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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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# EXECUTIVE SUMMARY

## INTRODUCTION

Non-adherence to medication is a serious problem in the United States (US). It is associated with increased emergency department visits and hospitalizations, higher costs of care, and greater mortality. 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.

There are a wide range of interventions for medication adherence. Interventions that target patients include psychosocial and behavioral interventions, including cognitive behavioral therapy (CBT) and Motivational Interviewing (MI), shared decision-making, customized adherence enhancement (CAE), Adherence and Compliance Therapies, and interventions involving family members. Other interventions target providers, such as provider education and training in MI. Interventions at the organization level may involve system-level interventions, such as financial incentives or reducing economic barriers through cost sharing; blister packaging for improving patient recall and tracking; and care coordination. Other interventions implemented at the organizational level include information and communication technology, such as electronic monitoring (e-monitoring), refill reminders via telephone or short message service (SMS); or other strategies, 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. This review examined interventions for medication adherence in patients with depression, but did not include other serious mental illnesses.

The goal of this report is to synthesize 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; and the related costs and any associated intervention specific harms. The key questions used to guide our report are:

### *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?

# METHODS

## Data Sources and Searches

To identify relevant studies, 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) from database inception through January 2015. We also searched ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform (ICTRP), ISRCTN Registry, Conference Papers Index, and Dissertations & Theses Global, and searched the bibliographies of included studies for additional relevant citations.

## Study Selection

Criteria for population, interventions, comparators, outcomes, timing, and setting (PICOTS) were developed in collaboration with our stakeholders and Technical Expert Panel. We included only studies with adult populations in general mental health settings (both inpatient and outpatient) that reported both an objective measure of adherence or validated subjective measure of adherence and a patient outcome measure. Studies conducted in forensic settings with incarcerated participants were excluded due to limited applicability. Two independent reviewers assessed all articles for inclusion, with discrepancies resolved through discussion or consultation with a third reviewer.

## Data Abstraction and Quality Assessment

One investigator abstracted data into a customized Systematic Review Data Repository (SRDR) database, which was then reviewed for accuracy by a second investigator. Study quality was dual rated using risk of bias (ROB) assessment criteria based on the guidance and tools developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPC), with any disagreements resolved through discussion or a third reviewer.

### Data Synthesis and Analysis

We qualitatively synthesized the literature for each key question/clinical population. We compiled evidence tables of study characteristics, and analyzed individual study findings to draw conclusions. We assessed the overall strength of evidence for outcomes using a method developed for AHRQ's EPCs.

## RESULTS

### Results of Literature Search

From 7,944 titles and abstracts we identified 152 potentially relevant studies. After full-text review, we excluded 127 studies for a total of 24 included studies from 25 publications. Of the 518 clinical trial protocols identified by our search of trial registry websites, one study met inclusion criteria; however, this study and all data reported on ClinicalTrials.gov are represented in an included publication. 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 Results for Key Questions

*Key Question 1. In adults with psychotic spectrum disorders:*

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

Multicomponent Behavioral Interventions: Findings of the 7 included studies are mixed, with insufficient evidence from which to draw firm conclusions. Of the 4 studies examining Compliance Therapy, an intervention described in the 1997 manual by Kemp et al, one study found improved adherence at one month, but no differences by 6 months follow-up; another study found significantly greater adherence up to 18 months, and the other 2 studies found no significant differences between the Compliance Therapy and control groups, and no improvement in adherence in either group. Two studies of Adherence Therapy, an intervention based on Compliance Therapy, found no benefit over comparators. The seventh multicomponent behavioral intervention compared CBT to psychoeducation, with MI in both arms, and found no difference between groups at any time point.

Interventions Involving Family Members: The 3 studies examining interventions involving family members show a generally positive effect, with low strength of evidence. Caution in interpretation and generalization is advised due to the limited number of studies, the heterogeneity among the interventions, and mixed findings. Two studies found family interventions to be more effective than usual care, and one study found no significant difference when controlling for time.

System-level Intervention: One study found that although adherence associated with a system-level intervention was better as compared to Compliance Therapy, the differences were not significant. There is insufficient evidence to determine the efficacy of system-level interventions.

Pharmacist-led Interventions: One study found no difference between a pharmacist-led intervention and usual care. There is insufficient evidence regarding the efficacy of pharmacist-led interventions.

