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Interventions to Improve Pharmacological Adherence among Adults with Psychotic Spectrum Disorders, Bipolar Disorder, and Posttraumatic Stress Disorder

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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INTRODUCTION

Non-adherence to medication is a serious problem in the United States (US). It is associated with increased emergency department visits and hospitalizations,[2-7] higher costs of care,[2,6,7] and greater mortality.[8,9] For patients with serious mental illness, including schizophrenia and other psychotic spectrum disorders, bipolar disorder, and posttraumatic stress disorder (PTSD), adherence to psychopharmacological and/or non-psychopharmacological medications is an important concern. While some similarities exist, in general, these 3 populations are largely distinct in the factors associated with medication non-adherence and related outcomes, with some overlap in the interventions used to increase adherence.

For individuals with schizophrenia and other psychotic spectrum disorders, antipsychotic medications are a primary focus of treatment.[10] Among people with schizophrenia, adherence to antipsychotic medication is estimated to be between roughly 25%[11,12] to 50%[13]; in a study of patients with schizophrenia or schizoaffective disorder in the Veterans Affairs (VA) system, an adherence rate of 60% was reported.[14] Wide variation exists in reported adherence rates, and largely depend on the length of time examined and the method used to measure adherence.[15] Factors related to non-adherence in individuals with psychotic spectrum disorders may include patient-level factors such as lack of awareness or insight into the illness, negative attitudes towards medication,[15,16] comorbid substance use, and cognitive impairment; demographic factors such as younger age, male gender, and lower socioeconomic status; relationship factors such as a poor therapeutic alliance and poor social support; and system-level factors such as co-pays, medication supervision, and access to mental healthcare providers.[16] In addition to poor adherence to antipsychotic medications, individuals with schizophrenia and other psychotic spectrum disorders may be prone to poor adherence to medications prescribed for comorbid conditions, with one study reporting similar adherence rates for psychopharmacologic and non-psychopharmacologic therapies,[17] and another study using VA data reporting a higher rate of non-adherence to oral hypoglycemic medications among Veterans with schizophrenia than without.[18]

Similar to individuals along the psychotic spectrum, psychopharmacological medications (*eg*, antipsychotics and mood stabilizers) are the first line of treatment for patients with bipolar disorder,[19] with reported rates of adherence between 30%-57%.[20-22] Studies conducted in VA settings reported an adherence rate of 51.9%.[16,23] While many of the factors associated with non-adherence to antipsychotic medications – such as lack of insight into illness, comorbid substance use, cognitive function, and a poor therapeutic alliance – are similar to those found in individuals with psychotic spectrum disorders, other factors are more specific to patients with bipolar disorder, such as being unmarried, female, and homeless, having an external locus of control (*eg*, events are controlled by external factors rather than their own actions), having more suicide attempts, and receiving less-intensive psychopharmacologic treatments.[23]

Unlike patients with psychotic spectrum disorders or bipolar disorder, for individuals with PTSD, trauma processing therapy is often the first line of treatment.[24] Pharmacologic treatment is also used to treat PTSD, including serotonergic antidepressants, adrenergic receptor antagonists such as prazosin, second-generation antipsychotics, and anticonvulsants.[24] For

patients with PTSD, in addition to pharmacologic treatment for PTSD symptoms, non-adherence to medications for comorbid disorders may be a particular concern, with studies reporting higher rates of non-adherence to medications for cardiovascular disease.[25,26] While few studies examine medication adherence rates in patients with PTSD, one study of individuals discharged from a VA PTSD treatment program reported that 66% were non-adherent during the 12 months following discharge. A second study of Veterans stated that 12% of participants reported not taking their medication, 41% reported forgetting to take their medication, and 24% reported skipping medication.[26,27]

Current measures of medication adherence vary widely, with a broad range of inherent limitations, often related to validity or cost. Objective measures of adherence include observed intake, pill counts, electronic monitoring (e-monitoring), administrative pharmacy claims, and blood plasma concentration levels; subjective measures include patient report, self-reported scales, patient diaries, reports by caregivers or case managers, and clinician's views on adherence based on therapeutic response.[28-30]

Due to the extensiveness of medication non-adherence and its severe health consequences for patients with severe mental illness, many interventions have been developed to try to combat this problem. Interventions for medication adherence include patient-level interventions such as Adherence and Compliance Therapies; adherence skills trainings; psychosocial and behavioral interventions, including cognitive behavioral therapy (CBT) and Motivational Interviewing (MI), shared decision-making, customized adherence enhancement (CAE), and interventions involving family members. Provider-level interventions include provider education and training in MI. System-level interventions include financial incentives; methods related to information and communication technology (*eg*, phone follow-up, electronic reminder systems, e-Health interventions, refill reminders); reducing economic barriers (*eg*, cost-sharing, reducing co-pays); blister or unit dose packaging; case management or care coordination; and simplified dosing or dosing frequency strategies, including long-acting injectables. A recent review of interventions for medication adherence in patients with chronic illness found that educational interventions and case management were consistent in improving adherence across different clinical conditions, as were clinical reminders, pharmacist-led multicomponent approaches, and reducing out of pocket expenses for patients.[31] While this review did examine interventions for medication adherence in patients with depression, it did not include other serious mental illnesses.

The goal of this evidence report is to summarize the current evidence examining the effectiveness of interventions to improve medication adherence in patients with psychotic spectrum disorders, bipolar disorder, and PTSD, the effect of these interventions on patient outcomes, as well as the related costs and any associated intervention specific harms. As the Veterans Health Administration (VHA) continues to strive to provide high quality care, a better understanding of adherence interventions for these distinct populations will help to aid the VA in determining the programs and policies most appropriate for improving Veterans' health.

METHODS

TOPIC DEVELOPMENT

This topic was submitted to the ESP Coordinating Center by Anthony Morreale, PharmD, MBA, BCPS, FASHP, Assistant Chief Consultant for Clinical Pharmacy Services and Health Services Research, in the VA Office of Pharmacy Benefits Management Services. We further refined the scope and key questions for this topic through a preliminary search of peer-reviewed literature, and in concert with internal partners and investigators, Dr. Morreale, and a Technical Expert Panel comprised of both VA and non-VA experts (Appendix A). The key questions for the review are as follows:

KQ1. In adults with psychotic spectrum disorders:

a. What are the effects of medication adherence interventions on ***psychopharmacological*** adherence?
b. What are the effects of medication adherence interventions on *long-acting injectable (depot)* ***psychopharmacological*** adherence?
c. What are the effects of medication adherence interventions on ***non-psychopharmacological*** adherence?
d. What are the effects of these interventions on patient outcomes?
e. What are the harms and costs related to these interventions?

KQ2. In adults with bipolar disorder:

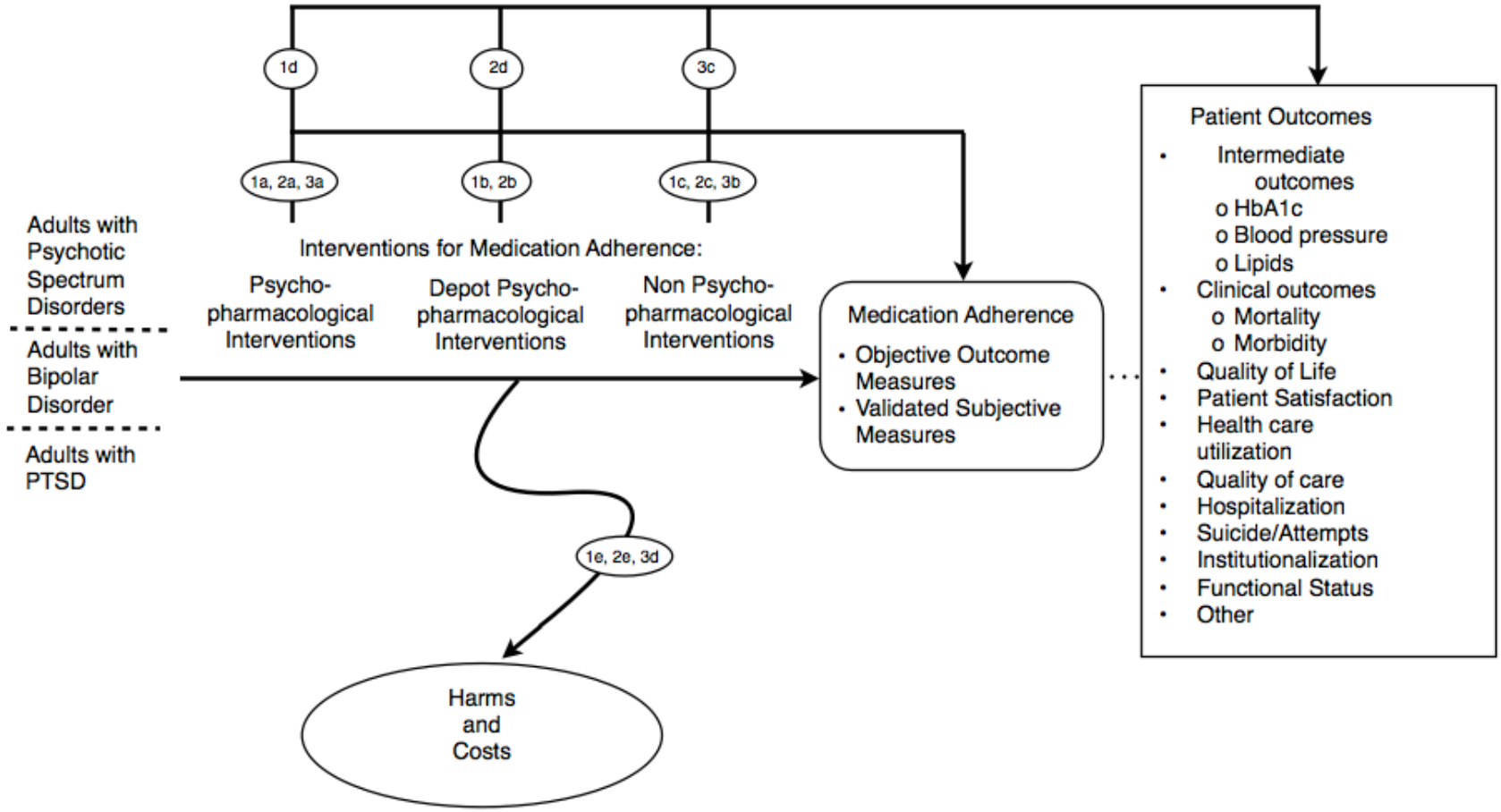
a. What are the effects of medication adherence interventions on ***psychopharmacological*** adherence?
b. What are the effects of medication adherence interventions on *long-acting injectable (depot)* ***psychopharmacological*** adherence?
c. What are the effects of medication adherence interventions on ***non-psychopharmacological*** adherence?
d. What are the effects of these interventions on patient outcomes?
e. What are the harms and costs related to these interventions?

KQ3. In adults with posttraumatic stress disorder (PTSD):

a. What are the effects of medication adherence interventions on ***psychopharmacological*** adherence?
b. What are the effects of medication adherence interventions on ***non-psychopharmacological*** adherence?
c. What are the effects of these interventions on patient outcomes?
d. What are the harms and costs related to these interventions?

Our approach was guided by the analytic framework shown in Figure 1.

Figure 1. Analytic Framework: Interventions for Medication Adherence in Adults with Psychotic Spectrum Disorders, Bipolar Disorder, and Posttraumatic Stress Disorder



Abbreviations: HbA1c = Glycated hemoglobin; PTSD = Posttraumatic Stress Disorder.

SEARCH STRATEGY

A search strategy was developed in consultation with a research librarian, and was peer reviewed by a second research librarian using the instrument for Peer Review of Search Strategies (PRESS).[32,33] We conducted a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the key questions from database inception to January 27, 2015. To identify relevant articles, we searched MEDLINE®, PubMed, PsycINFO©, Embase®, CINAHL©, and the Cochrane Library (Ovid EBM Reviews: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and NHS Economic Evaluation Database). In addition, we evaluated the bibliographies of included primary studies and any relevant systematic or nonsystematic reviews that were identified. To identify studies not published in peer-reviewed journals, we searched ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform (ICTRP), ISRCTN Registry, Conference Papers Index, and Dissertations & Theses Global. The complete search strategy is provided in Appendix B.

STUDY SELECTION

Criteria for population, interventions, comparators, outcomes, timing, and setting (PICOTS) were developed in collaboration with our stakeholders and Technical Expert Panel, and are provided in Table 3. We included only studies with adult populations examining interventions designed to improve medication adherence in general mental health settings (both inpatient and outpatient) that reported both a patient outcome measure and an objective or validated subjective measure of adherence.[1] Studies set in forensic settings with incarcerated participants were excluded due to limited applicability (*eg*, including increased supervision, medication distribution). Eligible study designs included randomized controlled trials (RCTs) or methodologically rigorous observational studies, including before/after studies with at least 3 time points and that completed analyses that controlled for time. Using pre-specified inclusion/exclusion criteria (Appendix C), 2 independent reviewers reviewed titles and abstracts using Abstrackr[34] and agreed on a final inclusion/exclusion decision for 10% of the search yield, with the remaining 90% decided by a single reviewer. Clinical trials were reviewed for inclusion according to the same pre-specified inclusion criteria by the primary investigator. At the full-text screening stage, 2 independent reviewers assessed all articles for inclusion (Appendix D). Discordant results were resolved through discussion or consultation with a third if discrepancies could not be resolved between the first 2 reviewers. Articles meeting eligibility criteria were included for data abstraction.

Table 3. PICOTS by Key Question

Key Question	**KQ1.** In patients with psychotic spectrum disorders: a. What are the effects of medication adherence interventions on ***psychopharmacological*** adherence? b. What are the effects of medication adherence interventions on *long-acting injectable (depot)* ***psychopharmacological*** adherence? c. What are the effects of medication adherence interventions on ***non-psychopharmacological*** adherence? d. What are the effects of these interventions on patient outcomes? e. What are the harms and costs related to these interventions?	**KQ2**. In patients with bipolar disorder: a. What are the effects of medication adherence interventions on ***psychopharmacological*** adherence? b. What are the effects of medication adherence interventions on *long-acting injectable (depot)* ***psychopharmacological*** adherence? c. What are the effects of medication adherence interventions on ***non-psychopharmacological*** adherence? d. What are the effects of these interventions on patient outcomes? e. What are the harms and costs related to these interventions?	**KQ3.** In patients with posttraumatic stress disorder (PTSD): a. What are the effects of medication adherence interventions on ***psychopharmacological*** adherence? b. What are the effects of medication adherence interventions on ***non-psychopharmacological*** adherence? c. What are the effects of these interventions on patient outcomes? d. What are the harms and costs related to these interventions?
Populations	Adults with psychotic spectrum disorders	Adults with bipolar disorder	Adults with PTSD
Intervention	Studies where the primary outcomes include medication adherence, including: § Patient-level interventions specifically designed to address medication adherence, such as: Compliance or Adherence Therapies, adherence skills training, psychosocial interventions (*eg*, psychoeducation, behavioral interventions, MI, cognitive interventions), customized adherence enhancement, family-supervised treatment, shared decision-making or § Provider-level interventions specifically designed to address medication adherence, such as provider education, and training in MI or § Systems-level interventions specifically designed to address medication adherence, such as: financial incentives, information and communication technology (*eg*, follow-up by phone, electronic reminder systems), reduction of economic barriers to adherence (*eg*, reducing copayments or prescription cost, cost-sharing), blister or unit-dose packaging, augmented pharmacy services, internet-based or eHealth interventions, simplified dosing or dosing frequency strategies, long-acting injectables (depot), case management or care coordination (*eg*, assertive community treatment, nurse-facilitated enhanced-treatment)		
Comparator	· Other active interventions · No treatment · Usual care · Studies with no comparison group only if outcome data are provided for baseline and at least 2 additional time points		
Outcomes	Medication adherence: § Measured objectively (*eg*, medication container with electronic monitoring [*eg*, MEMS], pill counts, biological markers, observed intake, medication possession ratio, medication plasma level, electronic ingestible event marker) § Measured subjectively by a validated patient self-report scale or measure (*eg*, Morisky Medication Adherence Scales [MMAS-8, MMAS-4 or MAQ]). See Nguyen et al for a list of validated measures.[1]		

	Patient outcomes: § Intermediate patient outcomes (HbA1c, blood pressure, lipids), clinical outcomes (mortality, morbidity), quality of life, patient satisfaction, health care utilization, quality of care, hospitalization, suicide/attempts, institutionalization, functional status, other. Costs **Exclude:** Medication adherence not the primary outcome –OR– Patient self-report, caregiver report, case manager report, clinician's view based on therapeutic response, and other non-validated subjective outcomes.
Timing	Short- and long-term outcomes
Study Design	RCTs; Methodologically rigorous observational studies (case control/cohort studies) that adjust for important confounders, and if no comparison group exists, data must be provided for baseline and at least 2 additional time points with analyses examining the trend and controlling for time.

DATA ABSTRACTION

Data from published reports were abstracted into a customized Systematic Review Data Repository (SRDR)[35] database by one investigator (among KK, DH, KJ, AM, AL) and confirmed by a second reviewer. From each study, we abstracted the following where available: study design, objectives, setting, population characteristics (including sex, age, race/ethnicity, diagnosis), subject eligibility and exclusion criteria, number of subjects, years of enrollment, duration of follow-up, the study and comparator interventions, important co-interventions, medication/class, number of medications, medication adherence outcomes, medication adherence thresholds, clinical outcomes, implementation factors, and harms.

QUALITY ASSESSMENT

Two reviewers (among KK, DH, KJ, AM, AL, MM) independently assessed the quality of each study using the risk of bias (ROB) assessment criteria developed for a recent high-quality comparative effectiveness review examining medication adherence interventions that did not address the populations included in this report.[31] This report followed the guidance and tools developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPC), and allows for the assessment of ROB for a wide range of study designs.[36,37] Disagreements were resolved through discussion with a third reviewer evaluating methodological quality if consensus could not be reached between the first 2 reviewers. Each study was given an overall summary assessment of low, medium, high, or unclear ROB (Appendices G & H):[36]

- Low ROB = We have confidence that the results represent the true treatment effect. The study reporting is adequate to judge that no major or minor sources of bias are likely to influence results.
- Medium ROB = We have some confidence that the results represent the true treatment effect. The study is susceptible to some bias, but the problems are not sufficient to invalidate the results.
- High ROB = We have low confidence that results represent the true treatment effect. The study has significant flaws that imply biases of various types that may invalidate its results; these may arise from serious errors in conduct, analysis, or reporting, large amounts of missing information, or discrepancies in reporting.
- Unclear ROB = The study is missing information, making it difficult to assess limitations and potential problems.

DATA SYNTHESIS

We summarized the primary literature by abstracting relevant data and qualitatively synthesizing the literature for each key question/clinical population. Due the heterogeneity in the literature, a meta-analysis was not performed. We constructed evidence tables outlining study characteristics, organized by key question, and analyzed individual study findings to draw conclusions.

