before assignment (baseline assessment) and at discharge or 3 months following hospitalization (post-assessment).

The DAI is a questionnaire consisting of a self-assessment scale developed to measure subjective responses and attitudes of chronic people with schizophrenia to treatment. A positive total score means a positive subjective attitude. The DAI questionnaire was used to assess attitudes toward treatment.<sup>50,51</sup> The DAI is available in 30-item and 10-item versions. The 10-item version (DAI-10) consists of a subset of DAI-30 items.<sup>52</sup>

The Medication Adherence Rating Scale (MARS) is a 10-item self-report instrument in which a yes or no response is given to questions asked. The total scores range from 0 (low likelihood of medication adherence) to 10 (high likelihood). Assessment of patient medication adherence was measured from follow-up 1 to follow-up 2 and follow-up 2 to follow-up 3. The average improvement in medication adherence in the intervention and control groups was assessed.<sup>32</sup>

The single-item ARS developed by Staring et al,<sup>53</sup> is a self-report measurement to measure medication adherence. ARS items were assessed on a 5-point Likert scale (1 = total non-adherence, 2 = poor compliance, 3 = inadequate compliance, 4 = moderate compliance, and 5 = good compliance).

Farooq et al study<sup>28</sup> adapted the Herz et al<sup>54</sup> methods of measuring medication adherence, which is measured during the interview using a questionnaire with a 5-point scale (where 1 is always and 5 is never). Medication adherence assessments were performed every three months beginning at baseline, using the information provided by participants and relatives. If available, drugs calculated from the previous prescription add to this information. Participants were considered to be in full adherence to treatment if they took their medication as prescribed without missing a dose during the assessment period. Non-adherence was defined as missing medication for more than a week at a time. Partial adherence occurs when participants take some medications but do not take them every day of the week.<sup>28</sup>

The Ngoc et al<sup>42</sup> study used a medication adherence inventory scale to assess nonadherence that was adapted for Vietnam, and this instrument consists of 8 items rated on a frequency scale of 0–2, with higher scores indicating higher non-compliance.<sup>55</sup>

Concentration to dose Ratio (CDR) is a measurement of compliance using the calculation of the ratio of concentration to serum dose, namely the higher the CDR, the more patients are adherent. If a patient is taking more than one antipsychotic drug the psychiatrist is asked to specify the primary antipsychotic drug used for analysis. All blood

samples were collected between 8 and 10 am by the nurse or psychiatrist working on the ward. For follow-up testing, subjects are invited to the clinic for blood collection. If patients are unable to attend, blood is drawn at their homes.<sup>39</sup>

Xu et al<sup>36</sup> and Cai et al<sup>31</sup> used pill counts to measure adherence. The number of undeclared home pills as a proportion of the doses taken in the previous month (number of first counts – number of second counts + number of additional pills taken – number of pills discarded) / (the number of pills determined). If two or more types of antipsychotic drugs were taken, adherence was calculated by combining the number of tablets of the drug required by the prescription as the denominator and the actual number of pills taken as the numerator. However, pill counts were not performed at baseline. Instead, refill records and 2 rating scales were used at baseline i.e Brief Adherence Rating Scale (BARS) and Drug Attitude Inventory-10 (DAI-10). Adherence by refill record was calculated as a cumulative medication possession ratio (0–100%) over 1 year, ie, the number of days medication obtained over 365 days divided by 365 days. DAI-10 adherence was originally from –10 to +10 (highest score equals more positive attitude toward medication), which was rescaled to be 0 to 1. BARS adherence is the self-reported percentage of dosages taken over the past month.<sup>31,36</sup>

An electronic monitor was used to measure compliance in a study conducted by Velligan et al<sup>43</sup> The med-monitor is calculated by comparing the number of doses that the patient is supposed to take with the number of times the container is opened in a certain dose window and the patient indicates that the pill was consumed. In addition to adherence to the electronic monitor, participants' homes were visited monthly for unannounced pill counts.