Technology Interventions: The 4 included studies provide low strength of evidence showing a positive effect associated with technology interventions. Two RCTs compared e-monitoring using smart pill containers/dispensers to a variety of comparators. One study, which examined e-monitoring both as an intervention and a measure of adherence, reported a significant effect of the e-monitoring intervention as assessed by pill counts and no effect as assessed by e-monitoring; a second study found adherence in the e-monitoring group to be significantly higher than both pill counts by a pharmacist and self-report. 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, differences were not significant, nor did adherence improve significantly for any of the groups over the duration of the study. 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.

Other Interventions: The 4 studies examining other interventions for medication adherence provided insufficient evidence from which to draw conclusions. One study of MI found no significant differences between the intervention group and controls. Similarly, no difference was found in adherence for a shared decision making intervention compared with usual care. Two studies examined Cognitive Adaptation Training and/or the medication adherence components of Cognitive Adaptation Training alone, with one study concluding no difference between standard Cognitive Adaptation Training and the use of only the medication adherence components (with significant benefit of both as compared with usual care), and one study that found no difference between the medication adherence components of Cognitive Adaptation Training and e-monitoring.

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

The 2 studies of interventions for medication adherence in patients prescribed depot antipsychotics found limited evidence of a positive effect; however, there is insufficient evidence from which to draw firm conclusions. One study of patients prescribed a depot antipsychotic included an intervention for family members, psychoeducation, and early warning sign detection. Results indicated better adherence as compared with controls up to 24 months. The second study included depot in combination with a customized multicomponent behavioral intervention, and found significantly better adherence through 25 weeks.

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

One study examined the effect of an intervention for medication adherence on non-psychopharmacological adherence and provides insufficient evidence from which to draw conclusions. The study compared a telephone plus SMS intervention to telephone or text only. There was no significant difference between groups.

**Table 1. 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)<br>1 NRCT (N = 70)<br>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 MI and group psychoeducation plus MI (moderate ROB). | Insufficient | Evidence from only one study. |
| Depot plus Behavioral Multicomponent | 1 Trial (randomization unclear) (N = 57)<br>1 Prospective Cohort (N = 30) | Findings indicated improved adherence related to the use of depot antipsychotic injections 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 3rd 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 one 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; e-Monitoring = Electronic monitoring; 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; SMS = Short message service; TRQ = Tablet Routine Questionnaire.

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

Positive and Negative Symptom Severity: Findings related to positive and negative symptom severity were mixed, and insufficient from which to draw conclusions. Four studies evaluated the effect of interventions for medication adherence in patients along the psychotic spectrum on positive and negative symptoms. One study of an intervention involving family members resulted in a significant improvement in positive and negative symptoms. Another study examining SMS reminder messages resulted in significantly fewer negative symptoms. No other significant differences were found.

Overall Symptom Severity: Findings related to overall symptom severity were mixed and insufficient from which to form conclusions. Of the 17 studies examining overall symptom severity, 4 of 9 studies reported better total symptom severity as measured by the Positive and Negative Syndrome Scale (PANSS), 2 of 8 studies reported better score on the Brief Psychiatric Rating Scale (BPRS), and 2 of 3 studies reported better Clinical Global Impression scale (CGI) scores associated with the intervention.

Quality of Life: Findings from the 4 studies examining quality of life generally indicated no improvement associated with medication adherence interventions; however, given the heterogeneity of the interventions and limited evidence, the evidence is insufficient to form conclusions. Of the 4 studies, one study of an intervention involving SMS reminder messages resulted in better quality of life scores at the end of the intervention (3 months) but not at the 6-months follow-up.

Functional Impairment: Findings from the 10 studies examining functional impairment are mixed, and insufficient from which to form conclusions. Two studies found a positive effect on improving functional impairment associated with interventions involving family members, and functional impairment was improved in participants prescribed depot injections along with CAE. One of 3 studies examining Compliance Therapy reported greater functional improvement associated with the intervention, and one of 2 studies examining Cognitive Adaptation Training reported higher functioning associated with both standard Cognitive Adaptation Training and the use of only the medication adherence components, as compared to usual care at 3 and 6 months, with no difference thereafter.

Time to First Readmission/Hospitalization: Findings from the 10 studies examining time to first readmission or hospitalization are mixed and provide insufficient evidence from which to draw conclusions. Three studies examining interventions involving family members showed a positive effect of the intervention on hospital admissions and/or time to readmission or hospitalization. A system-level intervention resulted in a longer time to readmission as compared with Compliance Therapy, with 2 other studies also finding no effect of Compliance Therapy on readmission/hospitalization.