RATING THE BODY OF EVIDENCE

We assessed the overall strength of evidence for outcomes using a method developed for AHRQ's EPCs.[38] The AHRQ EPC method considers study limitations, directness, consistency, precision,

and reporting bias to classify the strength of evidence for individual outcomes independently for randomized controlled trials and observational studies, with supplemental domains of dose-response association, plausible confounding that would decrease the observed effect, and strength of association, as well as separate guidance for applicability as follows:[39]

- High = We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable; in other words, another study would not change the conclusions.
- Moderate = We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low = We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient = We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion

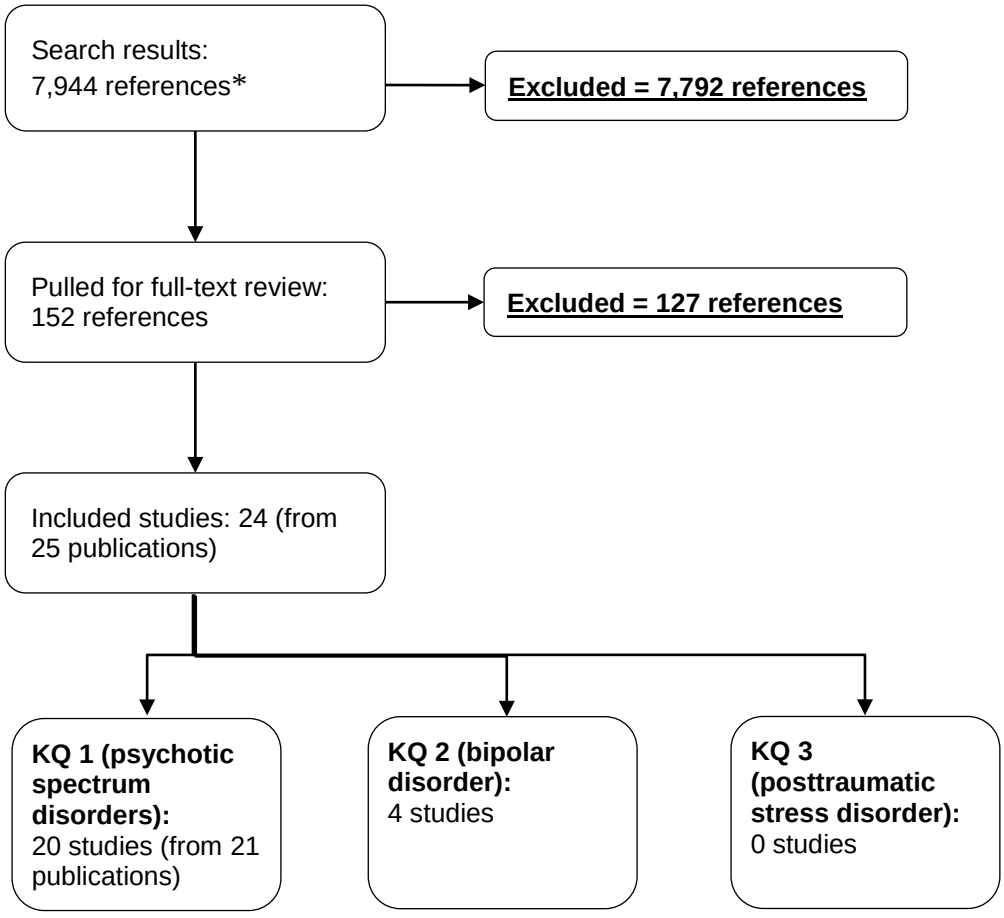
RESULTS

Our search of electronic databases, bibliographies, and other sources resulted in a total of 7,944 studies. After title and abstract review, 152 were selected for full-text review. Upon review of the full-text articles, we excluded 127 citations for a total of 24 included studies from 25 publications. Additionally, a search of the ClinicalTrials.gov online trial registry identified 518 clinical trials, and one study met inclusion criteria;[40] however, this study and all data reported on ClinicalTrials.gov are represented in an included publication.[41] We identified 21 articles (20 individual primary studies) for Key Question 1, 4 primary studies for Key Question 2, and no primary studies for Key Question 3.

LITERATURE FLOW

Figure 2 shows the citation yield from electronic database searches and other sources, numbers for exclusions at the abstract and full-text phases, and the final yield of included studies delineated by key question.

Figure 2. Literature Flow Chart



* 7,895 were identified through database searches (Appendix B), and an additional 49 were identified from the bibliographies of relevant systematic reviews and primary studies.

KEY QUESTION 1. ADULTS WITH PSYCHOTIC SPECTRUM DISORDER

We identified 21 articles meeting inclusion criteria for patients along the psychotic spectrum, with 20 independent studies reporting medication adherence outcomes, and one article[42] reporting a cost analysis of another included study.[43] Seven studies examined multicomponent behavioral interventions;[43-49] 3 studies examined interventions involving family members;[50-52] one study examined a system-level intervention;[49] one study examined a pharmacist-led intervention;[53] 4 studies examined technology interventions (Medication Event Monitoring System [MEMS], telephone, short message service [SMS]);[54-57] and 4 studies examined other interventions such as MI (1 study),[58] shared decision-making (1 study),[59] and environmental supports (2 studies).[57,60] Two studies examined the combination of depot antipsychotics and an intervention designed to increase medication adherence,[61,62] one study reported the intervention effect on non-psychopharmacologic medications,[54] and 2 studies reported outcomes related to costs.[42,57] Study details are found in Tables 4-11.

Studies were conducted in community mental health outpatient settings (12 studies) and in hospitals with inpatients (4 studies), with other interventions spanning pre- and post-discharge periods (3 studies), and one multi-site study that included both inpatient and outpatient settings. Six studies were conducted in the US and 12 were conducted in Europe, with one study conducted in South Korea, and another in Mexico. The included studies measured adherence using objective measures such as e-monitoring/MEMS, pill counts, and blood plasma concentration levels; validated scales measuring adherence such as the Medication Adherence Questionnaire (MAQ), the Medication Adherence Rating Scale (MARS), and the Drug Attitude Inventory (DAI), which has been shown to correlate with other measures of adherence;[1] and a variety of other measures of adherence, some of which used multiple sources. The patient outcomes most frequently reported were positive and negative symptoms, symptom severity, functional impairment, and time to first readmission or hospitalization. Commonly used measures included the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression scale (CGI), the Brief Psychiatric Rating Scale (BPRS), and the Global Assessment of Functioning (GAF). Tables 4-11 provide study detail, and a brief description of adherence and patient outcome measures are provided in Appendices E and F.

1a. What are the effects of medication adherence interventions on psychopharmacological adherence?

Multicomponent Behavioral Interventions

Summary: Findings of the included studies are mixed, and there is no consistent evidence from which to draw conclusions about the efficacy of multicomponent behavioral interventions on pharmacological adherence. Table 4 provides study detail.

Details: There are a wide range of behavioral interventions targeting medication adherence, including functional analysis (*eg*, identifying the antecedents to specific behaviors), positive reinforcement, relaxation techniques. CBT combines behavioral interventions with the identification and challenging of cognitive distortions (*eg*, overgeneralization, black and white thinking). Other interventions commonly combined into multicomponent interventions include psychoeducation and MI, a non-confrontational goal-oriented style focused on overcoming ambivalence related to behavior change. Compliance Therapy is a multicomponent intervention first studied by Hayward et al in 1995[63] and described fully in a manual by Kemp et al in 1997[64]

that combines MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma. Adherence Therapy[65] is a manualized intervention that builds on Compliance Therapy, and is a patient-centered cognitive behavioral approach incorporating MI and emphasizing joint decision-making, medication problem solving, exploring ambivalence, and the discussion of beliefs and concerns about medication.

We identified 7 studies (2 high ROB,[43,45] 3 moderate ROB,[44,47,49] 2 low ROB[46,48]) examining multicomponent behavioral interventions, of which 2 examined Adherence Therapy. The first was an RCT examining clinically unstable outpatients and found that over a period of 12 months, there was no difference between Adherence Therapy and the health education controls.[46] The second study, also an RCT, included 5 sessions while participants were inpatients, and 3 sessions after release. At 12 weeks post-discharge, there was no difference in medication adherence between the Adherence Therapy group and controls.[48]

Four studies examined Compliance Therapy with mixed findings. A prospective cohort study conducted in a community setting found a significant improvement in adherence between baseline and the end of treatment (1 month) as assessed using the MARS; however, there was no significant improvement by 6 months follow-up, and no significant improvement as assessed using MEMS at either time point.[45] An RCT of inpatients compared Compliance Therapy to supportive counseling, and found significantly better adherence in the Compliance Therapy group at discharge, with differences between the 2 groups continuing through the 18-month follow-up period.[43] Two studies however, found no significant improvement in medication adherence associated with Compliance Therapy.[47,49]

Finally, one RCT of inpatients compared group CBT with MI to group psychoeducation with MI and found no difference between groups at 24 months follow-up.[44] Table 4 provides study detail.

Table 4. Psychotic Spectrum Disorders: Multicomponent Behavioral Interventions Medication Adherence Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Adherence Therapy						
Gray et al, 2006[46] G1: 204 G2: 205	Adults with clinically unstable schizophrenia requiring antipsychotic medication for ≥ 1 year post-baseline. Outpatient settings in the Netherlands, Germany, England, and Italy	G1: Usual care plus Adherence Therapy (AT), a brief cognitive behavioral approach focused on joint decision making including: assessments, medication problem solving, a medication timeline, exploring ambivalence, discussing beliefs and concerns about medication, medication in the future G2: Usual care plus didactic health education	Eight individual 30- to 50-minute weekly sessions	MAQ M(SD) G1 (N = 172): 2.98 (1.24) G2 (N = 194): 2.97 (1.20)	12 Months: M(SD) G1 (N = 172): 3.20 (1.07) G2 (N = 194): 3.33 (1.02) Difference between groups (all available cases): -0.13 (CI, -0.35 to 0.08), *P* = .23 Difference between groups (complete cases): -0.15 (CI, -0.34 to 0.05), *P* = .15	
				SAI-C M(SD) G1 (N = 173): 5.04 (1.39) G2 (N = 189): 4.73 (1.63)	12 Months: M(SD) G1 (N = 173): 5.22 (1.57) G2 (N = 189): 5.03 (1.55) Difference between groups (all available cases): 0.19 (CI, -0.12 to 0.52), *P* = .24 Difference between groups (complete cases): -0.16 (CI, -0.32 to 0.29), *P* = .92	
Schulz et al, 2013[48] G1: 93 G2: 105	Adults diagnosed with a schizophrenic disorder (without comorbid disorders) recently	G1: Usual care plus Adherence Therapy (AT), a brief cognitive behavioral approach focused on joint decision making including: assessments, medication problem solving, a medication timeline, exploring ambivalence, discussing beliefs and concerns about medication, medication in the future	Eight individual sessions, 5 as an inpatient, additional 3 after discharge.	CDR (blood serum) M(SD) G1 (N = 54): 3.83(6.80) G2 (N = 39): 4.19(5.79)	12 Weeks Post Discharge M(SD) G1 (N = 54): 3.34(5.36 G2 (N = 39): 6.36(10.56) F = 2.29, *P = NS*	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	discharged and prescribed antipsychotic medication with a recommendation of treatment for a least one year following discharge. Hospitals in Germany (3) and Switzerland	G2: Usual care followed national guidelines for the treatment of schizophrenia and generally included medication, psychotherapy, occupational therapy, and psychoeducation.		DAI-30 M(SD) G1 (N = 69): 22.46(6.83) G2 (N = 46): 22.70(6.69)	12 Weeks Post Discharge M(SD) G1 (N = 69): 22.70(6.59) G2 (N = 69): 22.83(5.89) Difference = -.13, F = .039, *P = NS*	
				MARS M(SD) G1 (N = 69): 7.55(2.07) G2 (N = 46): 7.46(1.73)	12 Weeks Post Discharge M(SD) G1 (N = 69): 7.74(2.01) G2 (N = 46): 7.65(1.87) Difference = 0. F not reported.	
Compliance Therapy[64]						
Byerly et al, 2005[45] G1: 30	Adults diagnosed with schizophrenia or schizoaffective disorder taking only one oral antipsychotic, and who had been admitted to a psychiatric ward or emergency department for psychiatric purposes within 2 years. Community mental health	G1: Compliance Therapy is a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma.	Four to 6 individual face-to-face 30- to 60-minute sessions over the period of a month.	MEMS NR	1 Month G1: 4% decline (*P* = .12)	6 Month G1: Adherence increased by .19 each month from Months 1-6 (*P* = .83)
					Diagnosis of schizoaffective disorder was associated with a larger decrease in adherence between months -1 and +1 (HLM, *P* = .03)	Greater insight at baseline was associated with a greater increase in adherence in months 2-6 (HLM, *P*<.01)
				MARS NR	1 Month G1: 8.9% increase (*P* = .04)	6 Months G1: 1.4% decline per month in months 2-6 (*P* = .07)
				DAI NR	3 Month G1: 15.2% increase (*P* = .15)	6 Months G1: .5% decrease (*P* = .81)

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Kemp et al, 1998[43] G1: 39 G2: 35	Adult inpatients with psychotic disorders Hospital in England	G1: Routine management plus Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma. G2: Routine management plus supportive counseling (no medication issues addressed)	Four to 6 individual face-to-face sessions (M = 4.7) lasting 20-60 minutes twice weekly	DAI M(SD) G1 (N = 39): 45.3(6.8) G2 (N = 35): 44.1(7.7)	At Discharge M(SD) G1 (N = 39): 52.0(5.9) G2 (N = 35): 45.7(8.5)	1 Month M(SD) G1 (f35): 50.1(6.3) G2 (N = 28): 44.4(8.1)
						6 Months M(SD) G1 (N = 18): 50.4(7.4) G2 (N = 14): 41.9(5.9)
						12 Months M(SD) G1 (N = 28): 49.5(6.9) G2 (N = 16): 44.6(7.5)
						18 Months M(SD) G1 (N = 16): 50.9(6.2) G2 (N = 13): 48.2(8.5)
					Advantage of Compliance Therapy (95% CI 2.5-7.2). Compliance Therapy group had more favorable scores immediately post-treatment and this advantage was retained over all post-intervention assessments, with a mean difference of 15.6%.	
				Compliance (Kemp) rated by multiple sources including primary nurse M(SD) G1 (N = 39): 3.7(1.2) G2 (N = 35): 4.1(1.2)	At Discharge: M(SD) G1 (N = 39): 5.5(0.8) G2 (N = 35): 4.3(1.4)	3 Months: M(SD) G1 (N = 38): 5.7(1.3) G2 (N = 34): 3.8(2.1)
						6 Months: M(SD) G1 (N = 36): 5.7(1.8) G2 (N = 33): 3.5(1.9)

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
						12 Months: M(SD) G1 (N = 35): 5.5(1.8) G2 (N = 31): 3.6(2.1)
						18 Months: M(SD) G1 (N = 25): 5.6(1.7) G2 (N = 23): 4.2(2.3)
				There was a significant advantage for the Compliance Therapy group at discharge, and this was maintained throughout post-treatment.		
				AMQ M(SD) G1 (N = 39): 14.8(3.9) G2 (N = 35): 14.0(6.4)	At Discharge: M(SD) G1 (N = 39): 19.4(3.7) G2 (N = 35): 14.9(6.1) *P* = Significant (NR)	NR
O'Donnell et al, 2003[47] G1: 28 G2: 28	Adults 65 and under with a diagnosis of schizophrenia and an IQ>80 recently admitted to the hospital. Hospital in Ireland	G1: Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma. G2: Nonspecific counseling	Five individual face-to-face sessions lasting 30-60 minutes.	DAI M(SD) G1 (N = 28): 50(8) G2 (N = 28): 50(7)	1 Year: M(SD) G1: 51.3(8.2) G2: 53.4(6.2) Difference = -2.1(95% CI, -6.3 to 2.1), *P* = .32	
				4-point self-report scale and adjusted by key informants G1 (N = 23): 8/23 (35%) G2 (N = 21): 4/21 (19%)	1 Year: G1: 12/28 G2: 15/28 OR = .65 (95% CI .197 to 2.123)	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Skarsholm et al, 2014[49] G1: 30 G2: 40	Adult inpatients close to discharge 23-70 with a diagnosis of schizophrenia or schizoaffective disorder under the care of a community mental health team. Community mental health in Denmark	G1: System-Oriented Intervention included providing a brochure and questionnaire on antipsychotic treatment as a basis for conversation between participant/provider, a screening form for identification of compliance problems as the basis for participant/nurse conversation, a reminder box that contained medicine cards, dosage boxes, electronic alarm systems, medication reconciliation, adherence to clinical guidelines G2: Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma.	G1: NA G2: Six individual face-to-face sessions and 3 booster sessions 30-45 minutes in length.	Compliance based on self-report, DAI, appointment keeping, PANSS G-12 NR	6 Months: Difference in compliance score from baseline to follow-up, LOCF: G1: (N = 40): 0.400, 95% CI (−.174 to 0.974), *P*<0.05 G2: (N = 30): 1.103, 95% CI (.434 to 1.733), P>0.05 Difference between intervention groups, coefficient: Regression, MI: 0.476 (SE 0.362, CI -0.247 to 1.120), *P* = 0.193	
Other Multicomponent Behavioral Intervention						
Bechdolf et al, 2005[44] G1: 40 G2: 48	Adult inpatients 18-64 years who met criteria for a schizophrenic or related disorder Hospital in Germany	G1: Group CBT included MI, coping strategies, problem solving, relapse prevention, and focused on the treatment of auditory hallucinations and delusions, associated symptoms, relapse prevention, and med adherence. G2: Group psychoeducation focused on improvements in medication compliance and rehospitalization rates and included MI	G1: 16 group sessions over 8 weeks lasting 60-90 minutes. G2: 8 sessions in 8 weeks lasting 60-90 minutes	Compliance (similar to Kemp) w/corroboration with key informants M(SD) G1 (N = 40): 3.9(.3) G2 (N = 48): 3.77(.5)	Post-treatment: M(SD) G1 (N = 37): 3.9(.3) G2 (N = 43): 3.7(.6)	24 Months: M(SD) G1 (N = 16): 3.4(.7) G2 (N = 25): 2.9(1.1) F = 1.31, *P* = .26

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of medication adherence assessments are reported in Appendix E.
Abbreviations: AMQ = Attitude towards Medication Questionnaire; CBT = Cognitive behavioral therapy; CDR = Concentration to Dose Ratio; CI = Confidence Interval; DAI = Drug Attitude Inventory; M = Mean; MAQ = Medication Adherence Questionnaire; MARS = Medication Adherence Rating Scale; MEMS = Medication Event Monitoring System; PANSS = Positive and Negative Syndrome Scale; SAI-C = Schedule for the Assessment of Insight – C; SD = Standard deviation.

Interventions Involving Family Members

Summary: Findings of the included studies show a generally positive effect associated with interventions for medication adherence involving family members.

Details: Interventions involving family members are often conducted in group settings, and often include psychoeducation, support for families, behavioral problem solving, and crisis management.[66]

Three RCTs (all moderate ROB) meeting inclusion criteria examined the effect of interventions involving family members.[50-52] Two studies included both an individual and a family component, with individual treatment conducted in a group setting.[51,52] Two studies involved interventions that included both the participant and family together,[50,52] with one study including a group intervention for relatives only.[51] Two studies found family interventions to be more effective than usual care,[51,52] and one study found no significant difference when controlling for time.[50] Table 5 provides study detail.