## Duration of Follow-Up

The duration of follow-up varied between all studies. The duration ranged from 3 months to 18 months. One study started follow-up after 1 week of intervention, followed by 6 months and 12 months.<sup>35</sup> In Chien et al study,<sup>41</sup> had the longest follow-up, first at 2 weeks, continued for 6 months and 18 months. One study did not report the duration of the intervention.<sup>32</sup>

## Effectiveness of Interventions on Medication Adherence

Summary study results is summarized in Table 2. Motivational interviewing interventions were performed in five studies. The intervention was based on motivational interviewing conducted in approximately 5–8 sessions during the 6-month to 18-month program. Four studies<sup>33,35,40,41</sup> showed significant improvement in medication adherence; one study<sup>38</sup> did not. The same results were also shown in the adherence therapy intervention,<sup>39</sup> which showed a change in the mean score of adherence that was not significant in the intervention group compared to the control group.

The remaining ten studies with more heterogeneous interventions — STOPS (Supervised Treatment in Outpatients for Schizophrenia),<sup>28</sup> Meds-Help,<sup>29</sup> SMS-based interventions,<sup>37</sup> Pharm-CAT and Med-eMonitor,<sup>43</sup> FSPP (Family Schizophrenia Psychoeducation Program),<sup>42</sup> collaborative care,<sup>32</sup> IOT (Individualized Occupational Therapy),<sup>34</sup> and the last one, LEAN (Lay Health supporters, E-platform, Award, and integration),<sup>31,36</sup> mostly showed positive results on medication adherence. The intervention SDM-PLUS (Shared Decision-Making PLUS)<sup>30</sup> did not show a significant improvement in adherence.

## Effectiveness of Interventions on Other Outcomes

In these studies, other outcome measures such as symptom and clinical severity,<sup>27,28,35–37,39–41,43</sup> Global Functioning and Psychosocial Functioning,<sup>28,30,35,37,40,41,43</sup> Quality of Life (QoL),<sup>29,32,37,42</sup> hospitalization rates or rehospitalisation,<sup>31,34–36,38,40,41</sup> insight into illness,<sup>33,35,40,41</sup> stigma,<sup>42</sup> and intrinsic motivation<sup>34</sup> were also measured.

Some of the measurements showed positive effects, while others did not. The effects appear to depend on the interventions and characteristics of participants, which are different in each study.

## Discussion

This systematic review summarises the evidence available on interventions designed to improve medication adherence in patients with schizophrenia. The majority of interventions found positive improvements in adherence, across a range of intervention types, including motivational interviewing, technology-enhanced/mHealth interventions, collaborative

**Table 2** Summary of Study Results

Study	Follow-Up Times	Medication Adherence Measurements	Medication Adherence Outcomes	Other Outcomes
Farooq et al, 2011 <sup>28</sup>	3 months, 6 months, and 12 months	Evaluation of medication adherence as described originally by Herz et al <sup>54</sup> using a questionnaire with a 5-point scale	Participants in the STOPS group had better adherence: Complete adherence: 37 (67.3%) in STOPS versus 25 (45.5%) in TAU; $P = 0.02$	There was a significant improvement in symptoms (PANSS scale total score; $P = 0.003$ ) and functioning (GAF scores; $P = 0.008$ ) in the STOPS group than in the TAU group
Valenstein et al, 2011 <sup>29</sup>	6 months, and 12 months	MPR	Meds-Help interventions had a statistically significant higher MPR at 6 and 12 months ( $p < 0.0001$ )	There were no significant differences between the intervention group and control group in PANSS ( $P = 0.46$ ) and QWB ( $P = 0.24$ )
Montes et al, 2012 <sup>37</sup>	3 months, 6 months	MAQ DAI-10	A significantly greater improvement in adherence was observed among patients receiving SMS text messages compared to the control group. The mean change in the total score from baseline to month 3 was $-1.0$ (95% CI $-1.02, -0.98$ ) in the intervention group versus $-0.7$ (95% CI $-0.72, -0.68$ ) in the control group; $P = 0.02$ The mean change in the total MAQ score from month 3 to month 6 (3 months after stopping the SMS-based intervention) was $-1.1$ (95% CI $-1.12, -1.08$ ) in the intervention group versus $-0.8$ (95% CI $-0.81, -0.78$ ) in the control group; $P = 0.04$	There were no significant differences between the intervention group and control group after 6 months of follow-up in CGI-SCH-SI global ( $P = 0.48$ ), CGI-SCH-DC global ( $P = 0.32$ ), and EQ-5D VAS ( $P = 0.75$ ).
Velligan et al, 2013 <sup>43</sup>	3, 6, and 9 months	Electronic monitor (Med-eMonitor) and Pill count	The PharmCAT and Med-eMonitor intervention groups had a statistically significant improvement in medication adherence at all time points throughout treatment and after 9 months of follow-up when compared with the control group ( $P < 0.001$ ). No significant differences between MI and HE at 6 months and 12 months follow-up $P = 0.34$	There was no significant effect for on SOFAS scores and BPRS (all $P$ values $> 0.09$ ).
Barkhof et al, 2013 <sup>38</sup>	6 months, and 12 months	MAQ	AT had no significant difference in mean score at follow-up ( $p > 0.05$ ) AT had no different in mean score compared to the control group AT had no significant difference mean score at follow-up ( $p > 0.05$ )	There were significant differences in hospitalization rates at follow-up between MI and HE
Schulz et al, 2013 <sup>39</sup>	3 months	CDR MARS DAI-30	AT had no significant difference in mean score at follow-up ( $p > 0.05$ )	There was a significant improvement in the PANSS-total in the AT group compared to the TAU group
Chien et al, 2015 <sup>40</sup>	4 months, 6 months	ARS	Motivational interviewing-based adherence therapy has been found to have a significant effect on medication adherence $P = 0.007$	There were significant improvements in insight into illness, psychosocial functioning, symptom severity, and number of rehospitalizations in the intervention group compared to usual care or control group