Table 5. Psychotic Spectrum Disorders: Family Intervention Medication Adherence Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Kopelowicz et al, 2012[50] G1: 64 G2: 54 G3: 60	Adults 18-50 of Mexican origin and fluent Spanish speaker with a diagnosis of schizophrenia or schizoaffective disorder who had been without antipsychotic medication for at least one week in the past month without authorization, and lived with their family of origin with a relative willing to participate in family treatment. Community mental health	G1: Usual care plus Multifamily group – Adapted, a culturally modified version of multifamily group therapy, a behavioral family treatment combining psychoeducation and skills training. G2: Multifamily group – Standard plus usual care G3: Usual care	G1: Three individual family joining sessions, a 6 hour multifamily workshop, and twenty-one 90-minute multifamily group sessions twice a month. G2: Same as G1 G3: Monthly 20-minute sessions or more if participant was unstable.	Clinician assessed, self-report, family report, pharmacy data NR	4 Months: Estimated from graph % Compliant G1: 30% G2: 27% G3: 25% More participants G1 were fully adherent than those in G3 (P<0.01).	8 Months: Estimated from graph % Compliant G1: 46% G2: 27% G3: 22% G1 was significantly better than G2 (P = .03), 12 Months: Estimated from graph % Compliant G1: 52% G2: 32% G3: 25% G1 was significantly better than G2 (P = .04). 18 Months: Estimated from graph % Compliant G1: 43% G2: 20% G3: 16% G1 was significantly better than G2 (P = .01). 24 Months: Estimated from graph % Compliant G1: 33% G2: 23% G2: 11% *P = NS*

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				Across the 24 months of the study (12 months of treatment and 12 months of follow-up), there were significant main effects of treatment on adherence for group (F[2,172] = 6.41, P = .003) and for time (F[4,172] = 3.5, P = .009), but not the group X time interaction (F[8,171] = 1.4, P = .22)., and There was no significant difference at any point between the G2 and G3.		
Pitschel-Walz et al, 2006[51] G1: 102 G2: 92	Adults 18-65 with a diagnosis of schizophrenia or schizoaffective disorder Inpatient wards in Germany	G1: Patients psychoeducation group focused on symptoms, etiology, acute treatment, relapse prevention, psychosocial treatment, and coping strategies. Family psychoeducation group focused on the same as patients, and how they could best support patient. G2: Usual care	G1: Patient groups were eight 60-minute sessions, with 1-4 weekly, then 5-8 monthly. Relative groups were 8 bi-weekly 90-minute sessions.	Clinician assessed, plasma verified NR	Discharge % Very Good/Good Compliance G1: 85, 69/81 G2: 81, 64/79 *P = NS*	12 Months: % Very Good/Good Compliance G1: 80, 65/81 G2: 58, 46/79 *P*<.01
						24 Months: % Very Good/Good Compliance G1: 80, 53/73 G2: 55, 34/64 *P*<.01
Valencia et al, 2010[52] G1: 41 G2: 36	Adult outpatients with a diagnosis of schizophrenia who were adherent to their medication and clinically stable Community mental health in Mexico	G1: Group/family psychosocial skills including medication, decision making, relapse prevention, avoiding drug and alcohol, friendships, improving family relations + usual care G2: Usual care	G1: Patients – 90-minute group session weekly – 40 total sessions in 12 months. Family + patient – 5 sessions G2: 20 minute monthly appointments	Pharmacy data, family report NR	End of Treatment: Adherence = 90% adherent G1: 91.5% G2: 77.8% *P*<.05	

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of medication adherence assessments are reported in Appendix E.
Abbreviations: NR = Not reported; NS = Not significant.

System-level Interventions

Summary: There is insufficient evidence regarding the efficacy of system-level interventions to improve medication adherence.

Details: System-level interventions include policies implemented at the system-level for all patients meeting predefined criteria, and may include screening, education, and other interventions.

One included RCT (moderate ROB) compared a system-level intervention to Compliance Therapy.[49] The system-level intervention included a brochure and questionnaire on antipsychotic treatment as a basis for conversation between participant/provider, a screening form for identification of compliance problems as the basis for participant/nurse conversation, a reminder box that contained medicine cards, dosage boxes, electronic alarm systems, medication reconciliation, and the requirement that providers adhere to clinical guidelines. Although the system-level group showed better adherence outcomes, differences were not significant. Table 6 provides study detail.

Pharmacist-led Interventions

Summary: Findings of the included studies are insufficient to determine the efficacy of pharmacist-led interventions.

Details: Pharmacist-led interventions are often brief interventions focused on education specific to medication, including the benefits, side effects, and potential consequences for discontinuing medication.

We identified one study (high ROB) examining a pharmacist-led intervention, which involved a group session that included a question and answer session about medication, rationale, risks of stopping, side effects, risk/benefit evaluations.[53] One session focused on antipsychotics, the second session focused on mood stabilizers. There was no significant difference between the pharmacist-led intervention and usual care. Table 6 provides study detail.

Technology Interventions

Summary: Findings of the included studies show a generally positive effect, with low strength of evidence.

Details: Technology interventions vary, and may include SMS or telephone reminders, e-monitoring using a variety of platforms, including MEMS caps, which record the time and date each time the cap is opened.[54]

We identified 4 studies (one high ROB,[55] 2 moderate ROB,[54,56] one low ROB[57]) examining technology interventions to improve psychopharmacologic adherence. Two RCTs compared e-monitoring to a variety of comparators.[55,57] One study found significantly better adherence when assessed using the e-monitor as compared with usual care, but not as assessed by pill counts.[57] The second study, which examined e-monitoring both as an intervention and a measure of adherence, compared adherence measured by e-monitoring, pill counts, and self-report using a validated scale, and found adherence in the e-monitoring group to be significantly higher than both pill counts by a pharmacist and self-report.[55] The third study compared a telephone and

SMS intervention to telephone only and SMS only. Results indicated that although adherence was better in the group receiving both phone and SMS, the differences were not significant, nor did adherence improve significantly for any of the groups over the duration of the study.[54] The fourth study compared daily SMS to usual care, and found significantly better adherence in the intervention group both at the end of the active phase (3 months) and at 6-months follow-up.[56] Table 6 provides more details about the included studies.

Other Interventions

Summary: Findings are insufficient to evaluate the efficacy of other interventions for psychopharmacologic adherence in patients along the psychotic spectrum.

Details: Four studies (one high ROB,[59] one moderate ROB,[60] 2 low ROB[57,58]) examined other interventions for medication adherence for people along the psychotic spectrum. Included studies examined MI, shared decision making, and Cognitive Adaptation Therapy (CAT). One study examined an MI intervention targeting positive and negative symptoms and cognitive deficits.[58] Results indicated no significant difference between the intervention and comparison group, with better adherence in patients prescribed depot antipsychotics regardless of group. A second study examined a shared decision intervention that included a shared decision aid booklet covering pros/cons of medication, psychoeducation, and a treatment agreement with their clinician.[59] No difference in adherence was found as compared to usual care. Two studies examined CAT, an intervention focused on individualized strategies and environmental supports – one comparing standard CAT to the medication adherence component of CAT alone (Pharm-CAT) and usual care,[60] and the other comparing Pharm-CAT to e-monitoring and usual care.[57] Results indicated no difference between CAT and Pharm-CAT, and that both CAT and Pharm-CAT resulted in better adherence than usual care through 15 months as evaluated by pill counts. The study also found CAT, but not Pharm-CAT, to be better than usual care over 15 months as evaluated by pharmacy refill rates.[60] There were no differences between Pharm-CAT and e-monitoring over 3 months as assessed using the e-monitor, and Pharm-CAT was associated with better adherence than e-monitoring alone or usual care as assessed by pill counts.[57] Table 7 provides more detail.

Table 6. Psychotic Spectrum Disorders: System and Pharmacist Medication Adherence Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
System-level Interventions						
Skarsholm et al, 2014[49] G1: 30 G2: 40	Adult inpatients close to discharge 23-70 with a diagnosis of schizophrenia or schizoaffective disorder under the care of a community mental health team. Community mental health in Denmark	G1: System-Oriented Intervention included providing a brochure and questionnaire on antipsychotic treatment as a basis for conversation between participant/provider, a screening form for identification of compliance problems as the basis for participant/nurse conversation, a reminder box that contained medicine cards, dosage boxes, electronic alarm systems, medication reconciliation, adherence to clinical guidelines G2: Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma.	G1: NA G2: Six individual face-to-face sessions and 3 booster session 30-45 minutes in length.	Compliance Scale – self-report, DAI, PANSS G12 NR	6 Months: Difference in compliance score from baseline to follow-up, LOCF: G1: (N = 40): 0.400, 95% CI (-.174 to 0.974), $P<0.05$ G2: (N = 30): 1.103, 95% CI (.434 to 1.733), $P>0.05$ Difference between intervention groups, coefficient: Regression, MI: 0.476 (SE 0.362, CI -0.247 to 1.120), $P = 0.193$	
Pharmacy Interventions						
Kavanagh et al, 2003[53] G1: 15 G2: 15	Adults diagnosed with psychotic disorders who were inpatients in a psychiatric ward. Hospital in London	G1: Pharmacist-led group including Q & A about medication, rationale, risks of stopping, side effects, risk/benefit evaluations. One session focused on antipsychotics, the second session focused on mood stabilizers + usual care. G2: Usual care	G1: Two one-hour group sessions on consecutive weeks.	Compliance (Kemp), nurse assessed M(SD) G1 (N = 15): 4.60(1.30) G2 (N = 15): 4.47(1.19)	Post Session and 2 Weeks Follow-up: There were no significant differences between groups, over time, nor an interaction.	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Technology Interventions (e-Monitoring, SMS, Phone)						
Beebe et al, 2014[54] G1: 10 G2: 10 G3: 10	Adults 21-68 with a diagnosis of schizophrenia or schizoaffective disorder receiving outpatient care. Community mental health	G1: TIPS + Text. TIPS is a manualized intervention providing weekly telephone support addressing taking medication, attending appointments, coping with symptoms, abstaining from alcohol and other drugs, and getting along with others. G2: TIPS only G3: Text only – text format of the TIPS protocol. Texts were delivered daily	G1: Weekly phone calls and daily texts for 3 months G2: Weekly phone calls for 3 months G3: Daily text messages for 3 months	Home pill counts or % of injections M(SD) NR	1 Month: M(SD) Month 1: G1 (N = 10): 84.2(22.4) G2 (N = 10): 72(33.7) G3 (N = 10): 72(20.1)	2 Months: M(SD) G1 (N = 10): 87.5(13.0) G2 (N = 10): 70.1(33.2) G3 (N = 8): 83.9(18.0) 3 Months: M(SD) G1 (N = 10): 81.1(25.5) G2 (N = 10): 71.5(26.6) G3 (N = 8): 80.9(16.3)
				There was no significant Group x Time interaction for psychiatric medication adherence, $F(4,26) = 1.24$, $P = .31$). Nevertheless, findings were in the predicted direction: Mean psychiatric adherence scores for G1 were higher than both G2 (by an average of 5.3%) and G3 (by an average of 13%) at months 1, 2, 3. A *post hoc* analysis revealed that the power to examine psychiatric medication adherence was 34%.		
Frangou et al, 2005[55] G1: 36 G2: 36 G3: 36	Adult outpatients 18-64 with a diagnosis of schizophrenia who had at least 2 admissions in preceding 12 months, and prescribed oral medication. Community mental health in London	G1: e-monitoring (MEMS) – medication dispenser that recorded access and transmitted data via the @HOME platform. Staff was alerted if participant took less than prescribed amount. G2: Pill counting by pharmacists at study visits G3: Self-report of adherence using Morisky scale.	G1: e-Monitoring G2: Pharmacist G3: Self-report	See Groups NR	8 weeks M%(SD) G1 (N = 36): 92.3(4.8) G2 (N = 36): 78.5(14) G3 (N = 36): 75.3(27.6) $P = .0001$, G1 significantly better than G2 ($P = .001$) and G3 ($P = .007$)	
Montes et al, 2012[56] G1: 100 G2: 154	Adult outpatients 18-65 with a diagnosis of schizophrenia who were clinically stable, prescribed a single antipsychotic, and	G1: Daily SMS reminders to take their medication, "Please remember to take your medication." + usual care G2: Usual care	G1: Daily SMS for 3 months	MAQ M(95% CI) G1 (N = 100): 2.2(2.02 to 2.38) G2 (N = 154):	3 Months: Mean changes M(95% CI) G1: -1.0(-1.02 to -.98) G2: -.7(-.72 to -.68) $P = .02$	6 Months: Mean changes M(95% CI) G1: -1.1(-1.12 to -1.08) G2: -.8(-.81 to -.78) $P = .04$

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	one affirmative answer on the MAQ Community mental health in Spain			2.2(2.06 to 2.34)		
Velligan et al, 2013[57] G1: 47 G2: 48 G3: 47	Adults 18-60 diagnosed with schizophrenia or schizoaffective disorder treated with oral antipsychotic(s) who had missed at least one dose in the previous week. Community mental health	G1: Pharm-CAT consists of manualized individualized strategies and environmental supports targeting medication adherence G2: Med-eMonitor (MM) is a smart pill container capable of cueing and warning patients, recording side effect complaints, alerting staff of failure to take medication as prescribed. G3: Usual care	G1: Home visits 30 minutes long weekly for 9 months. G2: MM support and phone contact as needed.	MEMS NA	Aggregated 3 Month: Mixed-effects regression model yielded a significant treatment group for group (F[2m 365] = 47.29, P<.0001). Time and group X time effects were nonsignificant. G1 and G2 were significantly better than G3 at all time points through treatment and follow-up (P's<.0001). There was no significant difference between G1 and G2.	
				Pill Counts NA	Aggregated 3 Month: The mixed-effects regression model yielded a significant main effect of group (F[2, 116] = 7.83, P<.0001). Time and group X time effects were nonsignificant. G1 had higher adherence by pill count (91%) than either G2 (86%, t[116] = 2.05, P = .04) or G3 (80%, t[115] = 3.95, P = .0001).	
				DAI M(95% CI) G1 (N = 100): 3.4(2.49 to 4.31) G2 (N = 154): 3.1(2.43 to 3.77)	3 Months: Mean changes M(95% CI) G1: 2.0(1.94 to 2.06) G2: .4(.35 to .45) P = .0003	6 Months: Mean changes M(95% CI) G1: 2.3(2.24 to 2.36) G2: .9(.85 to .95) P = .002

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of medication adherence assessments are reported in Appendix E.
Abbreviations: CAT = Cognitive Adaptation Training; CI = Confidence Interval; DAI = Drug Attitude Inventory; M = Mean; MAQ = Medication Adherence Questionnaire; MEMS = Medication Event Monitoring System; MM = Med-eMonitor; PANSS = Positive and Negative Syndrome Scale; SD = Standard deviation; TIPS = Telephone Intervention Problem Solving for Schizophrenia.

Table 7. Psychotic Spectrum Disorders: Other Medication Adherence Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Motivational Interviewing(MI)						
Barkhof et al, 2013[58] G1: 55 G2: 59	Adults with schizophrenia or schizoaffective disorder with a psychotic relapse or deterioration following non-adherence to antipsychotics, who have resumed antipsychotics with some clinical improvement. Three sites - Inpatient and outpatients in Amsterdam	G1: A manualized MI intervention based on negative symptoms, positive symptoms, cognitive deficits. G2: Health education on general health topics.	Eight individual 20- to 45-minute sessions over 26 weeks.	MAQ M(SD) G1 (N = 30): 3.00(1.34) G2 (N = 32): 3.13(1.24)	26 Weeks: M(SD) G1 (N = 30): 3.34(0.99) G2 (N = 32): 3.13(1.12) *P* = .34	6 Months: M(SD) G1 (N = 30): 2.97(1.42) G2 (N = 32): 3.38(1.11) *P* = .21
					There was a significant interaction between MAQ and route of medication administration, suggesting higher adherence rates when using depot medication and received MI, $F(1, 59) = 4.53$, $P = .037$, $\eta^2 = .14$.	
				DAI M(SD) G1(N = 30): 6.86(2.18) G2 (N = 32): 6.03(2.30)	26 Weeks: M(SD) G1(N = 30): 6.86(2.50) G2 (N = 32): 6.38(1.98) *P* = .72	6 Months: M(SD) G1(N = 30): 6.89(2.39) G2 (N = 32): 6.67(2.52) *P* = .70
					There was a trend level interaction between DAI and age group: $F(1,49) = 3.93$, $P = 05$, $\eta^2 = 0.07$, suggesting that participants ≤35 years showed more favorable attitudes toward medication at 6 months follow-up when they received MI vs HE.	
Shared Decision-making						
Hamann et al, 2007[59] G1: 39 G2: 47	Adult inpatients 18-65 with a diagnosis of schizophrenia or schizophreniform disorder Hospital in Germany	G1: Shared decision aid booklet covering pros/cons of medication, psychoeducation, treatment agreement with clinician + usual care G2: Usual care	G1: Decision aid session with nurse and extra planning talk with psychiatrist	MARS and blood plasma NR	6 Months: #(%) Good Compliance G1 (N = 39): 16(41) G2 (N = 47): 26(55) *P = NS*	18 Months: #(%) Good Compliance G1 (N = 30): 18(60) G2 (N = 38): 22(58) *P = NS*
Cognitive Adaptation Therapy (CAT)						
Velligan et al, 2008[60] G1: 37	Adult outpatients 18-60 diagnosed with schizophrenia and prescribed an	G1: CAT consists of manualized individualized strategies and environmental	G1: Individual face-to-face weekly visits lasting 30-45	Unannounced Home Pill Counts	3 Months: G1 vs G3: *P* = .04 G2 vs G3: *P* = .05 15 Months:	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
G2: 32 G3: 29	oral antipsychotic Community mental health	supports designed to include medication adherence, grooming, and activities of daily living G2: Pharm-CAT consisted of only the medication adherence components of CAT G3: Usual care	minutes for 9 months G2: Same as G1, but sessions were generally shorter	NA	G2 vs G3: *P* = .002 All other time points: G1 vs G3: *P* = .001 G2 vs G3: *P* = .0001 G1 vs G2 at all time points: *P = NS* All effect sizes >1 for G1 and G2 at 6 months and after.	
				Pharmacy Refill Rates NA	15 Months: Mixed effects regression main effect for group: *F*(2, 105) = 3.93, *P*<.02 No significant effect for time or group X time. G1 significantly more adherent than G3.	
Velligan et al, 2013[57] G1: 47 G2: 48 G3: 47	Adults 18-60 diagnosed with schizophrenia or schizoaffective disorder treated with oral antipsychotic(s) who had missed at least one dose in the previous week. Community mental health	G1: Pharm-CAT consists of manualized individualized strategies and environmental supports targeting medication adherence G2: Med-eMonitor (MM) is a smart pill container capable of cueing and warning patients, recording side effect complaints, alerting staff of failure to take medication as prescribed. G3: Usual care	G1: Home visits 30 minutes long weekly for 9 months. G2: MM support and phone contact as needed.	MEMS NA	Aggregated 3 Months: Mixed-effects regression model yielded a significant treatment group for group (*F*[2m 365] = 47.29, *P*<.0001). Time and group X time effects were nonsignificant. G1 and G2 were significantly better than G3 at all time points through treatment and follow-up (*P*'s<.0001). There was no significant difference between G1 and G2.	
				Unannounced Home Pill Counts NA	Aggregated 3 Months: The mixed-effects regression model yielded a significant main effect of group (*F*[2, 116] = 7.83, *P*<.0001). Time and group X time effects were nonsignificant. G1 had higher adherence by pill count: (91%) than either G2 (86%, *t*[116] = 2.05, *P* = .04) or G3 (80%, *t*[115] = 3.95, *P* = .0001).	

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of medication adherence assessments are reported in Appendix E.
Abbreviations: CAT = Cognitive Adaptation Training; CI = Confidence Interval; DAI = Drug Attitude Inventory; M = Mean; MAQ = Medication Adherence Questionnaire; MARS = Medication Adherence Rating Scale; MEMS = Medication Event Monitoring System; MM = Med-eMonitor; SD = Standard deviation.

1b. What are the effects of medication adherence interventions on *long-acting injectable (depot) psychopharmacological* adherence?

Two studies (both moderate ROB) examined interventions targeting people along the psychotic spectrum using long-acting injectable (depot) antipsychotics, and both reported improved adherence.[61,62] The first study was an RCT of outpatients prescribed depot antipsychotics receiving an intervention that included psychoeducation, early warning sign detection, and family education. Results indicated better adherence for the intervention group versus usual care at both the end of the intervention phase (12 months) and at 24-months follow-up.[61] The second study was a prospective cohort study of homeless outpatients in a community setting receiving depot plus CAE, a manualized individual multicomponent behavioral intervention consisting of 4 modules (psychoeducation, substance use/modified Motivational Enhancement Therapy [MET], provider communication, medication management).[62] CAE is customized based on an assessment at baseline to identify each patient's adherence vulnerabilities and reasons for non-adherence, with one to 4 of the modules assigned based on the results of the assessment. Results indicated significantly improved adherence through 25 weeks. Table 8 provides more detail.

1c. What are the effects of medication adherence interventions on *non-psychopharmacological* adherence?

One RCT (moderate ROB) examined the effect of an intervention for medication adherence on non-psychopharmacological adherence in patients along the psychotic spectrum.[54] The intervention was a technology intervention comparing telephone and SMS to telephone or SMS alone. There was no significant difference between groups. Table 9 provides study detail.

Table 8. Outcomes Associated with Long-Acting Injectable Adherence

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Lee et al, 2010[61] G1: 24 G2: 33	Participants were outpatients between 17-60 years old, diagnosed with schizophrenia or schizoaffective disorder, and prescribed treatment with a long-acting injectable antipsychotic (depot). Community mental health in Korea	G1: Psychosocial Intervention for Relapse Prevention for depot; included psychoeducation, early warning sign detection, family education with biweekly intervention + usual care. G2: Usual care	G1: 60-minute sessions monthly for 12 months	Biweekly injection visits NA	12 Months: M%(SD) G1 (N = 21): 94.6(12.2) G2 (N = 25): 75.9(22.2) *t*(45) = 3.5, *P*<.01	24 Months: M%(SD) G1 (N = 21): 92.1(16.5) G2 (N = 25): 74.2(26.6) *t*(45) = 2.7, P<.01
Sajatovic et al, 2013[62] G1: 30	Adults 18+ with a diagnosis of schizophrenia or schizoaffective disorder who had missed 20%+ of prescribed antipsychotics and were homeless within the past 12 months. Community-based mental health	G1: Depot + CAE is a manualized individual behavioral intervention that consists of 4 modules (psychoeducation, substance use/modified MET, provider communication, medication management). CAE is customized based on an assessment at baseline, with one to 4 modules assigned.	Eight monthly, in-person, 30- to 40-minute sessions	TRQ Screening: M(SD) Past Week: G1: 57.2(33.2) Past Month: G1: 46.1(31.2)	Week 13: M(SD), Change from Baseline (95% CI) Past Week: G1 (N = 10): 12.4(17.3), -42.9 (-60.6 to -25.2) Past Month: G1 (N = 10): 8.2(11.6), -36.3(-52.9 to -19.8)	Week 25: M(SD), Change from Baseline (95% CI) Past Week: G1 (N = 10): 13.9(31.4), -38.9(-75.7 to -2.0) Past Month: G1 (N = 10): 10.1(16.7), -29.6(-54.3 to -4.8)
					Past Week: *P* = .047 Past Month: *P* = .028	
				Morisky Scale M(SD) G1 (N = 30): 2.5(1.2)	Week 13: M(SD) G1 (N = 30): 1.4(1.3)	Week 25: M(SD) G1 (N = 30):1.4(1.6)
					P = .001	
				Injection Frequency NA	Week 13: M(SD) G1 (N = 29): 83(35)	Week 25: M(SD) G1 (N = 29): 76(35)

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of medication adherence assessments are reported in Appendix E.
Abbreviations: CAE = Customized adherence enhancement; M = Mean; MET = Motivational Enhancement Therapy; NA = Not applicable; SD = Standard deviation; TRQ = Tablet Routine Questionnaire.

Table 9. Psychotic Spectrum Disorders: Non-Psychopharmacological Medication Adherence Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Beebe et al, 2014[54] G1: 10 G2: 10 G3: 10	Adults 21-68 with a diagnosis of schizophrenia or schizoaffective disorder receiving outpatient care. Community mental health	G1: TIPS + Text. TIPS is a manualized intervention providing weekly telephone support addressing taking medication, attending appointments, coping with symptoms, abstaining from alcohol and other drugs, and getting along with others. G2: TIPS only G3: Text only – text format of the TIPS protocol. Texts were delivered daily	G1: Weekly phone calls and daily texts for 3 months G2: Weekly phone calls for 3 months G3: Daily text messages for 3 months	Home pill counts or percentage of injections received vs prescribed for depot NR	1 Month: M(SD) G1 (N = 7): 82.1(19.9) G2 (N = 7): 73.1(21.8) G3 (N = 6): 82.2(26.5)	2 Months: M(SD) G1 (N = 8): 86.6(7.6) G2 (N = 6): 58.5(27.2) G3 (N = 5): 69.4(33.9)
						3 Months: M(SD) G1 (N = 8): 76.9(20.9) G2 (N = 6): 69.3(24.9) G3 (N = 5): 70.2(27.2)
				Mean non-psychiatric medication adherence scores for G1 were higher (by an average of 11.9%) than G3 at 2 of the 3 follow-ups, and higher than G2 (by an average of 14.9%) months 1, 2, 3. Post hoc analysis revealed that the power to examine non-psychiatric medication adherence was 25%.		

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of medication adherence assessments are reported in Appendix E.
Abbreviations: M = Mean; NR = Not reported; SD = Standard deviation; SMS = Short message service; TIPS = Telephone Intervention Problem Solving for Schizophrenia.

1d. What are the effects of these interventions on patient outcomes?

Twenty included studies examined a wide range of patient outcomes, including symptom severity, quality of life, functional impairment, insight, time to first readmission/hospitalization, time spent in the hospital, and time to relapse. Patient outcome scales are described in Appendix F.

Symptom Severity

Seventeen studies examined the effect of interventions for medication adherence on positive (*eg*, delusions, hallucinations, disorganized speech or behavior), negative (*eg*, reduced emotional responsiveness, speech, movement, socialization, motivation), or total symptom severity in patients along the psychotic spectrum.

Positive Symptoms

Four studies evaluated positive symptoms using PANSS or CGI. Interventions included MI,[58] a multicomponent behavioral intervention,[44] an intervention involving family,[52] and SMS reminders.[56] Only the family intervention resulted in a significant decrease in positive symptoms.[52] See Table 10 for more detail.

Negative Symptoms

Four studies evaluated negative symptoms using the PANSS scale or CGI, and findings associated with the interventions were mixed. Interventions included MI,[58] a multicomponent behavioral intervention,[44] an intervention involving family,[52] and SMS reminders.[56]

The group family intervention resulted in a significant decrease in negative symptoms as assessed by the PANSS at 12 months; however, there was no significant difference as assessed by the CGI negative symptom scale at 3 months. SMS reminder messages were associated with a greater degree of change at 3 months and a decrease in severity of negative symptoms at 6 months.[56] No other interventions were associated with a decrease in negative symptoms. Table 10 provides more detail.

Overall Symptom Severity

Seventeen studies evaluated total symptom severity using the PANSS, CGI, or BPRS, with mixed findings associated with the intervention. Of the 10 studies reporting PANSS scores,[44,45,47-49,52,55,58,61,62] four[48,52,55,62] reported significantly fewer symptoms associated with the intervention, including depot plus a customized multicomponent behavioral intervention at 25 weeks,[62] a group family intervention,[52] Adherence Therapy at 12-weeks post-discharge,[48] and e-monitoring and pill counts as compared with self-reported adherence. MI did not reduce symptom severity for the full sample; however, it was associated with greater general symptom score reductions in women.[58]

Nine studies assessed symptoms using the BPRS,[43,46,50,51,53,54,57,59,60,62] with 2 reporting better scores associated with the intervention. The first study, a study of homeless outpatients included depot plus a customized multicomponent behavioral intervention and reported improved scores at 13 and 25 weeks.[62] The second study compared family psychoeducation to usual care, with better BPRS scores for the intervention group at 12 and 24 months.[51] The other 6 studies did not find a difference in BPRS scores between groups.

Three studies reported CGI scores,[55,59,62] with e-monitoring[55] (at 8 weeks) and depot plus a customized multicomponent behavioral intervention for homeless participants[62] reporting better scores at 13 and 25 weeks. Table 10 reports study detail.

Quality of Life

Four studies[46,47,49,56] evaluated the effect of the interventions on quality of life, with no improvements associated with Adherence Therapy,[46] Compliance Therapy,[47,49] or a system-level intervention.[49] However, daily SMS reminders as compared with usual care resulted in better quality of life scores at the end of the intervention (3 months), but not at 6 months follow-up.[56] Table 10 reports study detail.

Functional Impairment

Eleven studies evaluated functional impairment using the GAF, Global Assessment Scale (GAS), or the Social and Occupational Functioning Scale (SOFAS).[43,47-49,51,52,57,59-62] The studies reported mixed findings, with some showing no effect and others a positive effect of medication adherence interventions on functional impairment. The 2 studies comparing interventions involving family members to usual care found the intervention group to be less impaired,[51,52] as did one study of depot plus CAE.[62] However, no improvement or group differences were found in studies examining Adherence Therapy,[48] e-monitoring,[57] a system-level intervention,[49] and shared decision-making.[59] Results of the 3 studies examining Compliance Therapy were mixed, with 2 studies reporting no effect of Compliance Therapy on functional impairment,[47,49] and one study reporting improvement in functional impairment associated with Compliance Therapy as compared to routine management and supportive counseling for up to 18 months.[43] Similar results were found for studies examining CAT and Pharm-CAT, with one study reporting no improvement over time and as compared to e-monitoring,[57] and a second study reporting higher functioning for CAT versus Pharm-CAT and usual care.[60] Higher functioning was associated with Pharm-CAT as compared to usual care at 3 and 6 months, with no difference thereafter. Table 10 reports study detail.

Time to First Readmission/Hospitalization

The 10 studies examining time to first readmission or hospitalization reported mixed findings associated with interventions to improve medication adherence. Three studies comparing interventions involving family members to usual care reported significantly fewer admissions or longer time to readmission/hospitalization associated with the family intervention.[50-52] One study comparing a system-level intervention to Compliance Therapy found that over one year, the system-level intervention resulted in longer time to readmission.[49] Two other studies examining Compliance Therapy[43,47] found that the intervention had no effect on readmission/ hospitalization, nor did MI,[58] depot plus CAE,[62] or shared decision making.[59] Table 10 provides more detail.

Time Spent in the Hospital

Three studies examined whether the interventions aimed at improving medication adherence had any effect on time spent in the hospital. Neither Compliance Therapy[43] nor a group multicomponent behavioral intervention[44] was associated with shorter stays; however, a family intervention was associated with fewer days in the hospital after rehospitalization at 24 months.[51] Table 10 provides study detail.

Time to Relapse

The 2 studies examining time to relapse reported better outcomes associated with the intervention, with longer time to relapse associated with a family intervention,[52] as well as both CAT and Pharm-CAT as compared to usual care.[60] Table 10 provides study detail.

Side Effects

One study compared a system-level intervention to Compliance Therapy and examined side effects (*eg*, psychic, neurological, autonomic) related to psychopharmacological interventions, and found fewer side effects associated with Compliance Therapy. Table 10 reports study detail.

Table 10. Psychotic Spectrum Disorders: Patient Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Adherence Therapy						
Gray et al, 2006[46] G1: 204 G2: 205	Adults with clinically unstable schizophrenia requiring antipsychotic medication for ≥ 1 year post-baseline.	G1: Usual care plus Adherence Therapy (AT), a brief cognitive behavioral approach focused on joint decision making including: assessments, medication problem solving, a medication timeline, exploring ambivalence, discussing beliefs and concerns about medication, medication in the future G2: Usual care plus didactic health education	Eight individual 30- to 50-minute weekly sessions	BPRS–E M(SD) G1 (N = 175): 45.96 (13.23) G2 (N = 196): 44.31 (12.79)	12 Months: M(SD) G1 (N = 175): 38.11 (11.33) G2 (N = 196): 37.34 (9.79)	
					Difference between groups (all available cases): 0.77 (CI, -1.39 to 2.93), *P* = .48 Difference between groups (complete cases): 0.13 (CI, -1.84 to 2.09), *P* = .90	
				SF-36 M(SD) G1 (N = 175): 38.34 (10.89) G2 (N = 192): 40.12 (12.25)	12 Months: M(SD) G1 (N = 175): 40.24 (11.97) G2 (N = 192): 41.32 (11.49)	
					Difference between groups (all available cases): -1.08 (CI, -3.49 to 1.33), *P* = .38 Difference between groups (complete cases): -0.40 (CI, -2.56 to 1.76), *P* = .72 Sensitivity analysis confirmed the findings.	
Schulz et al, 2013[48] G1: 93 G2: 105	Adults diagnosed with a schizophrenic disorder (without comorbid disorders), who were recently discharged and prescribed antipsychotic medication with a	G1: Usual care plus Adherence Therapy (AT), a brief cognitive behavioral approach focused on joint decision-making including: assessments, medication problem solving, a medication timeline, exploring ambivalence, discussing beliefs and concerns about	Eight individual sessions, 5 as an inpatient, additional 3 after discharge.	PANSS M(SD) G1 (N = 63): 48.32(13.83) G2: (N = 42): 49.33(14.74)	12 Weeks Post Discharge M(SD) G1 (N = 63): 44.13(10.67) G2 (N = 42): 50.29(13.67) Difference = -6.16, F = 6.19, *P*<.05	
				GAF M(SD) G1 (N = 67): 67.05(12.17) G2 (N = 46): 64.2(13.49)	12 Weeks Post Discharge M(SD) G1 (N = 67): 72.51(11.52) G2 (N = 46): 67.15(13.81)	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	recommendation of treatment for a least one year following discharge. Hospitals in Germany (3) and Switzerland	medication, medication in the future G2: Usual care followed national guidelines for the treatment of schizophrenia and generally included medication, psychotherapy, occupational therapy, and psychoeducation.			Difference = 5.4, F = .039, *P* = *NS*	
Compliance Therapy[64]						
Byerly et al, 2005[45] G1: 30	Adults diagnosed with schizophrenia or schizoaffective disorder taking only one oral antipsychotic, and who had been admitted to a psychiatric ward or emergency department for psychiatric purposes within 2 years. Community mental health	G1: Compliance Therapy is a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma.	Four to 6 individual face-to-face 30- to 60-minute sessions over the period of a month.	PANSS M(SD) G1: 71.6(17.8) Range 38-105	3 Months G1: .8% increase (*P* = .59)	6 Months G1: .4% decrease (*P* = .33)
Kemp et al, 1998[43] G1: 39 G2: 35	Adult inpatients with psychotic disorders Hospital in England	G1: Routine management plus Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms,	Four to 6 individual face-to-face sessions (M = 4.7) lasting 20-60 minutes twice	BPRS M(SD) Full: G1 (N = 39): 59.6(14.9) G2 (N = 35): 55.7(13.6)	At Discharge M(SD) Full: G1 (N = 39): 37.6(10.1) G2 (N = 35): 37.4(8.5)	6 Months M(SD) 7-item: G1 (N = 36): 14.5(7.2) G2 (N = 31): 16.7(6.9) 12 Months

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
		focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma. G2: Routine management plus supportive counseling (no medication issues addressed)	weekly	7-item: G1 (N = 39): 20.3(7.6) G2 (N = 35): 19.2(6.6)	*P* = Significant (NR) 7-item: G1 (N = 39): 12.6(5.8) G2 (N = 35): 11.7(3.3)	M(SD) 7-item: G1 (N = 35): 13.8(6.3) G2 (N = 28): 15.3(6.2)
						18 Months M(SD) 7-item: G1 (N = 25): 12.5(5.6) G2 (N = 20): 14.8(4.1)
					There was a significant effect on the 7-item measure, but no significant effect when accounting for time.	
				GAF M(SD) G1 (N = 39): 36.8(9.5) G2 (N = 35): 37.7(8.9)	At Discharge M(SD) G1 (N = 39): 49.7(13.2) G2 (N = 35): 47.9 11.2)	3 Months: M(SD) G1 (N = 37): 54.0(17.3) G2 (N = 33): 44.5(10.4)
						6 Months: M(SD) G1 (N = 36): 55.9(17.5) G2 (N = 31): 43.3(10.6)
						12 Months: M(SD) G1 (N = 35): 57.9(16.6) G2 (N = 30): 44.4(14.8)
						18 Months: M(SD) G1 (N = 25): 62.8(18.4) G2 (N = 23) 48.3(14.5)
					There was a significant treatment effect and a significant time x treatment effect with the intervention group showing greater improvement.	
				SAI-E	At Discharge:	6 Months:

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				M(SD) G1 (N = 39): 39.7(19.7) G2 (N = 35): 35.4(28.5)	M(SD) G1 (N = 39): 63.0(23.6) G2 (N = 35) 40.6(31.2)	M(SD) G1 (N = 34): 62.6(23.5) G2 (N = 29): 41.9(30.8)
						12 Months: M(SD) G1 (N = 30): 63.4(25.5) G2 (N = 20): 42.6(36.5)
						18 Months: M(SD) G1 (N = 16): 70.7(24.4) G2 (N = 15): 55.3(42.5)
					Patients who received Compliance Therapy had significant greater insight and retained this over the follow-up period with a mean difference of 18.8% on the insight scale.	
				Time to Readmission NA	NA	18 Months: G1 30% G2 52% Hazard Ratio = 2.2 (95% CI 1.16 to 4.18) for G2 relative to G1
				Time Spent in the Hospital NA	M(SD) G1 41.7(75.5) G2 61.6(90.8) Mann-Whitney U test *P* = .208	NA
O'Donnell et al, 2003[47] G1: 28 G2: 28	Adults 65 and under with a diagnosis of schizophrenia and an IQ >80 recently admitted	G1: Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms,	Five individual face-to-face sessions lasting 30-60 minutes.	PANSS M(SD) G1 (N = 28): 71(22) G2 (N = 28): 66(17)	1 Year: M(SD) G1: 58.2(17) G2: 2.1(21)	NA