Chien et al, 2016 <sup>41</sup>	2 weeks, 6 months, and 18 months	ARS	Motivational interviewing-based adherence therapy has been found to have a significant effect on medication adherence $P = 0.005$	There was significant improvement in the intervention group in symptom severity ( $P < 0.003$ ), insight into illness ( $P < 0.001$ ), functioning ( $P < 0.005$ ), and duration of re-hospitalizations ( $P < 0.005$ ).
Ngoc et al, 2016 <sup>42</sup>	6 months	Assessed using Dunja at al <sup>55</sup> medication compliance, inventory, adapted for Viet Nam	FSPP has been found to have better medication compliance than control	There were significant effects on QoL and stigma
Mishra et al, 2017 <sup>32</sup>	Unknown	MARS	The collaborative care group can significantly improve patient medication adherence	There was a significant improvement in the mean QoL
Erteem & Duman, 2018 <sup>33</sup>	3 and 6 months	MAQ	Motivational interviewing showed a significant effect on medication adherence after 3 months of follow-up post-intervention ( $P < 0.001$ ) and 6 months of follow-up ( $P < 0.001$ )	There was a statistically difference between the intervention and control groups in levels of insight at post-MI ( $P = 0.026$ ), third-month follow-up ( $P = 0.011$ ), and lastly sixth-month follow-up ( $P = 0.002$ )
Shimada et al, 2018 <sup>34</sup>	3 months	MMAS-8	IOT+GOT has been found to have a significant effect on medication adherence. MMAS-8 score ( $p < 0.01$ ) compared to GOT alone	IOT+GOT showed significant improvements in verbal memory ( $P < 0.01$ ); working memory ( $P = 0.02$ ); verbal fluency ( $P < 0.01$ ); attention ( $P < 0.01$ ); and composite score ( $P < 0.01$ ) on the BACS-J; perceived choice ( $P < 0.01$ ), IMI-J total ( $P < 0.01$ ); and CSQ-8J ( $P < 0.01$ ).
Chien et al, 2019 <sup>35</sup>	1 week, 6 months, and 12 months	ARS	Motivational interviewing-based adherence therapy has been found to have a significant effect on medication adherence $P = 0.008$	There was statistical difference between MI-based AT and routine care in insight and treatment attitudes ( $P = 0.009$ ), PANSS scale ( $P = 0.008$ ), and re-hospitalization ( $P = 0.010$ ).
Xu et al, 2019 <sup>36</sup>	6 months	Pill-count Refill Record DAI-10 BARS	Medication adherence the difference was 0.48 in the control group and 0.61 in the intervention group (95% CI 0.03 to 0.22; $p = 0.013$ ) Medication adherence the difference was 0.76 in the control and 0.83 in the intervention (95% CI -0.01 to 0.10; $p = 0.12$ ) Medication adherence the difference was 0.67 in the control and 0.68 in the intervention (95% CI -0.05 to 0.08; $p = 0.67$ ) Medication adherence the difference was 0.68 in the control and 0.71 in the intervention (95% CI -0.04 to 0.10; $p = 0.37$ )	The LEAN program is effective to reduce relapses and re-hospitalizations
Hamann et al, 2020 <sup>30</sup>	12 months	MARS	No significant improvements in adherence in the 6- and 12-month follow-up	SDM-PLUS higher perceived involvement in decision-making, but no significant improvements in rehospitalisations
Cai et al, 2020 <sup>31</sup>	6 months	Pill-count Refill Record DAI-10 and iBARS	Adherence to antipsychotic medications improved from 0.48 in the control period to 0.58 in the extended intervention period (95% CI 0.04 to 0.19; $p = 0.004$ ) Medications refill assessment had no significant ( $p = 0.70$ ) LEAN had no significant effect on medication adherence	In an extended implementation, the LEAN program was more effective than the 686 program alone in improving symptoms and reducing rehospitalization