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	to the hospital.	focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma. G2: Nonspecific counseling			Difference = 6.1 (95% CI, − 4.7 to 16.9), *P* = .26	
				SAI M(SD) G1 (N = 28): 9(4) G2 (N = 28): 9(4)	1 Year: M(SD) G1: 9.9(4.1) G2: 10.4(2.8) Difference = -.5 (95% CI, − 2.4 to 1.5), *P* = .65	NA
				GAF M(SD) G1 (N = 28): 36(14) G2 (N = 28): 31(12)	1 Year: M(SD) G1: 52.7(17.8) G2: 56.9(25.3) Difference = -4.2 (95% CI, 16.8 to 8.4), *P* = .50	NA
				QLF M(SD) G1 (N = 28): 67(22) G2 (N = 28): 66(22)	1 Year: M(SD) G1: 71.8(21) G2: 75.2(25) Difference = -3.4 (95% CI, − 16.6 to 9.9), *P* = .61	NA
				Occupancy of hospital beds NA	1 Year: M(SD) G1: 26(45) G2: 33(57) Difference = -7 (95% CI, − 35 to 21), *P* = .61	2 Years: M(SD) G1: 43(60) G2: 50(70) Difference = -7 (95% CI, − 42 to 28), *P* = .69
				Time to first rehospitalization NA	M G1: 440 days (95% CI, 346 to 534)	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
					G2: 482 days (95% CI, 378 to 586) *P* = *NS*	
Skarsholm et al, 2014[49] G1: 30 G2: 40	Adult inpatients close to discharge 23-70 with a diagnosis of schizophrenia or schizoaffective disorder under the care of a community mental health team. Community mental health in Denmark	G1: System-Oriented Intervention included providing a brochure and questionnaire on antipsychotic treatment as a basis for conversation between participant/provider, a screening form for identification of compliance problems as the basis for participant/nurse conversation, a reminder box that contained medicine cards, dosage boxes, electronic alarm systems, medication reconciliation, adherence to clinical guidelines G2: Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma.	G1: NA G2: Six individual face-to-face sessions and 3 booster sessions 30-45 minutes in length.	PANSS NR	6 Months: LOCF: G1 (N = 30): 22 G2 (N = 40): 26 *P* = .036 (adjusted for baseline score, *P* = .001) Estimate of difference by regression: 4.93, 95% CI (−7.835 to −2.015) MI: −4.478 (CI −9.259 to 0.403), *P* = .072 (adjusted for baseline score)	
				GAF Median (10; 90th percentile) G1 (N = 30): 33(25, 45) G2 (N = 40): 33(25, 40)	6 Months: *P* = *NS* (MI and LOCF)	
				SWN NR	6 Months: *P* = *NS* (MI and LOCF)	
				Time to first readmission NA	Kaplan-Meier survival proportion estimated from graph: 100 days follow-up: G1 (N = 30): 0.9 G2 (N = 40): 0.7 200 days follow-up: G1 (N = 30): 0.7 G2 (N = 40): 0.5 300 days follow-up: G1 (N = 30): 0.6 G2 (N = 40): 0.4 365 days follow-up:	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
					G1 (N = 30): 0.55 G2 (N = 40): 0.35 *P* = .049	
				Occupancy of hospital beds NA	12 Months: *P = NS*	
System-level Interventions						
Skarsholm et al, 2014[49] G1: 30 G2: 40	Adult inpatients close to discharge 23-70 with a diagnosis of schizophrenia or schizoaffective disorder under the care of a community mental health team. Community mental health in Denmark	G1: System-Oriented Intervention included providing a brochure and questionnaire on antipsychotic treatment as a basis for conversation between participant/provider, a screening form for identification of compliance problems as the basis for participant/nurse conversation, a reminder box that contained medicine cards, dosage boxes, electronic alarm systems, medication reconciliation, adherence to clinical guidelines G2: Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs	G1: NA G2: Six individual face-to-face sessions and 3 booster sessions 30-45 minutes in length.	PANSS NR	6 Months: LOCF: G1 (N = 30): 22 G2 (N = 40): 26 *P* = .036 (adjusted for baseline score, *P* = .001) Estimate of difference by regression: 4.93, 95% CI (−7.835 to −2.015) MI: −4.478 (CI −9.259 to 0.403), *P* = .072 (adjusted for baseline score)	
				GAF Median (10; 90th percentile) G1 (N = 30): 33(25, 45) G2 (N = 40): 33(25, 40)	6 Months: *P = NS* (MI and LOCF)	
				SWN NR	6 Months: *P = NS* (MI and LOCF)	
				Time to first readmission NA	Kaplan-Meier survival proportion estimated from graph: 100 days follow-up: G1 (N = 30): 0.9 G2 (N = 40): 0.7 200 days follow-up: G1 (N = 30): 0.7	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
		and understanding of the illness, and ambivalence towards treatment and stigma.			G2 (N = 40): 0.5 300 days follow-up: G1 (N = 30): 0.6 G2 (N = 40): 0.4 365 days follow-up: G1 (N = 30): 0.55 G2 (N = 40): 0.35 *P* = .049	
				Occupancy of hospital beds NA	12 Months: *P = NS*	
				UKU – Side Effects NA	6 Months: #(%) G1 (N = 30): 21(70%) G2 (N = 40): 17(43%) *P* = .03	
Other Multicomponent						
Bechdolf et al, 2005[44] G1: 40 G2: 48	Adult inpatients 18-64 years who met criteria for a schizophrenic or related disorder Hospital in Germany	G1: Group CBT included MI, coping strategies, problem solving, relapse prevention, and focused on the treatment of auditory hallucinations and delusions, associated symptoms, relapse prevention, and med adherence. G2: Group psychoeducation focused on improvements in medication compliance and rehospitalization rates and included MI	G1: 16 group sessions over 8 weeks lasting 60-90 minutes. G2: 8 sessions in 8 weeks lasting 60-90 minutes	PANSS M(SD) Positive Scale: G1 (N = 40): 14.7(4.9) G2 (N = 48): 14.4(5.1) Negative Scale: G1 (N = 4): 16.5(6.1) G2 (N = 48): 15.5(6.0) General Score: G1 (N = 48): 33.7(9.1) G2 (N = 40): 29.6(7.6)	Post-treatment: M(SD) Positive Score: G1 (N = 37): 13.34.8) G2 (N = 43): 10.4(2.1) Negative Score: G1 (N = 37): 13.9(4.5) G2 (N = 43): 12.5(5.2) General Score: G1 (N = 38): 31.7(9.9) G2 (N = 43): 24.1(4.9)	24 Months: M(SD) Positive Scale: G1 (N = 16): 13.5(5.6) G2 (N = 25): 13.5(6.5) F = .5, *P* = .49 Negative Scale: G1 (N = 16): 13.7(5.0) G2 (N = 25): 14.5(6.3) F = .001, *P* = .94 General Score: G1 (N = 16): 28.1(6.3) G2 (N = 25): 26.4(6.9) *F* = .29, *P* = .50

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				Rehospitalization rates NA	NA	24 Months: No(%) G1 (N = 16): 6(37.5%) G2 (N = 27): 16(59.3%) χ^2 = 2.50, *P* = .114
				Length of hospitalization NA	At Discharge: G1: 92 days G2: 163 days Mann–Whitney U = 31.5, *P* = .224	NA
Lee et al, 2010[61] G1: 24 G2: 33	Participants were outpatients between 17-60 years old, diagnosed with schizophrenia or schizoaffective disorder, and prescribed treatment with a long-acting injectable antipsychotic (depot). Community mental health in Korea	G1: Psychosocial Intervention for Relapse Prevention for depot; included psychoeducation, early warning sign detection, family education with biweekly intervention + usual care. G2: Usual care	G1: 60-minute sessions monthly for 12 months	PANSS M(SD) G1 (N = 21): 61(11) G2 (N = 25): 58.7(7.7)	Both groups experienced significant decreases (P<.01) over time, with no significant difference between groups.	
				CGI –SGH M(SD) G1 (N = 21): 4.1(.5) G2 (N = 25): 4.0(1.2)	Both groups experienced significant decreases (P<.01) over time, with no significant difference between groups.	
				GAF M(SD) G1 (N = 21): 46.4(9.8) G2 (N = 25): 45.8(14.3)	Both groups experienced significant decreases (P<.01) over time, with no significant difference between groups.	
				Relapse – increases to moderately severe PANSS positive score or GAF of 30 or less NA	12 Months: N(%) G1 (N = 21): 2(9) G2 (N = 25): 10(45) *P*<.01	24 Months: N(%) G1 (N = 21): 5(24) G2 (N = 25): 12(48) *P* = .04
				Injection discontinuation -	Over 24 Months:	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				declined to take further injections/ preferred oral medication, or when the patient no longer visited the hospital NA	N(%) G1 (N = 21): 5(23) G2 (N = 25): 18(68) $\chi^2(1) = 13.0$, P<.01	
				Treatment discontinuation - no longer visited the hospital for treatment NA	Over 24 Months: N(%) G1 (N = 21): 3(14) G2 (N = 25): 11(28) $\chi^2(1) = 6.0$, *P* = .01	
Sajatovic et al, 2013[62] G1: 30	Adults 18+ with a diagnosis of schizophrenia or schizoaffective disorder who had missed 20%+ of prescribed antipsychotics and were homeless within the past 12 months. Community-based mental health	G1: Depot + CAE is a manualized individual behavioral intervention that consists of 4 modules (psychoeducation, substance use/modified MET, provider communication, medication management). CAE is customized based on an assessment at baseline, with one to 4 modules assigned.	Eight monthly, in-person, 30- to 40-minute sessions	BPRS M(SD) G1 (N = 30): 47.1(11.5)	13 Weeks: M(SD) G1 (N = 30): 34.0(9.0)	25 Weeks: M(SD) G1 (N = 30): 32.8(10.0)
					P<.001	
				PANSS M(SD) G1 (N = 13): 78.2(26.6)	Week 13: NR	Week 25: M(SD) G1 (N = 13): 51.8(16.7) *P* = .005
				SOFAS M(SD) G1 (N = 19): 47.9(8.0)	13 Weeks: NR	25 Weeks: M(SD) G1 (N = 19): 59.3(9.8) P<.001
				CGI –SGH M(SD) G1 (N = 18): 4.6(.9)	13 Weeks: M(SD) G1 (N = 18): 3.5(.8)	25 Weeks: M(SD) G1 (N = 18): 3.3(.8)
					P<.001	
				Psychiatric hospitalizations M(SD) G1 (N = 17): 1.0(3.0)	13 Weeks: NR	25 Weeks: M(SD) G1 (N = 17): 0.1(.3)

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
						P = .13
				Medical hospitalizations M(SD) G1 (N = 17): 0.1(.3)	13 Weeks: NR	25 Weeks: M(SD) G1 (N = 17): 0.3(.7) *P* = .66
Family Interventions						
Kopelowicz et al, 2012[50] G1: 64 G2: 54 G3: 60	Adults 18-50 of Mexican origin and fluent Spanish speaker with a diagnosis of schizophrenia or schizoaffective disorder who had been without antipsychotic medication for at least one week in the past month without authorization, and lived with their family of origin with a relative willing to participate in family treatment. Community mental health	G1: Usual care plus Multifamily group – Adapted, a culturally modified version of multifamily group therapy, a behavioral family treatment combining psychoeducation and skills training. G2: Multifamily group – Standard plus usual care G3: Usual care	G1: Three individual family joining sessions, a 6-hour multifamily workshop, and twenty-one 90-minute multifamily group sessions twice a month. G2: Same as G1 G3: Monthly 20-minute sessions or more if participant was unstable.	BPRS NR	At the end of treatment (12 months after baseline), all 3 groups improved significantly on the BPRS relative to baseline, but there was no group X time difference (*F*[2,171] = 1.14,*P* = .32). There was no significant change in BPRS scores between the end of treatment and the 24-month follow-up in any of the 3 treatment groups.	
				Time to Hospitalization NR	4 Months: Estimated from graph G1: 75% G2: 60% G3: 60%	8 Months: Estimated from graph G1: 72% G2: 48% G3: 45%
						12 Months: Estimated from graph G1: 62% G2: 45% G2: 35%
						18 Months: Estimated from graph G1: 63% G2: 38% G3: 29%
						24 Months: Estimated from graph G1: 61% G2: 34%

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
						G3: 30%
				The overall test for group differences in time to first hospitalization (log-rank χ^2 = 13.3, *P* = .001). Follow-up comparisons using proportional hazard regression indicated that G1 participants had longer time to first hospitalization than G2 (χ^2 = 6.3, *P* = .01) and G3 (χ^2 = 8.7, *P* = .003). Across the entire follow-up period, hospitalization was less likely for those in Multifamily group – Adapted (39%) than for those in Multifamily group – Standard (66%, χ^2 = 8.2, *P* = .004) or TAU (70.2%, χ^2 = 11.3, P<.001), with no differences between G2 and G3. Tests of regression show significant direct paths from treatment to hospitalization (*B* = -0.29, SE = 0.07, t = -3.88, *P*<.001), and with significant paths from G1 to adherence (*B* = 0.91, SE = 0.26, t = 3.53, *P*<.001), and G1 as a mediator between adherence and hospitalization (Sobel test = 2.92, SE = 0.033, *P* = .004).		
Pitschel-Walz et al, 2006[51] G1: 102 G2: 92	Adults 18-65 with a diagnosis of schizophrenia or schizoaffective disorder Impatient wards in Germany	G1: Patients psychoeducation group focused on symptoms, etiology, acute treatment, relapse prevention, psychosocial treatment, and coping strategies. Relative psychoeducation group focused on the same as patients, and how they could best support patient. G2: Usual care	G1: Patient groups were eight 60-minute sessions, with 1-4 weekly, then 5-8 monthly. Relative groups were eight bi-weekly 90-minute sessions.	GAS M G1: 49 G2: 51	Discharge: M G1: 67 G2: 64 *P = NS*	12 Months: M G1: 78 G2: 68 P<.001
						24 Months: M G1: 75 G2: 66 P<.01
				BPRS M G1: 41 G2: 38 *P = NS*	Discharge: M G1: 30 G2: 31 *P = NS*	12 Months: M G1: 26 G2: 32 P<.001
						24 Months: M G1: 28 G2: 34 P<.01
				Rehospitalization within the	NA	12 Months:

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				first 2 years and days in the hospital NA		# M(SD), Days M(SD) G1: .3(.7), 12(46.6) G2: .6(.8), 30(54.4) *P* = *NS*
						24 Months: # M(SD), Days M(SD) G1: .6(1.1), 39(90.4) G2: 1.1(1.4), 78(127.2) #: *P* = .031 Days: *P* = .034
Valencia et al, 2010[52] G1: 47 G2: 36	Adult outpatients with a diagnosis of schizophrenia who were adherent to their medication and clinically stable Community mental health in Mexico	G1: Group/family (plus individual component) psychosocial skills psychoeducation including medication, decision making, relapse prevention, avoiding drug and alcohol, friendships, improving family relations + usual care G2: Usual care	G1: Patients – 90-minute group session weekly – 40 total sessions in 12 months. Family + patient – 5 sessions G2: 20-minute monthly appointments	GAF M(SD) G1 (N = 47): 42.4(5.9) G2 (N = 36): 42.7(6.1)	End of Treatment (12 Months): M(SD) G1 (N = 47): 57.6(9.4) G2 (N = 36): 44.3(9.0) There was a significant main effect for time (P<.001) and group (P<.01), and group X time (P<.01)	
				PANSS M(SD) Total: G1 (N = 47): 87.0(44.5) G2 (N = 36): 76.4(35.5) Positive: G1 (N = 47): 19.1(12.3) G2 (N = 36):15.8(9.6) Negative: G1 (N = 47): 23.2(12.1) G2 (N = 36): 20.6(9.8) General Psychopathology: G1 (N = 47): 44.8(21.7) G2 (N = 36): 40.1(17.5)	End of Treatment (12 Months): M(SD) Total: G1 (N = 47): 51.8(12.1) G2 (N = 36): 57.3(17.7 Positive: G1 (N = 47): 8.6(2.4) G2 (N = 36): 11.4(4.7) Negative: G1 (N = 47): 11.2(5.2) G2 (N = 36): 14.9(6.6) General Psychopathology: G1 (N = 47): 22.0(5.6) G2 (N = 36): 30.9(8.9)	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
					There was a significant main effect for time for all scales and total (all Ps<.001). There was a significant group X time interaction: Total: P<.001 Positive: P<.01 Negative: P<.001 General Psychopathology: P<.01	
				LEE M(SD) G1 (N = 44): 62.32(12.31) G2 (N = 34): 64.71(13.2)	End of Treatment (12 Months): M(SD) G1 (N = 44): 58.59 G2 (N = 34): 62.0(10.95) P<.05	
				Rehospitalization NA	End of Treatment (12 Months): G1: 2.1% G2: 14% P<.05	
				Relapse - defined as a significant exacerbation of psychotic symptoms with at least a 25% increase on the PANSS total score from baseline NA	End of Treatment (12 Months): G1: 12.8% G2: 33.3% P<.05	
Motivational Interviewing(MI)						
Barkhof et al, 2013[58] G1: 55 G2: 59	Adults with schizophrenia or schizoaffective disorder with a psychotic relapse or deterioration following non-	G1: A manualized MI intervention based on negative symptoms, positive symptoms, cognitive deficits. G2: Health education on	Eight individual 20- to 45-minute sessions over 26 weeks.	Hospitalized # M(SD) G1 (N = 55): 24(44%) G2 (N = 59): 25(44%)	26 Weeks: # M(SD) G1 (N = 45): 17(38) G2 (N = 49): 19(39%)	6 Months: # M(SD) G1 (N = 45): 12(27%) G2 (N = 48): 19(40)
				There were no significant differences by intervention at any time point.		

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	adherence to antipsychotics, who have resumed antipsychotics with some clinical improvement. 3 sites - Inpatient and outpatients in Amsterdam	general health topics.		In participants 35 and under, fewer in the MI group (3/21, 14% vs 11/22, 50%) were hospitalized over the 6-month period (*P* = .012)		
				PANSS M(SD) Total Score: G1 (N = 30): 72(17.9) G2 (N = 32): 72(17.5) Positive Symptoms: G1 (N = 30): 16.2(5.87) G2 (N = 32): 17.2(6.69 Negative Symptoms: G1 (N = 30): 18.7(5.8) G2 (N = 32): 19.1(6.56) General Symptoms: G1 (N = 30): 37.7(9.74) G2 (N = 32): 35.8(8.28)	26 Weeks: M(SD) Total Score: G1 (N = 30): 65.6(22.0) G2 (N = 32): 63.5(16.9) Positive Symptoms: G1 (N = 30): 15.2(6.29) G2 (N = 32): 15.0(6.05) Negative Symptoms: G1 (N = 30): 16.0(5.83) G2 (N = 32): 16.4(6.53) General Symptoms: G1 (N = 30): 35.4(12.98) G2 (N = 32): 32.2(7.07)	6 Months: M(SD) Total Score: G1 (N = 30): 64.0(30.3) G2 (N = 32): 66.2(16.7) Positive Symptoms: G1 (N = 30): 15.7(8.84) G2 (N = 32): 15.9(6.32) Negative Symptoms: G1 (N = 30): 16.2(7.31) G2 (N = 32): 17.3(6.66) General Symptoms: G1 (N = 30): 32.1(14.33) G2 (N = 32): 32.2(7.89)
				For all subscales *P = NS*		
				There was no significant interaction between type of intervention and time (*P* = .68), with a large effect for time with both groups showing reductions in the severity of psycho-pathology (F(2, 110) = 5.59, *P* = .005, but no differences between interventions (*P* = .99). Female patients showed a larger decrease than males in reduction of general PANSS symptoms in G1 (Δ 7.9, SD = 4.0) compared with the HE group (Δ 3.4, SD = 2.4); t (11) = −2.40, *P* = .035.		
Shared Decision-making						
Hamann et al, 2007[59] G1: 39 G2: 47	Adult inpatients 18-65 with a diagnosis of schizophrenia or schizophreniform disorder Hospital in	G1: Decision aid booklet covering pros/cons of medication, psychoeducation, interventions + usual care G2: Usual care	G1: Decision aid session with nurse and extra planning talk with psychiatrist	CGI NR	NR	18 Months: M(SD) G1 (N = 35): 4.0(1.5) G2 (N = 40): 4.1(1.4) *P = NS*
				GAF	NR	18 Months: M(SD)

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	Germany			NR		G1 (N = 30): 54.7(16.5) G2 (N = 37): 51.0(18.5) *P = NS*
				Rehospitalization NA	6 Months: #(%) G1 (N = 36): 8(22) G2 (N = 37): 8(22) *P = NS*	18 Months: #(%) G1 (N = 38): 20(53) G2 (N = 41): 19(46) *P = NS*
					In a backwards stepwise regression, having received the intervention showed a positive trend (OR = .19, *P* = .08) in the direction of fewer hospitalizations.	
Cognitive Adaptation Therapy (CAT)						
Velligan et al, 2008[60] G1: 37 G2: 32 G3: 29	Adult outpatients 18-60 diagnosed with schizophrenia and prescribed an oral antipsychotic Community mental health	G1: CAT consists of manualized individualized strategies and environmental supports designed to include medication adherence, grooming, and activities of daily living G2: Pharm-CAT consisted of only the medication adherence components of CAT G3: Usual care	G1: Individual face-to-face weekly visits lasting 30-45 minutes for 9 months G2: Same as G1, but sessions were generally shorter	BPRS–E NR	Results of a mixed-effects regression model with the base- line symptom scores used as covariates yielded no significant main effects or interactions (all Ps>.09).	
				Relapse – index based on BPRS psychosis items, suicidality, hospitalization, inability to care for self unsupervised NR	The time to relapse differed by group ($\chi^2_{(2)}$ = 11.09; *P*<.004). G1 vs G3: χ^2 = 8.29; *P*<.004 G2 vs G3: χ^2 = 8.20; *P*<.005, respectively). Over 65% of patients in G1 and G2 survived the 15 months without a relapse vs only 19% of G3. There were no differences between G1 and G2.	
				SOFAS NR	G2 was higher functioning than G3 at 3 and 6 months (*P*'s<.05) but not at any time point thereafter. G1 was significantly higher functioning than G3 at all assessment points during the treatment period (all *P*'s<.0001), and significantly better than G1 in the first 3 months of follow-up (*P*<.0001), but there was only a nonsignificant positive trend by the end of 6-month follow-up.	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
					G1 was significantly better than G2 at all time points (*P*'s <.0004) with the exception of the 6-month follow-up. Effect sizes for G1 were large during the treatment phase and moderate 6 months after withdrawal of home visits. The effect size for G2 was small.	
Velligan et al, 2013[57] G1: 47 G2: 48 G3: 47	Adults 18-60 diagnosed with schizophrenia or schizoaffective disorder treated with oral antipsychotic(s) who had missed at least one dose in the previous week. Community mental health	G1: Pharm-CAT consists of manualized individualized strategies and environmental supports targeting medication adherence G2: Med-eMonitor (MM) is a smart pill container capable of cueing and warning patients, recording side effect complaints, alerting staff of failure to take medication as prescribed. G3: Usual care	G1: Home visits 30 minutes long weekly for 9 months. G2: MM support and phone contact as needed.	Hospital and emergency services contact NA	There were no differences between groups (χ^2 = 0.53, *P* = .77).	
				BPRS–E	There were no significant main effects or interactions (all *P* values >.09).	
				SOFAS	There were no significant main effects or interactions (all *P* values >.09).	
Pharmacy Interventions						
Kavanagh et al, 2003[53] G1: 15 G2: 15	Adults diagnosed with psychotic disorders who were inpatients in a psychiatric ward. Hospital in London	G1: Pharmacist-led psychoeducation group including Q & A about medication, rationale, risks of stopping, side effects, risk/benefit evaluations. One session focused on antipsychotics, the second session focused on mood stabilizers + usual care. G2: Usual care	G1: Two one-hour group sessions on consecutive weeks.	SAI-E M(SD) G1 (N = 15): 3.60(4.88) G2 (N = 15): 2.67(5.81) *P = NS*	Post Session and 2 Weeks Follow-up: There was no main effect.	
				BPRS M(SD) G1 (N = 15): 36.47(2.77) G2 (N = 15): 28.87(4.05) *F* = 11.843, *P* = .004	Post Session and 2 Weeks Follow-up: There was no main effect of time and no significant time X group interaction.	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Technology Interventions (e-Monitoring, SMS, Phone)						
Beebe et al, 2014[54] G1: 10 G2: 10 G3: 10	Adults 21-68 with a diagnosis of schizophrenia or schizoaffective disorder receiving outpatient care. Community mental health	G1: TIPS + Text. TIPS is a manualized intervention providing weekly telephone support addressing taking medication, attending appointments, coping with symptoms, abstaining from alcohol and other drugs, and getting along with others. G2: TIPS only G3: Text only – text format of the TIPS protocol. Texts were delivered daily	G1: Weekly phone calls and daily texts for 3 months G2: Weekly phone calls for 3 months G3: Daily text messages for 3 months	BPRS M(SD) G1 (N = 10): 37.7(6.1) G2 (N = 10): 50.1(11.7) G3 (N = 10): 41.3(5.2)	1 Month: M(SD) G1 (N = 10): 38.2(11.9) G2 (N = 10): 38.5(9.1) G3 (N = 10): 31.8(9.7)	2 Months: M(SD) G1 (N = 10): 36.8(10.9) G2 (N = 10): 47.6(9.5) G3 (N = 8): 46.5(10.9) 3 Months: M(SD) G1 (N = 10): 35.8(12.8) G2 (N = 10): 41.7(12.4) G3 (N = 8): 44.5(11.6)
				Analyses yielded a statistically significant main effect for group (F (4,26) = 4.2, P = .005, with mean G1 scores lower than G3 (average mean difference of 9.2 points) at 2 of 3 post-intervention measurement points. Mean G1 scores were lower than G2 scores (average mean difference of 5.7 points) at months 1, 2, 3.		
Frangou et al, 2005[55] G1: 36 G2: 36 G3: 36	Adult outpatients 18-64 with a diagnosis of schizophrenia who had at least 2 admissions in preceding 12 months, and prescribed oral medication. Community mental health in London	G1: e-monitoring (MEMS) – provided with a medication dispenser that recorded access and transmitted data via the @HOME platform. Staff was alerted if participant took less than prescribed amount. G2: Pill counting by pharmacists at study visits G3: Self-report of adherence using Morisky scale.	G1: eMonitoring G2: Pharmacist G3: Self-report	CGI –SGH M(SD) G1 (N = 36): 3.1(1) G2 (N = 36): 3.0(1.1) G3 (N = 36): 3.1(1)	8 Weeks: M(SD) G1 (N = 36): 2.1(1.6) G2 (N = 36): 2.5(1) G3 (N = 36): 3.3(1.2) P = .008, G1 significantly better than G2 (P = .04) and G3 (P = .01). G2 also significantly better than G3 (P = .05)	
				PANSS M(SD) G1 (N = 36): 43(14.9) G2 (N = 36): 43.4(15.5) G3 (N = 36): 46.6(15.9)	8 Weeks: M(SD) G1 (N = 36): 28.1(2) G2 (N = 36): 28.3(13.1) G3 (N = 36): 42.7(21.4) P = .004, G3 less improved compared to G1 (P = .04) and G2 (P	

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
					= .008). No difference between G1 and G2	
				Resource utilization – total number of psychiatric and CPN contacts, and emergency visits M(SD) Psychiatric: G1 (N = 36): 2.1(.7) G2 (N = 36): 2.2(.8) G3 (N = 36): 2.2(1.2) CPN: G1 (N = 36): 8.5(2.6) G2 (N-36): 8.5(2.1) G3 (N = 36): 8.3(2.7) Emergency department visits: G1 (N = 36): .6(.7) G2 (N = 36): .5(.6) G3 (N = 36): .5(.8)	8 Weeks: M(SD) Psychiatric: G1 (N = 36): 1.7(.6) G2 (N = 36): 2.1(.6) G3 (N = 36): 2.2(.8) CPN: G1 (N = 36): 7.4(1.2) G2 (N = 36): 8.0(1.6) G3 (N = 36): 8.1(2.0) Emergency department visits : G1 (N = 36): .1(.3) G2 (N = 36): .9(.9) G3 (N = 36): .8(1.0) MANOVA: *P* = .002 Significantly fewer psychiatric and emergency department visits for G1 (G2, *P* = .01; G3, *P* = .0001).	
Montes et al, 2012[56] G1: 100 G2: 154	Adult outpatients 18-65 with a diagnosis of schizophrenia who were clinically stable, prescribed a single antipsychotic, and one affirmative answer on the MAQ Community mental health in	G1: Daily SMS reminders to take their medication, "Please remember to take your medication." + usual care G2: Usual care	G1: Daily SMS for 3 months	CGI –SGH M(95% CI) Severity: Positive: G1 (N = 100): 2.5(2.24 to 2.76) G2 (N = 154): 2.8(2.61 to 2.99) Negative: G1 (N = 100): 3.3(3.06 6o 3.54) G2 (N = 154): 3.4(3.22 to 3.58) Depressive: G1 (N = 100): 2.3(2.06 to 2.54) G2 (N = 154): 2.3(2.11 to 2.49)	3 Months: Mean changes M(95% CI) Severity: Positive: G1: -.4(-.42 to -.38) G2: -.3(-.32 to -.28) *P* = .26 Negative: G1: -.4(-.42 to -.38) G2: -.3(-.32 to -.28) *P* = .16 Depressive: G1: -.2(.22 to -.18)	6 Months: Mean changes M(95% CI) Severity: Positive: G1: 3(-.32 to -.28) G2: 3(-.32 to -.28) *P* = .89 Negative: G1: -.6(-.62 to -.58) G2: 3(-.32 to -.28) *P* = .03 Depressive: G1: -.2(.22 to -.18)

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	Spain			Cognitive: G1 (N = 100): 2.8(2.58 to 3.02) G2 (N = 154): 3.0(2.84 to 3.16) Global: G1 (N = 100): 3.0(2.78 to 3.22) G2 (N = 154): 3.2(3.06 to 3.34) Degree of Change: NR	G2: -.1(-.12 to -.08) *P* = .09 Cognitive: G1: -.4(-.42 to -.38) G2: -.3(-.32 to -.28) *P* = .13 Global: G1: -.5(-.52 to -.48) G2: -.3(-.32 to -.28) *P* = .11 Degree of Change: Positive: G1: 3.2(3.0 to 3.4) G2: 3.4(3.24 to 3.56) *P* = .1 Negative: G1: 3.3(3.10 to 3.50) G2: 3.5(3.36 to 3.64) *P* = .02 Depressive: G1: 3.3(3.10 to 3.50) G2: 3.5(3.34 to 3.66) *P* = .07 Cognitive: G1: 3.3(3.12 to 3.48) G2: 3.6(3.46 to 3.74) *P* = .01 Global: G1: 3.2(3.02 to 3.38) G2: 3.5(3.36 to 3.64) *P* = .012	G1: -.1(-.11 to -.08) *P* = .35 Cognitive: G1: -.4(-.42 to -.38) G2: -.3(-.32 to -.28) *P* = .48 Global: G1: -.5(-.52 to -.48) G2: -.4(-.42 to -.38) *P* = .48 Degree of Change: Positive: G1: 3.4(3.38 to 3.42) G2: 3.3(3.14 to 3.46) *P* = .63 Negative: G1: 3.4(3.38 to 3.42) G2: 3.4(3.24 to 3.56) *P* = .82 Depressive: G1: 3.4(3.38 to 3.42) G2: 3.4(3.22 to 3.58) *P* = .88 Cognitive: G1: 3.5(3.48 to 3.52) G2: 3.5(3.34 to 3.66) *P* = .8 Global: G1: 3.3(3.10 to 3.50) G2: 3.5(3.32 to 3.68) *P* = .32
				EQ-5D	3 Months:	6 Months:

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				M(95% CI) G1 (N = 100): 65.9(62.5 to 69.2) G2 (N = 154): 64.3(61.7 to 66.8)	Mean changes M(95% CI) G1: 6.6(6.3 to 6.8) G2: 3.1(2.91 to 3.29) *P* = .03	Mean changes M(95% CI) G1: 6.1(5.84 to 5.36) G2: 5.6(5.42 to 5.78) *P* = .75
Velligan et al, 2013[57] G1: 47 G2: 48 G3: 47	Adults 18-60 diagnosed with schizophrenia or schizoaffective disorder treated with oral antipsychotic(s) who had missed at least one dose in the previous week. Community mental health	G1: Pharm-CAT consists of manualized individualized strategies and environmental supports targeting medication adherence G2: Med-eMonitor (MM) is a smart pill container capable of cueing and warning patients, recording side effect complaints, alerting staff of failure to take medication as prescribed. G3: Usual care	G1: Home visits 30 minutes long weekly for 9 months. G2: MM support and phone contact as needed.	Hospital and emergency services contact NA	There were no differences between groups (χ^2 = 0.53, *P* = .77).	
				BPRS–E	There were no significant main effects or interactions (all *P* values >.09).	
				SOFAS	There were no significant main effects or interactions (all *P* values >.09).	

Note. Studies were conducted in the US unless otherwise specified. Studies comparing interventions may be represented in the table more than once. Brief descriptions of patient outcome assessments are reported in Appendix F.
Abbreviations: BPRS = Brief Psychiatric Rating Scale ; BPRS–E = Brief Psychiatric Rating Scale – Expanded; CAE = Customized adherence enhancement; CAT = Cognitive Adaptation Training; CBT = Cognitive behavioral therapy; CGI = Clinical Global Impression scale; CGI-SGH = Clinical Global Impression – Schizophrenia scale; EQ-5D = EuroQoL; GAF = Global Assessment of Functioning; GAS = Global Assessment Scale; LEE = Level of Expressed Emotion; M = Mean; MAQ = Medication Adherence Questionnaire; MET = Motivational Enhancement Therapy; MM = Med-eMonitor; PANSS = Positive and Negative Syndrome Scale; QLF = Quality of Life Scale; SAI = Schedule for Assessment of Insight; SAI-E = Schedule for Assessment of Insight- Expanded; SD = Standard deviation; SF-36 = Short Form Health Survey; SOFAS = Social and Occupational Functioning Scale; SWN = Subjective Well-being on Neuroleptic Treatment Scale; TIPS = Telephone Intervention Problem Solving for Schizophrenia.

1e. What are the harms and costs related to these interventions?

Two studies evaluated costs related to interventions to improve medication adherence in patients along the psychotic spectrum.[42,57] The first study compared the costs related to the frequency and duration of service contacts for Compliance Therapy as compared with routine management and supportive counseling.[1] Results indicated no difference in costs between the 2 interventions, and a positive relationship between costs and adherence for both groups (*ie*, regardless of intervention, better adherence was related to more contact).[42] The second study[2] compared Pharm-CAT to e-monitoring and usual care, and found that the average costs of treatment per patients were higher (significance not reported) for participants in the Pharm-CAT group as compared to e-monitoring.[57] Table 11 reports study detail.

No studies reported harms specific to an intervention.

[1] Healey et al (1998)[42] found significantly better adherence associated with CT.

[2] Velligan et al (2008)[60] found no difference in adherence when comparing pharm-CAT to e-monitoring, with both groups significantly more adherent than usual care.

Table 11. Costs Associated with Medication Adherence Interventions

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure (range, direction)	Source	Baseline	First Follow-up	Additional Follow-ups
Healey et al, 1998[42] G1: 39 G2: 35	Adult inpatients with psychotic disorders Hospital in England	G1: Routine management plus Compliance Therapy, a combination of MI, cognitive, and psychoeducation approaches targeting psychotic symptoms, focusing on illness and treatment history, beliefs and understanding of the illness, and ambivalence towards treatment and stigma. G2: Routine management plus supportive counseling (no medication issues addressed)	Four to 6 individual face-to-face sessions (M = 4.7) lasting 20-60 minutes twice weekly	Client Service Receipt Inventory (CSRI), which measures the frequency and duration of service contacts.	Self-report information, supplemented case note and agency data, including hospital admission records	3 months pre-entry: £ Mean/MDN (SD) G1 (N = 37): 113/27 (184) G2 (N = 35): 188/42 (131)	6 Months: £ Mean/ MDN(SD) G1 N = 36): 187/49 (292) G2 (N = 34): 252/230(234) *P* = .146	12 Months: £ Mean/ MDN(SD) G1 (N = 33): 232/161 (281) G2 (N = 34) 177/230(278) *P* = .216 18 Months: £ Mean/ MDN(SD) G1 (N = 24): 239/161(281) G2 (N = 21): 326/146(404) *P* = .468 When comparing Months 1-18: £ Mean/ MDN(SD) G1 (N = 23): 175/146(148) G2 (N = 18) 193/152(222) *P* = .920

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure (range, direction)	Source	Baseline	First Follow-up	Additional Follow-ups
						Statistically significant positive correlations were found for the entire sample between (a) costs and changes in compliance, and (b) costs and changes in insight between one and 6 months. When the Compliance Therapy and control groups were analyzed separately, neither revealed an obvious efficiency advantage in terms of translating service inputs into subject outcomes. A positive association was found for G1 between change in compliance and costs over 1-6 months (*P* = .004) and change in insight and costs over the same period (*P* = .022). The only other significant correlation was between residual costs and change in compliance in the control group over the 7-12 month period (*P* = .023).		
Velligan et al, 2013[57] G1: 47 G2: 48 G3: 47	Adults 18-60 diagnosed with schizophrenia or schizoaffective disorder treated with oral antipsychotic(s) who had missed at least one dose in the previous week. Community mental health	G1: Pharm-CAT consists of manualized individualized strategies and environmental supports targeting medication adherence G2: Med-eMonitor (MM) is a smart pill container capable of cueing and warning patients, recording side effect complaints, alerting staff of failure to take medication as prescribed. G3: Usual care	G1: Home visits 30 minutes long weekly for 9 months. G2: MM support and phone contact as needed.	Average cost of treatment per patient per month included mileage for home visits, monitor, web support, Pharm-CAT staff and supplies.	Multiple	NA	Average cost of treatment per patient per month G1: $180 G2: $130	

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of patient outcome assessments are reported in Appendix F.
Abbreviations: CAT = Cognitive Adaptation Training; MDN = Median; MI = Motivational interviewing; MM = Med-eMonitor.

KEY QUESTION 2. ADULTS WITH BIPOLAR DISORDER

We identified 4 studies (all moderate ROB) meeting inclusion criteria for patients with Type I or Type II bipolar disorder.[41,67-69] All 4 studies examined interventions that included psychoeducation. One study examined the addition of individual psychoeducation to psychotherapy,[68] another examined group psychoeducation alone,[69] and the third examined the Life Goals Program,[67] which includes psychoeducation and individualized problem solving skills with a focus on self-management. The fourth study evaluated CAE, a customized behavioral multicomponent intervention in which participants were assigned to one to 4 modules (psychoeducation, substance use/modified MET, provider communication, medication management) based on an assessment at baseline.[41]

Two of the 4 studies were conducted in Iran (one in an outpatient hospital clinic and the other in private and university clinics), with the other 2 conducted in community mental health clinics in the US. Studies assessed adherence using the MARS, the DAI, pill counts, and other measures. Common patient outcomes reported were severity of depression, mania, and functional impairment, as assessed by the Hamilton Depression Rating Scale (HAM-D), the Young Mania Rating Scale (YMRS), and the GAF. Appendices E and F provide brief descriptions of adherence and patient outcome assessment tools.