care and complex interventions. Included studies were all randomized trials and were mostly judged to be at low risk of bias.

Three of the included studies, all using patient-therapist interactions, did not find evidence that the intervention improved the adherence of people with schizophrenia.<sup>30,38,39</sup> Hamann et al<sup>30</sup>, reported on the SDM-PLUS intervention, which used an approach to increase motivation through communication between patients and health workers. This method is similar to motivational interviewing which also emphasizes communication techniques to increase motivation. Two studies<sup>38,39</sup> using adherence therapy interventions based on motivational interviews also failed to find evidence of improved adherence. However, the remaining four motivational interviewing studies did find positive effects.<sup>33,35,40,41</sup>

Based on a review of the literature, it was found that one of the six studies reviewed showed a relationship between motivational interviewing (MI) and medication adherence. While the other five studies did not. They found association between MI and other outcomes such as improved psychotic symptoms and decreased re-hospitalization rates.<sup>23</sup> Motivational interviews may be beneficial for some patients with schizophrenia, but they should not be used as first-line therapy. Instead, they can be used as an adjunct treatment to improve patient outcomes, particularly for patients on a treatment program. Motivational interviews can assist in motivating patients and involving them in their treatment.<sup>56</sup> Motivational Interview is an opportunity to promote health patients are not motivated, but otherwise may be able to respond to interventions. Motivational interviews are useful tools for clinicians to encourage patients to seek help for mental health problems.<sup>57</sup>

According to intervention guidelines, Motivational Interview is divided into four phases (8 sessions).<sup>23,56</sup> In several studies in this review, there were differences in the number of Motivational Interview sessions given to participants. In the study of Chien et al<sup>40</sup> Motivational Interview was divided into 8 sessions, and 6 sessions in Chien et al<sup>41</sup> and Chien et al<sup>35</sup> But in Barkhof et al, patients were offered 8 sessions with a minimum of 5 sessions. A review and meta-analysis conducted by Gray et al<sup>44</sup> also showed evidence that AT was significantly able to reduce psychiatric symptoms compared to TAU in a follow-up period of less than 1 year, while the effect on adherence behavior and attitudes was not significant. Based on one study, it was found that the MI intervention provided a more dominant advantage over mental disorders patients with conditions who did not seek treatment, and from the study it was also found that the intensity of the MI intervention in short duration was as effective as a longer intervention, while two sessions of MI for 15 minutes was effective in increasing treatment attendance.<sup>57</sup>

The systematic review and meta-analysis of Loots et al<sup>20</sup> also explained that the significant effect of medication adherence could be achieved when the intervention was adequate and provided extended follow-up duration. Each duration selected in the intervention will have an effect size value. Motivational interviewing that focuses on medication and changes in medication used, achieving beneficial outcomes in adherence at six months of follow-up with moderate effect size.<sup>40</sup> Studies that include proper and extended follow-up periods are important, as researchers need to assess the impacts of the intervention on adherence to immediate, intermediate and long-term effects.<sup>20</sup> Based on the evidence, it is necessary to pay attention to several factors such as the patient's condition, how the patient seeks treatment, and the duration of follow-up in order to achieve the optimal outcomes for improving medication adherence.