2a. What are the effects of medication adherence interventions on *psychopharmacological* adherence?

Four studies examined interventions designed for psychopharmacological adherence. Two studies conducted in Iran examined psychoeducation alone, with one study focusing on individual sessions,[68] and the other focusing on a group intervention.[69] The first study randomized participants to standard psychotherapy plus individual psychoeducation (intervention group) or standard psychotherapy alone (control group), both of which included 8 weekly sessions followed by monthly question and answer sessions by phone for a total of 18 months.[68] The study evaluated the effect of the interventions on adherence using the MARS, and results indicated significantly better adherence in the intervention group at 6, 12, and 18 months (P = .008). Table 12 provides more detail.

In the second study participants were allocated to one of 3 groups – group psychoeducation, supportive group psychotherapy (placebo), or medication only (control).[69] The intervention group received weekly 90-minute sessions over a period of 9 weeks, with medication adherence assessed using the MARS at 3 and 6 months. Data from this study indicated better adherence in the intervention group as compared to both placebo and control ($F(2, 31) = 55.09$, $P = .0001$). Table 12 provides more detail.

The third study was an RCT evaluating the effect of the Life Goals Program,[70] a manualized structured group psychotherapy program focused on psychoeducation and individual application of problem solving skills.[67] Participants were randomized to either the Life Goals Program plus usual care (medication management, counseling, access to social services and case management), or usual care alone. The Life Goals Program consists of 2 phases. Phase I included 6 weekly group (6-8 members) sessions and targets issues related to medication adherence, with Phase II comprised of ongoing monthly group sessions focused on functional goal attainment. Participants were enrolled in Phase I, and encouraged to attend Phase II. Medication adherence was assessed at baseline and at 3, 6, and 12 months using the DAI, which assesses attitudes

towards psychotropic medication, and has been shown to correlate significantly with validated measures of medication adherence.[1] Participants were also asked to provide an estimate of their adherence to all psychopharmacological medications combined. Data from this study indicated no significant difference between groups. However, there was a large amount of missing data (only 75% of the intervention group and 81% of the control group participated in baseline plus one other assessment) and only 49% of the intervention group participated in most or all of the group sessions, with 37% never participating. The authors conducted a secondary analysis comparing those who had participated in 4 to 6 sessions, those participating in 1 to 2 sessions, and those never attending a group session. Results of the secondary analysis indicated a difference in the effect of the intervention between those participating in 4 to 6 sessions (effect size = .59), and those participating in 1-2 (effect size = .16), and no sessions (effect size = .07). Table 12 provides more detail.

The fourth study was a cohort study evaluating the effect of CAE delivered over 4 weekly, individual, 60-minute sessions and up to 2 follow-up telephone sessions over a 6-week period.[41] The DAI, the Morisky Scale, the Tablet Routine Questionnaire (TRQ) for both the previous week and the previous month, and pill counts were used to assess medication adherence outcomes at 6 weeks, 3 months, and 6 months. Findings indicated better DAI scores at both 6 weeks (P = .005) and at 6 months (P = .001), and better treatment adherence according to the Morisky Scale at 6 months (P = .001). Table 12 provides more detail.

2b. What are the effects of medication adherence interventions on *long-acting injectable (depot) psychopharmacological* adherence?

We identified no studies examining medication adherence interventions for long-acting injectable (depot) psychopharmacological adherence.

2c. What are the effects of medication adherence interventions on *non-psychopharmacological* adherence?

We identified no studies examining medication adherence interventions for non-psychopharmacological adherence.

Table 12. Bipolar Disorder: Medication Adherence Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Psychoeducation (Individual)						
Javadpour et al, 2013[68] G1: 54 G2: 54	Adults 18-60 with a history of at least 2 episodes of relapse in the past 2 or 3 episodes in the last 5 years. Outpatient psychology clinic in a hospital in Iran	G1: Standard psychotherapy plus individual psychoeducation about bipolar disorder and medication, and a question and answer session by telephone. G2: Standard psychotherapy	Eight 50-minute face-to-face weekly sessions, followed by monthly 10-minute phone calls for 18 months.	MARS NR	6 months: M G1: 7.93 G2: 4.70	12 months: M G1: 7.80 G2: 4.00 18 months: M G1: 7.91 G2: 3.73 Group Difference: *P* = .008
Psychoeducation (Group)						
Bahredar, et al, 2014[69] G1: 15 G2: 15 G3: 15	Adults 18 to 50 with type I bipolar disorder experiencing euthymic mood. Private and university clinics in Iran	G1: Pharmacotherapy plus group psychoeducation about BD and medication. G2: Pharmacotherapy plus supportive psychotherapy (placebo) G3: Pharmacotherapy only	Nine 90-minute weekly group sessions.	MARS M(SD) G1 (N = 15): 6.27 (0.88) G2 (N = 15): 6.47 (0.52) G3 (N = 15): 6.53 (0.64)	3 months: M(SD) G1 (N = 15): 8.33 (0.65) G2 (N = 15): 4.91 (0.54) G3 (N = 15): 5.08 (0.79) Group Difference: *F*(2,31) = 55.09, *P* = .0001	6 months: M(SD) G1 (N = 15): 7.92 (1.38) G2 (N = 15): 4.36 (0.67) G3 (N = 15): 4.33 (0.49)
Other Multicomponent Behavioral Interventions						
Sajatovic et al, 2009[67] G1: 84 G2: 80	Adults with Type I or Type II bipolar disorder with >2 years since first BD episode. Community-based mental health	G1: Treatment as usual plus Life Goals Program (LGP), a manualized group psychotherapy program that includes education and individualized problem solving to promote illness self-management. G2: Treatment as usual (medication management	Six weekly group sessions	DAI M(SD) G1 (N = 73): 7.18 (2.42) G2 (N = 69): 7.52 (2.07)	3 months: M(SD) G1 (N = 53): 8.06 (1.81) G2 (N = 56): 7.50 (2.22) Group Difference*: P = NS*	6 months: M(SD) G1 (N = 45): 8.20 (1.75) G2 (N = 45): 7.51 (2.27) 12 months: M(SD) G1 (N = 34): 8.27 (1.90) G2 (N = 30): 7.93 (1.86)

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
		by a psychiatrist, psychosocial therapy and counseling by mental health clinicians and access to social services or case management)			Secondary analysis examining DAI by group session attendance found ES = .59 for those attending 4-6 sessions, ES = .16 for those attending 1-2 sessions, and ES = .07 for those never attending session.	
				Self-reported treatment adherence behaviors M(SD) G1 (N = 84): 79.46 (32.04) G2 (N = 80): 82.19 (30.34)	3 months: M(SD) G1 (N = 62): 83.87 (28.66) G2 (N = 61): 81.15 (32.49)	6 months: M(SD) G1 (N = 51): 90.20 (22.40) G2 (N = 55): 77.27 (35.12) 12 months: M(SD) G1 (N = 41): 95.73 (11.04) G2 (N = 39): 81.08 (30.85)
				Group Difference: *P = NS*		
				A mixed model repeated measures analysis found a trend (*P* = .56) that more time in any treatment predicted more positive attitudes towards medication		
Sajatovic et al, 2012[41] G1: 43	Adults with Type I or Type II bipolar disorder and poor adherence, with >2 years since first BD episode. Community-based mental health	G1: Customized adherence enhancement (CAE) is a manualized individual behavioral intervention consisting of 4 modules (psychoeducation, substance use/modified MET, provider communication, medication management). CAE is customized based on an assessment at baseline, with one to 4 modules assigned.	Four weekly, in-person, 60-minute sessions and up to 2 follow-up telephone sessions over a 6 week period.	DAI M(SE), MDN G1: 6.5 (0.3), 7.0	Six Weeks: M(SE), MDN G1: 7.5 (0.3), 8.0	3 Months: M(SE), MDN G1: 7.8 (0.4), 8.0 WSRT *Z* = 2.815, *P* = .005
						6 Months: M(SD), MDN G1: 8.1 (0.4), 9.0 *t*(30) = 4.252, *P*<.001
				Morisky Scale M(SE), MDN G1: 3.0 (0.2), 3.0	6 Months: M(SE), MDN G1: 1.3 (0.3),1.0 WSRT *Z* = -3.923, *P*<.001	
				TRQ *M%* (SE), MDN Previous Week:	6 Weeks: *M%* (SE), MDN Previous Week:	3 Months: *M%* (SE), MDN Previous Week:

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				G1: 48.0 (4.8), 43.0 Previous Month: G1: 51.4 (4.1), 43.0	G1: 23.5 (5.1), 14.0 Previous Month: G1: 20.7 (4.2), 14.0	G1 (N = 33): 24.0 (6.4), 0 WSRT *Z* = -3.054, *P* = .002 Previous Month: G1 (N = 33): 21.4 (5.6), 0 WSRT *Z* = -3.753, *P*<.001
						6 Months: *M*% (SE), MDN Previous Week: G1 (N = 28): 25.2 (6.8), 3.5 WSRT *Z* = -2.561, *P* = .01 Previous Month: G1 (N = 28): 21.3 (5.5), 7.0 WSRT *Z* = -3.679, *P*<.001
				Longitudinal mixed models for both the previous month and the previous week as dependent variables were fit. The fixed effect of time was statistically significant for TRQ adherence for both the previous month (*P*<.001) and previous week (*P* = .002), indicating improved adherence over time.		
				Pill Counts *M*% (SE), MDN 57.6 (7.6), 47.0	Six Weeks: *M*% (SE), MDN 58.8 (20.7), 72.0	3 Months: *M*% (SE), MDN 38.0 (19.2), 29.0
						6 Months: *M*% (SE), MDN 35.3 (9.9), 27.5
				Only one-third of participants provided pill bottles, with only 2 participants at baseline and 3-months, and one participant at baseline and 6-months.		

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of medication adherence assessments are reported in Appendix E.
[1] Only 75% of the intervention group and 81% of the control group participated in baseline plus one other assessment, and only 49% of the intervention group participated in most or all of the group sessions, with 37% never participating.
Abbreviations: CAE = Customized adherence enhancement; DAI = Drug Attitude Inventory; ES = Effect size; MARS = Medication Adherence Rating Scale; M = Mean; MDN = Median; SD = Standard deviation; SE = Standard error; TRQ = Tablet Routine Questionnaire; WSRT = Wilcoxon signed-rank test.

2d. What are the effects of these interventions on patient outcomes?

The 4 studies meeting inclusion criteria for medication adherence outcomes in patients with bipolar disorder also reported data related to patient outcomes, including quality of life, depression, mania, functional impairment, global functioning/severity, positive and negative affective symptoms, and hospital readmissions. Appendix F provides a summary of the included patient outcome scales.

Quality of Life

One study, which evaluated the addition of 8 weekly individual psychoeducation sessions and short telephone contact for 18 months compared to standard psychotherapy, assessed quality of life using the World Health Organization Quality of Life instrument (WHOQOL-BREF) at baseline, 6, 12, and 18 months.[68] The WHOQOL-BREF includes the domains of physical health, mental health, social health, and the environment, and results indicated that mean scores (all time points combined) for the intervention group were significantly higher than the comparison group along all of the domains, indicating better quality of life (*P* = .000). Table 13 provides more detail.

Depression

Three studies assessed depression using the HAM-D.[41,67,68] Data from the first study, which assessed the addition of individual psychoeducation sessions in participants who had experienced at least 2 episodes of relapse in the past 2 years or had a history of 3 episodes in the past 5 years (intervention group baseline mean [M] = 4.24), found significantly lower scores in the intervention group at 6, 12, and 18 months (*P* = .000).[68] The second study, which evaluated the CAE in bipolar participants with poor adherence, found that while there was no significant difference from baseline to 3 months (M[SE] = 16.2[1.2], *P* = .246), as compared to baseline, HAM-D scores were significantly lower at 6 months (M[SE] = 15.3[1.6], *P* = .044).[41]

The third study compared the Life Goals Program, a group psychotherapy program including psychoeducation and individualized problem-solving, to treatment as usual (intervention group baseline M[SD] = 19.98[11.45]), and found no significant differences at 3, 6, and 12 months.[67] However, a mixed model repeated measures analysis found a trend (*P* = .056) indicating that higher baseline HAM-D scores predicted more negative attitudes towards medications over time regardless of intervention. In this study, only 49% of the intervention group participated in most or all of the group sessions, and 37% never attended a group session. See Table 13 for more detail.

Mania

Three included studies assessed mania.[41,67,68] Using the Bech Rafaelsen Mania Scale, one study[68] assessed the addition of individual psychoeducation versus standard psychotherapy versus standard psychotherapy alone and found significantly lower mean mania scores at 6, 12, and 18 months (*P* = .000). Similar to findings for depression, another study[41] found that while CAE resulted in no significant differences from baseline to 3 months (*P* = .101) on the YMRS, mania scores were significantly lower at 6 months (M[SE] = 9.6[1.0]) as compared with baseline (M[SE] = 14.2[1.2], *P* = .002). Also similar to findings for depression outcomes, a study[67] comparing the Life Goals Program group to participants receiving usual care found no difference in YMRS scores. Table 13 provides more detail.

Functional Impairment

Three included studies examined outcomes related to functional impairment, 2 of which used the GAF,[41,69] with one utilizing the predecessor to the GAF, the GAS.[67] One study compared group psychoeducation to a placebo group receiving supportive psychotherapy, and to a control group composed of participants experiencing euthymic mood.[69] GAF scores for all 3 groups were similar at baseline. Findings indicated that while there was no difference between the placebo and control groups, GAF scores for the intervention group were significantly higher than both placebo and control at 3 and 6 months (P = .0001), indicating higher levels of functioning.

Similar to other patient outcomes associated with CAE, there was no significant difference in functional impairment between baseline (M[SE] = 51.6[1.2]) and 3 months (M[SE] = 55.7[1.3], P = .072), but a significant improvement was observed from baseline to 6 months follow-up (M[SE] = 58.0[1.7], P = .001).[41] Similarly, there was no difference between the Life Goals Program group and usual care at 3, 6, and 12 months.[67] See Table 13 for more detail.

Global Functioning/Severity – Bipolar Disorder

One study examined the severity of depressive and manic episodes and the degree of change from the immediately preceding phase and from the worst phase of illness using the Clinical Global Impression scale for use in bipolar illness (CGI-BP), and found that CAE resulted no improvement between baseline (M[SE] = 4.4[.16]) and 3 months (M[SE] = 3.9[.21], P = .072), with significant improvement from baseline to 6-months follow-up (M[SE] = 3.6[.24], P = .001).[41] See Table 13 for more detail.

Positive and Negative Affective Symptoms

One study assessed positive and negative affective symptoms using the BPRS.[41] Unlike other patient outcomes associated with CAE, there was significant improvement from baseline (M[SE] = 43.6[1.8]) to both 3-months (M[SE] = 37.3[2.1], P = .003) and 6-months follow-up (M[SE] = 36.1[2.3], P = .001). Table 13 provides more detail.

Hospital Readmissions

One study examined hospital records to evaluate whether individual psychoeducation in addition to standard psychotherapy was associated with fewer hospital readmissions. Data indicated that over the 18-month study period, fewer participants in the intervention group were readmitted to the hospital as compared with participants receiving standard psychotherapy alone (.22% versus 1.41%, P = .000). See Table 13 for more detail.

2e. What are the harms and costs related to these interventions?

We identified no studies addressing the harms or costs of interventions for medication adherence in patients with bipolar disorder.

KEY QUESTION 3. ADULTS WITH PTSD

We identified no studies examining medication adherence interventions for patients with PTSD.

Table 13. Bipolar Disorder: Patient Outcomes

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
Psychoeducation (Individual)						
Javadpour et al, 2013[68] G1: 54 G2: 54	Adults 18-60 with a history of at least 2 episodes of relapse in the past 2 or 3 episodes in the last 5 years. Outpatient psychology clinic in a hospital in Iran	G1: Standard psychotherapy plus individual psychoeducation about bipolar disorder and medication, and a question and answer session by telephone. G2: Standard psychotherapy	Eight 50-minute face-to-face weekly sessions, followed by monthly 10-minute phone calls for 18 months.	WHOQOL-BREF NR	Mean of Baseline + 6, 12, 18 months Physical Health: G1: 63.81 G2: 53.25 Mental Health: G1: 66.65 G2: 54.29 Social Health: G1: 74.07 G2: 51.68 Environment: G1: 65.05 G2: 48.93	
					Group Difference: P = .000 (all domains)	
				Recurrence of depression (HAM-D >7) M G1: 4.24 G2: 5.22	6 months: M G1: 6.27 G2: 10.19	12 months: M G1: 6.04 G2: 11.19
						18 months: M G1: 5.78 G2: 11.19
					Group Difference: P = .000	
				Recurrence of mania (Bech Rafaelsen Mania Scale >9) M	6 months: M G1: 4.64 G2: 8.83	12 months: M G1: 4.88 G2: 9.95

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
				G1: 4.18 G2: 4.34		18 months: M G1: 4.08 G2: 7.29
					Group Difference: *P* = .000	
				Hospital readmission 0	M over 18 months G1: 0.22 G2: 1.41 *P* = .000	
Psychoeducation (Group)						
Bahredar, et al, 2014[69] G1: 15 G2: 15 G3: 15	Adults 18 to 50 with type I bipolar disorder experiencing euthymic mood Private and University Clinics in Iran	G1: Pharmacotherapy plus group psychoeducation about BD and medication. G2: Pharmacotherapy plus supportive psychotherapy (placebo) G3: Pharmacotherapy only	Nine 90-minute weekly sessions.	GAF M(SD) G1 (N = 15): 56.6 (3.58) G2 (N = 15): 56.67 (4.5) G3 (N = 15): 56.27 (3.17)	3 months: M(SD) G1 (N = 15): 64.83 (1.9) G2 (N = 15): 56.27 (3.6) G3 (N = 15): 55.25 (3.91)	6 months: M(SD) G1 (N = 15): 64.17 (2.12) G2 (N = 15): 56.0 (4.36) G3 (N = 15): 54.17 (5.08)
					Group Difference: $F(2,31) = 90.93$, $P = .0001$	
Other Multicomponent						
Sajatovic et al, 2009[67] G1: 84 G2: 80	Adults with Type I or Type II bipolar disorder. Community-based mental health	G1: Treatment as usual plus Life Goals Program (LGP), a manualized group psychotherapy program that includes education and individualized problem-solving to promote illness and self-management. G2: Treatment as usual (medication management	Six weekly group sessions	HAM-D M(SD) G1 (N = 83): 19.98 (11.45) G2 (N = 80): 17.08 (10.99)	3 months: M(SD) G1 (N = 63): 16.30 (9.68) G2 (N = 65): 15.85 (10.52)	6 months: M(SD) G1 (N = 51): 16.35 (10.18 G2 (N = 55): 15.96 (12.47)
						12 month: M(SD) G1 (N = 41): 16.02 (11. 73) G2 (N = 39): 14.39

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
		by a psychiatrist, psychosocial therapy and counseling by mental health clinicians and access to social services or case management)				(10.87)
					Group Difference: *P* = *NS*	
					A mixed model repeated measures analysis found a trend (*P* = .056) that higher baseline HAM-D scores predicted more negative attitudes towards medications over time regardless of intervention.	
				YMRS M(SD) G1 (N = 84): 7.30 (5.41) G2 (N = 80): 7.58 (5.44)	3 months: M(SD) G1 (N = 63): 6.14 (4.85) G2 (N = 65): 8.02 (5.38)	6 months: M(SD) G1 (N = 51): 6.78 (5.36) G2 (N = 55): 7.69 (6.26)
						12 months: M(SD) G1 (N = 41): 5. 85 (4.74) G2 (N = 39): 7.15 (5.60
					Group Difference: *P* = *NS*	
				GAS M(SD) G1 (N = 83): 56.53 (12.43) G2 (N = 78): 58.22 (N = 12.00)	3 months: M(SD) G1 (N = 61): 60.10 (11.63) G2 (N = 61): 59.05 (12.44)	6 months: M(SD) G1 (N = 46): 61.72 (12.76) G2 (N = 53): 62.19 (14.42)
						12 months: G1 (N = 40): 63.70 (12.66) G2 (N = 39): 64.51 (15.90)
					Group Difference: *P* = *NS*	
Sajatovic et al, 2012[41] G1: 43	Adults with Type I or Type II bipolar disorder and poor	G1: Customized adherence enhancement (CAE) is a manualized individual behavioral intervention consisting of 4 modules	Four weekly, in-person, 60-minute sessions and up to 2 follow-up telephone	BPRS M(SE), MDN G1: 43.6 (1.8), 42.5	3 Months: M(SE), MDN G1: 37.3 (2.1), 36.0 WSRT *Z* = -2.931, *P* = .003	6 Months: M(SE), MDN G1: 36.1 (2.3), 36.0 WSRT *Z* = -3.267, *P* = .001

Study; N per Group	Sample and Setting	Intervention Groups	Intervention Intensity	Measure; Baseline	First Follow-up	Additional Follow-ups
	adherence, with >2 years since first BD episode. Community-based mental health	(psychoeducation, substance use/modified MET, provider communication, medication management). CAE is customized based on an assessment at baseline, with one to 4 modules assigned.	sessions over a 6-week period.	CGI-BP M(SE), MDN G1: 4.4 (0.16), 4.0	3 Months: M(SE), MDN G1: 3.9 (0.21), 4.0 *t*(31) = -1.717, *P* = .096	6 Months: M(SE), MDN G1: 3.6 (0.24), 3.0 *t*(29) = -3.657, *P* = .001
				GAF M(SE), MDN G1: 51.6 (1.2), 51.0	3 Months: M(SE), MDN G1: 55.7 (1.3), 51.0 WSRT *Z* = 1.797, *P* = .072	6 Months: M(SE), MDN G1: 58.0 (1.7), 60.0 *t*(29) = 3.671, *P* = .001
				HAM-D M(SE), MDN G1: 17.8 (1.1), 18.5	3 Months: M(SE), MDN G1: 16.2 (1.2), 16.0 *t*(31) = -1.182, *P* = .246	6 Months: M(SE), MDN G1: 15.3 (1.6), 15.0 WSRT *Z* = -2.010, *P* = .044
				YMRS M(SE), MDN G1: 14.2 (1.2), 14.0	3 Months: M(SE), MDN G1: 11.2 (1.4), 9.0 WSRT *Z* = -1.638, *P* = .101	6 Months: M(SE), MDN G1: 9.6 (1.0), 9.0 *t*(29) = -3.404, *P* = .002

Note. Studies were conducted in the US unless otherwise specified. Brief descriptions of patient outcome assessments are reported in Appendix F.
[1] Only 75% of the intervention group and 81% of the control group participated in baseline plus one other assessment, and only 49% of the intervention group participated in most or all of the group sessions, with 37% never participating.
Abbreviations: BPRS = Brief Psychiatric Rating Scale; CAE = Customized adherence enhancement; CGI-BP = Clinical Global Impression – Bipolar scale; GAF = Global Assessment of Functioning; GAS = Global Assessment Scale; HAM-D = Hamilton Depression Rating Scale; MET = Motivational Enhancement Therapy; WSRT = Wilcoxon signed-rank test.

SUMMARY AND DISCUSSION

We reviewed 7,944 titles and abstracts from the search of electronic databases, bibliographies, and other sources, and 152 were identified as potentially relevant. Upon full-text review, we excluded 127 studies for a total of 24 included studies from 25 publications. Of the 518 clinical trials identified by our search of trial registry websites, one study met inclusion criteria;[40] however, this study and all data reported on ClinicalTrials.gov are represented in an included publication.[41] We identified 21 articles (20 primary studies) for Key Question 1, 4 primary studies for Key Question 2, and no primary studies for Key Question 3.

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1. In adults with psychotic spectrum disorders:

Overall there is insufficient evidence from which to draw conclusions about the effectiveness of interventions to improve medication adherence in patients with psychotic spectrum disorders.

Interventions vary widely, with included studies evaluating multicomponent behavioral interventions, interventions involving family members, interventions involving technology, pharmacist-led interventions, system-level interventions, and others. Overall, findings are mixed. However, there is low strength of evidence that interventions involving family members, and those involving technology, such as e-monitoring or daily reminder messages may result in improved psychopharmacological adherence; this indicates that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. Table 14 provides additional detail.

There is limited evidence of the effectiveness of depot antipsychotics in combination with a medication adherence intervention, with studies reporting better adherence associated with a psychosocial intervention in patients prescribed a depot antipsychotic as compared with controls, and improved adherence in a homeless population associated with the prescription of depot and a customized multicomponent behavioral intervention. However, despite evidence suggesting a positive effect, the wide differences in the interventions, small sample sizes, the potential for sampling bias in populations prescribed depot antipsychotics, and lack of methodological rigor preclude drawing firm conclusions.

Only one study measured non-psychopharmacological adherence, and found no benefit associated with telephone and/or SMS support.

There is no clear evidence of the effect of medication adherence interventions on patient outcomes. Findings reported for positive, negative, and overall symptom severity are mixed, and there is little support that these interventions improve quality of life. Findings related to functional impairment are also mixed; however, there is limited evidence that interventions involving family members and those including the use of a depot antipsychotic may result in improved functioning. Similarly, while it is unclear whether medication adherence interventions in general are effective in reducing hospitalizations, the time to first hospital readmission, or time spent in the hospital, 2 studies reported a positive effect of interventions on time to relapse, and limited evidence suggests that in general, interventions involving family members may result in better patient outcomes.

Table 14. Psychotic Spectrum Disorders: Summary of Medication Adherence Outcomes

Type of Intervention	Study Design (Combined N)	Findings	Strength of Evidence	Comments
Behavioral Multicomponent - Adherence Therapy	2 RCTs (N = 370)	Mixed findings: one study (low ROB) reported better adherence compared to usual care on the MAQ and SAI-C at 12 months, and the other (low ROB) reporting no difference from usual care on the CDR, DAI-30, and MARS at 12 weeks post-discharge.	Insufficient	Evidence from only 2 studies, with mixed findings.
Behavioral Multicomponent - Compliance Therapy	2 RCTs (N = 130) 1 NRCT (N = 70) 1 Prospective Cohort (N = 30)	Mixed findings: better MARS scores with Compliance Therapy at 1 month but not 6 months in 1 study (high ROB); better DAI and compliance scores as compared with routine management plus supportive counseling through 18 month follow in 1 study (high ROB); no benefit to Compliance Therapy up to 6 months in 2 studies (compared to nonspecific counseling and Compliance Therapy; moderate ROB).	Insufficient	Inconsistent findings among 4 studies. Risk of bias due to study design.
Other Behavioral Multicomponent	1 RCT (N = 88)	No difference between group cognitive behavioral therapy (CBT) plus Motivational Interviewing (MI) and group psychoeducation plus MI (moderate ROB).	Insufficient	Evidence from only one study.
Depot plus Behavioral Multicomponent	1 Trial (randomization unclear) (N = 57) 1 Prospective Cohort (N = 30)	Findings indicated improved adherence related to the use of depot antipsychotics plus a behavioral multicomponent intervention (compared to usual care or no comparator) as measured by injection visits up to one year, and injection visits, TRQ, Morisky scale, DAI, and AMQ up to 25 weeks (moderate ROB).	Insufficient	Heterogeneity among interventions; risk of bias due to study design.
Family Intervention	3 RCTs (N = 449)	Better adherence with family interventions as measured by clinician rating/blood plasma and pharmacy records/family-report as compared to usual care in 2 studies (moderate ROB). No difference when controlling for time in a third study examining a culturally modified family intervention as compared to the standard family intervention and monthly sessions (moderate ROB).	Low	Heterogeneity among interventions.
System-level Intervention	1 NRCT (N = 70)	Nonsignificant trend towards better adherence for the system-level intervention, compared with Compliance Therapy (moderate ROB).	Insufficient	Evidence from only one study.
Pharmacist-led	1 Prospective Cohort w/post hoc comparison (N = 30)	No significant difference over time or between groups (high ROB).	Insufficient	Evidence from only one study; potential risk of bias due to study design flaws.
Technology Interventions	4 RCTs (N = 434)	Mixed findings on e-monitoring/MEMS: better adherence in 1 study as compared to pill counts and self-reported adherence (high ROB), conflicting results in 1 study as compared to a pharmacy based intervention and usual care (low ROB). Telephone plus SMS resulted in nonsignificant adherence improvement vs telephone or SMS alone (moderate ROB); SMS alone resulted in significantly better adherence than usual care (moderate ROB).	Low	Mixed findings and heterogeneous interventions.

Type of Intervention	Study Design (Combined N)	Findings	Strength of Evidence	Comments
Motivational Interviewing (MI)	1 RCT (N = 114)	One study found no benefit to MI over usual care as measured by the MAQ or DAI (low ROB).	Insufficient	Evidence from only one study.
Cognitive Adaptation Training (CAT)	2 RCTs (N = 240)	One study found that both CAT and Pharm-CAT resulted in better adherence than usual care, with no difference between the 2 (moderate ROB). The second study comparing Pharm-CAT to e-monitoring reported mixed results (low ROB).	Insufficient	Evidence from 2 studies that used different comparators.
Shared Decision Making	1 RCT (N = 107)	One study found no benefit to a shared decision-making over usual care as measured by the MARS and plasma levels (high ROB).	Insufficient	Evidence from only one single study.

Note. Studies comparing interventions may be accounted for more than once.
Abbreviations: AMQ = Attitude towards Medication Questionnaire; CAT = Cognitive Adaptation Training; CBT = Cognitive Behavioral Therapy; CDR = Concentration to Dose Ratio; DAI = Drug Attitude Inventory; MAQ = Medication Adherence Questionnaire; MARS = Medication Adherence Rating Scale; MEMS = Medication Event Monitoring System; MI = Motivational Interviewing; NRCT = Non-randomized controlled trial; ROB = Risk of bias; SAI-C = Schedule for the Assessment of Insight - C; TRQ = Tablet Routine Questionnaire.

Key Question 2. In adults with bipolar disorder:

The 4 studies meeting inclusion criteria for Key Question 2 provide limited evidence of the effectiveness of interventions for medication adherence in patients with bipolar disorder. Three of the 4 studies found a positive effect on psychopharmacological adherence associated with an adherence intervention, with high rates of attrition in the one study reporting no effect. Despite evidence suggesting a generally positive effect, the strength of the evidence is insufficient and thus precludes drawing conclusions, due to the fact that the interventions were heterogeneous, sample sizes were small, and 2 studies showing a positive effect were conducted in Iran, calling into question applicability (see Table 15).

There is no clear evidence to support conclusions regarding the effect of interventions for improving medication adherence on patient outcomes. Findings related to depression, mania, and functional impairment were mixed, and despite limited evidence supporting improvement, the lack of high quality studies, heterogeneity of the interventions, and setting preclude the ability to draw conclusions.

Key Question 3. In adults with PTSD:

We identified no studies meeting inclusion criteria for Key Question 3.

LIMITATIONS

Our review has a number of limitations. Despite restricting included studies to randomized and non-randomized controlled trials and observational studies that controlled for important confounding variables *and* included either a comparison group or examined a trend controlling for time (see Table 3), we rated only 4 of the 25 included studies (all 4 were trials) as high-quality studies with a low risk of bias,[46,48,57,58] with 4[42,43,55,59] of the 19 trials and 2[45,53] of the 6 observational studies determined to have a high risk of bias. In many studies, sample sizes were small, bringing into question statistical power. While it would have been ideal to overcome the issue of power by combining studies quantitatively, heterogeneity between studies precluded us from doing so. Studies included in this review evaluate a wide range of interventions in a variety of settings, with vast differences in intervention characteristics and implementation; specific interventions were rarely examined in more than one study. Furthermore, a wide range of measures were used to assess medication adherence, ranging from objective measures to validated short self-report scales, which often found different results even within the same study. Finally, although we did conduct a search for grey literature, we were unable to conduct a formal assessment of publication bias.

Table 15. Bipolar Disorder: Summary of Medication Adherence Outcomes

Type of Intervention	Study Design; (Combined N)	Findings	Strength of Evidence	Comments
Psychoeducation (individual/group)	1 RCT (N = 108) 1 NRCT (N = 45)	Both individual and group psychoeducation resulted in better medication adherence pharmacotherapy alone or pharmacotherapy with standard psychotherapy (moderate ROB).	Insufficient	Evidence from only 2 studies, external validity due to setting.
Psychoeducation plus problem solving	1 RCT (N = 164)	There was no improvement in medication adherence associated with the intervention as compared to usual care (moderate ROB).	Insufficient	Evidence from only one study. Only 75% of the intervention group and 81% of the control group participated in baseline plus one other assessment, and only 49% of the intervention group participated in most or all of the group sessions, with 37% never participating.
Customized Behavioral Multicomponent (psychoeducation, substance use/modified MET, provider communication, medication management)	1 Prospective Cohort (N = 43)	Customized adherence enhancement (CAE) was associated with better adherence and attitudes towards medication at 3 and 6 months (moderate ROB).	Insufficient	Evidence from only one study; risk of bias due to study design.

Abbreviations: CAE = Customized adherence enhancement; MET = Motivational Enhancement Therapy; NRCT = Non-randomized controlled trial; RCT = Randomized controlled trial; ROB = Risk of bias.

DISCUSSION

We found 24 studies in 25 publications with the potential to inform policies and practices related to medication adherence in patients with severe mental illness in the VHA. Twenty studies (reported in 21 articles) examined patients with psychotic spectrum disorders, and 4 studies were in patients with bipolar disorder. We identified no studies examining patients with PTSD. The interventions designed to improve medication adherence across Key Questions 1 and 2 differed widely, with very few studies evaluating the same specific interventions. Despite a variety of interventions designed to increase psychopharmacological adherence, study limitations (*eg*, differences in population and setting, heterogeneity among studies, a wide range of comparators, and the challenge of evaluating complex interventions), as well as concerns regarding applicability to the VHA, preclude us from drawing strong conclusions.

There is limited evidence that the involvement of family members, the use of technology (*eg*, e-monitoring, SMS, telephone), and that the combination of a depot antipsychotic and another intervention may be effective in improving adherence. However, these findings must be interpreted with caution, given the heterogeneity among interventions, the difficulty in determining the contribution of the depot antipsychotic versus the adherence intervention, the methodological limitations, and the lack of consistent replication of any specific intervention. With the exception of interventions involving technology and system-level interventions, many interventions include behavioral or other techniques (*eg*, MI) that are flexible and designed to adapt to different settings and patients. While these techniques have been found effective in the treatment of other mental health conditions (*eg*, anxiety, depression, substance abuse), additional research of standardized interventions designed to improve medication adherence is needed to replicate findings across settings and populations in order to better understand their effect on adherence and patient outcomes. Similarly, many of the included studies compare interventions for medication adherence to usual care, rather than an active comparator. Given the population and the nature of mental illness, it is possible that the lack of active controls may result in more frequent provider interaction for the intervention group than for those receiving usual care. More frequent contact alone has the potential to result in improved outcomes, and it is impossible to ascertain whether any effect was due to the intervention or to increased attention. Finally, sampling bias may exist related to baseline differences in the adherence of individuals selected to enroll in studies examining interventions designed to improve medication adherence and those who do not – particularly in studies examining long acting injectable depot antipsychotics.

An additional challenge in accurately assessing the body of research examining medication adherence is the wide range of methods used to assess adherence. We limited our inclusion to studies that assessed adherence using an objective measure such as blood plasma concentration levels, pill counts, e-monitoring/MEMS caps, or using a validated adherence scale.[1] For studies using multiple adherence measures, it was not uncommon for the determination of adherence to be incongruent, leading to questions related to the validity of commonly used and validated objective and subjective measures.

There is a paucity of research examining the effect of medication adherence interventions on non-psychopharmacological interventions. Given the risk of comorbid health conditions (*eg*, diabetes, hypertension) in persons with serious mental illness, future research should evaluate the impact of adherence interventions aimed at prevalent comorbid non-psychiatric conditions.

Furthermore, we identified no studies evaluating the potential harms that may result from these interventions. Despite the fact that the potential for harm appears to be low as compared to the risks associated with both the use of and non-adherence to prescribed medication, research documenting relative risk is warranted. Similarly, very few studies evaluated differential effects in subpopulations. It is important to understand whether both the benefits and potential harms differ by subgroup or clinical subpopulation and whether one type of intervention may be more effective than others for a given population or setting.

We identified no studies examining interventions to improve medication adherence in patients with PTSD. Although trauma processing therapies are often the first line of treatment for patients with PTSD, pharmacological interventions are commonly used as adjunctive therapy to alleviate associated symptoms and to treat comorbid conditions. There is limited evidence to suggest that adherence to medication is poor in Veterans with PTSD who are taking medication. Therefore, future research is warranted to determine whether improvements in adherence in this population can be achieved through the use of interventions, or by adapting interventions developed for other patient populations.

Recommendations for Future Research

Interventions to improve medication adherence in patients with psychotic spectrum disorders and bipolar disorder warrant further investigation, particularly in the form of well-designed RCTs with active comparators of adequate sample size and duration. Furthermore, few studies examine the same intervention, and replication is needed in order to draw conclusions about the effectiveness of a specific program. Several small studies suggest the effectiveness of some of the interventions (*eg*, interventions including family members). However, many of the interventions are multicomponent and complex, differ widely in their components and implementation, and thus research evaluating standardized interventions is needed.

Research evaluating the effectiveness of interventions to improve medication adherence in patients with PTSD is lacking and needed. For all populations examined in this report, future research is needed to evaluate the effect of these interventions on non-psychopharmacological interventions. In addition, future studies should examine potential adverse events associated with medication adherence interventions. Objective measures should be used to measure medication adherence, and the identification and validation of a gold-standard assessment tool for medication adherence is warranted. Finally, more research is necessary to determine the cost effectiveness and feasibility of interventions for medication adherence in the VHA.

CONCLUSION

Findings from the studies examining interventions to improve medication adherence in patients with psychotic spectrum disorders are mixed and evaluate a wide range of heterogeneous interventions. Sample sizes were generally small, studies often lacked an active comparison group, and there was wide variation in how adherence was measured among studies. There is limited evidence to support improved adherence associated with interventions involving family members, those involving technology, and those combining a depot antipsychotics with another intervention. Findings were mixed regarding the effectiveness of multicomponent behavioral interventions, with no support for Adherence or Compliance Therapies. In addition, no clear evidence exists to support conclusions regarding the effect of medication adherence interventions on patient outcomes. Very few studies examined interventions for medication adherence in

patients with bipolar disorder, and while in general there appears to be a positive effect of these interventions on adherence in this population, interventions were heterogeneous and more research is needed. No studies were found examining PTSD populations. For all populations, methodologically rigorous replication studies of standardized treatments using objective or validated subjective measures of adherence are needed to confirm preliminary results, as is research examining the costs and potential harms associated with the wide array of interventions designed to improve medication adherence.

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