Several studies used daily SMS as a reminder intervention, which increased medication adherence in people with schizophrenia.<sup>37</sup> Another study that also uses text messages for reminders of medication, called LEAN, was the study conducted by Xu et al<sup>36</sup> and Cai et al<sup>31</sup> Many studies have shown that text message interventions were effective in increasing the rate of medication adherence for people with HIV, asthma, diabetes, schizophrenia, and heart disease. The intervention period ranged from 1 week to 14 months. These studies were mostly conducted in developed countries, and applied a randomized controlled trial (RCT) design with intervening periods ranging from 1 week to 14 months.<sup>58</sup> The results of the narrative literature review<sup>59</sup> showed almost all studies suggest that SMS reminders help improve patient medication compliance and appointment reminders. In addition, it also reported the many benefits of using SMS reminders, including ease of use, relative cost, and fast and automated message delivery. The minimal risk was reported, and most participants found repeated reminders acceptable Text messaging appears to be an effective reminder mechanism to promote better medication compliance.

Another form of intervention that is also carried out was Meds Help, which is a pharmacy-based intervention that includes prescribing unit doses of drugs for psychiatric and medical conditions, education on packaged drugs, and refill

reminders sent 2 weeks earlier for 6 and 12 months. This intervention has significantly increased medication possession ratios (MPR).<sup>29</sup> Results of meta-analysis showed that pharmacist intervention had a statistically significant effect on medication adherence in patients with schizophrenia. The mean score of medication adherence of patients in the pharmacist intervention group was higher than in the control group (SMD = 0.60, 95% CI 0.41, 0.79) and the pooled relative risk for medication adherence was 1.13 (95% CI 1.07, 1.19).<sup>60</sup> The study conducted by Mishra et al<sup>32</sup> is also a pharmacy-based intervention. Patients are educated using Patient Information Leaflets (PIL). Based on these two studies, we can provide evidence that pharmacists' involvement in the care for patients with schizophrenia has an influential effect on increasing patient medication adherence. Evidence can be used as an example of an intervention that can be used or for the development of intervention models by pharmacists in the future, so that there will be more interventions that can be used to improve pharmaceutical services for patients with mental disorders, especially schizophrenia.

In another study conducted by Velligan et al,<sup>43</sup> used environmental support through home visits (Pharm CAT) and reminders to adhere to medication (Med-eMonitor). The intervention carried out in this study is a behavioral intervention. This intervention benefits individual patients, improves independent living skills, and improves cognitive abilities by training patients to adapt by providing education about treatment and providing support through medication reminders to improve patient compliance. The results showed an increase in patient compliance through measurement of the number of pills and electronic monitors in the measurement periods of 3, 6, and 9 months. Another study is in the form of a psychoeducational program (FSPP)<sup>42</sup> aimed at patients and their families. This intervention educates patients and their families about schizophrenia, including symptoms, and how to treat them, as well as the prognosis of schizophrenia if properly treated. In the end, it is hoped that after participating in this program, patients and their families will improve their stigma against schizophrenia, families will fully assist and support patients' treatment, medication adherence will increase and quality of life will also improve. This program consists of three sessions with a duration of approximately 1.5 h, which take place in the hospital. The sessions are interactive, with hospital staff providing information, but also facilitating discussion with families and patients. Sessions were conducted by a hospital psychiatrist, two psychologists, and two nurses. Sessions are usually provided for one and a half weeks. The FSPP program showed results that were able to significantly improve adherence to treatment adherence compared to controls.

The study conducted by Farooq et al used intervention in the form of a program called STOPS. This program is an adoption of the DOTS program for tuberculosis patients. This program focuses on the importance of the supervisor's role for patients during treatment, so the ultimate goal is to increase adherence to medication adherence and improve clinical outcomes.<sup>28</sup>

The study conducted by Shimada et al used a complex intervention. An individualized occupational therapy (IOT) program is a psychosocial program developed to facilitate proactive participation in treatment and improve cognitive function and other outcomes for hospitalized patients with acute schizophrenia. The program consists of motivational interviews, self-monitoring, individual visits, craft activities, individual psychoeducation, and discharge planning.<sup>34</sup>

In this review, several interventions to improve adherence have been described in patients with schizophrenia, although some of these interventions have not been successful in improving adherence to medications. Several problems arose in the studies included in this review, including those related to the reluctance of patients to participate in the study, dropouts that occurred during the study, and the unstable condition of patients who occasionally relapsed. Based on this review, there is also evidence that a single intervention or combination of interventions can improve adherence in patients with schizophrenia. The success of the intervention carried out is also influenced by the duration of the intervention given. Several studies in this review showed that the duration of the intervention differs from one another, adjusting to the type of intervention administered. In general, the duration of the intervention given is at least 3 months. The previous review found that interventions of a purely educational nature were the least successful in improving antipsychotic adherence, while those that employed combinations of education, behavioral, and affective strategies were the most successful in terms of adherence and secondary outcomes. Furthermore, interventions that reported improvements in adherence tended to be longer in duration and involved a larger number of participants, highlighting the importance of appropriate intensity and duration of therapy, along with the need to have a sample size large enough to determine the effectiveness of an intervention's effectiveness.<sup>61</sup>

A recent qualitative systematic review study found the conclusion that the strength of social attachment and the potential for joint decision-making programs in deciding treatment programs for people with schizophrenia are necessary so that patients are can rebuild perceptions to be able to live normally.<sup>62</sup> Therefore, in an intervention that is given, it is very necessary to have a relationship of trust between the therapist and the patient, education in the form of education to the patient or the patient's family about the disease and treatment, and motivation that must be continuously instilled in the patient to take treatment and return to normal life.

In all studies in this review, it was found that various health care professionals, such as psychiatrists, psychologists, mental nurses, and pharmacists, were found to act as people who provide interventions to people with schizophrenia. Most of the health care professionals who are heavily involved are psychiatrists, psychologists, and mental nurses. There is little direct involvement of pharmacists in the intervention. In general, pharmacists are only involved in the process of prescribing, procuring, and managing antipsychotic drugs.

Non-adherence in people with schizophrenia is influenced by a number of factors, including the disease, the patient, the treatment, environmental factors, and the patient's relationship with the physician.<sup>14</sup> These factors must be considered by the clinician when determining the appropriate intervention for the patient's needs, both individually and in groups. Furthermore, the active engagement and collaboration of health professionals such as psychiatrists, psychologists, psychiatric nurses, and pharmacists helps to improve the treatment of people with schizophrenia. The various interventions provided have benefits and weaknesses, and these interventions can be used as adjunctive therapy to antipsychotic therapy, which is still the mainstay of schizophrenia treatment. Furthermore, the variability in the research methodology applied, the intervention used, the definition of adherence, and the outcome measure of adherence chosen, becomes a problem in drawing conclusions regarding which intervention is most effective in improving medication adherence in people with schizophrenia.

## Limitations

This systematic review has some limitations. One limitation of this study was that it used a small number of databases and did not use large Embase databases. In addition, this review is limited to research published in English, research related to the discussed themes that were published in languages other than English may have been overlooked. This review concentrates on studies that used a randomized trial or randomized controlled trial design. As a result, the possibility of intervention using designs developed by others, such as a quasi-experimental or nonrandomized study, is not covered in this review. In the future, it is hoped that there will be not only quantitative research but also research with qualitative study designs to evaluate the evaluation of the interventions that have been given.

## Conclusion

Of the 15 studies, 2 have no significant effect on increasing adherence in people with schizophrenia. Interventions using various strategies have the potential to reduce medication nonadherence in schizophrenic patients, enables them to be used as adjunctive therapy to the main antipsychotic treatment to support people with schizophrenia. No intervention is superior or inferior because each has both benefits and drawbacks. Recent research will need to explore the major problems potentially causing patient nonadherence before developing intervention strategies, so that the interventions provided are based on the patient's needs to improve medication adherence.

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