Time Spent in the Hospital: Three studies examined time spent in the hospital, and the evidence is insufficient from which to draw conclusions. Findings were mixed, with only one study of a family intervention reporting a shorter stay associated with the intervention.

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, and both

standard Cognitive Adaptation Training and the use of only the medication adherence components, as compared to usual care.

Side Effects: One study compared a system-level intervention to Compliance Therapy and examined side effects related to psychopharmacological interventions, and found fewer side effects associated with Compliance Therapy.

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

Two studies examined costs associated with interventions to improve medication adherence in patients along the psychotic spectrum. One study found no difference between Compliance Therapy and routine management with supportive counseling, and the second study found a higher average cost per patient associated with the adherence components of Cognitive Adaptation Training as compared to e-monitoring.

### *Key Question 2. In adults with bipolar disorder:*

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

The 4 studies meeting inclusion criteria for Key Question 2 provide limited evidence regarding 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 due to the fact that the interventions were heterogeneous, sample sizes were small, and external validity questionable because 2 studies showing a positive effect were conducted in Iran (see Table 2).

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

Depression: Findings of the 3 studies examining the effect of medication adherence interventions on depressive symptomology are mixed and provide insufficient evidence from which to draw conclusions. Of the 3 included studies, one study examining an individual psychoeducation intervention found a positive effect on depression associated with the intervention. A second study found that CAE resulted in significantly improved depression scores, but only at 6 months, while the third study showed no effect.

Mania: Findings of the 3 studies examining the effect of medication adherence interventions on mania are mixed and provide insufficient evidence from which to draw conclusions. Of the 3 included studies, 2 showed significant effects on mania-related outcomes. One study examining an individual psychoeducation intervention found a positive effect on mania symptoms associated with the intervention. A second study of CAE found no difference in mania scores at 3 months, but mania scores were significantly lower at 6 months.

Functional Impairment: Similar to results examining depression and mania, 2 of 3 studies reporting functional impairment outcomes in patients with bipolar disorder reported positive effects. One study reported a positive effect on improving functional impairment associated with a group psychoeducation intervention, and a second study (examining CAE) found no improvement between baseline and 3 months, but did report improved function at 6 months.

Single studies examined symptom severity, positive and negative affect, quality of life, and hospital readmissions. One study found no improvement associated with CAE on symptom severity at 3 months, with significant improvements by 6-months follow-up. Positive and negative affective symptoms improved significantly from baseline at both 3 and 6 months. Another study found significantly higher quality of life scores and fewer hospital readmissions over an 18-month period associated with an individual psychoeducation intervention.

No studies were identified examining the effect of medication adherence interventions on *long-acting injectable (depot) psychopharmacological* adherence (Key Question 2b), *non-psychopharmacological* adherence (Key Question 2c), or reporting harms or costs associated with the intervention (Key Question 2e).

### *Key Question 3. In adults with PTSD:*

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

**Table 2. 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)<br>1 NRCT (N = 45) | Both individual and group psychoeducation resulted in better medication adherence than 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 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. Thus, 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.

### Conclusions

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.

## ABBREVIATIONS TABLE

| Abbreviation | Term |
|---|---|
| AHRQ | Agency for Healthcare Research and Quality |
| AMQ | Attitude towards Medication Questionnaire |
| BPRS | Brief Psychiatric Rating Scale |
| BPRS–E | Brief Psychiatric Rating Scale – Expanded |
| CAE | Customized Adherence Enhancement |
| CAT | Cognitive Adaptation Training |
| CBT | Cognitive Behavioral Therapy |
| CDR | Concentration to Dose Ratio |
| CGI | Clinical Global Impression |

| | |
|---|---|
| CGI-BP | Clinical Global Impression – Bipolar scale |
| CGI-SGH | Clinical Global Impression – Schizophrenia scale |
| CI | Confidence Interval |
| DAI | Drug Attitude Inventory |
| e-monitoring | electronic-monitoring |
| EPC | Evidence-based Practice Centers |
| EQ-5D | EuroQoL |
| ES | Effect size |
| GAF | Global Assessment of Functioning |
| GAS | Global Assessment Scale |
| HAM-D | Hamilton Depression Rating Scale |
| LEE | Level of Expressed Emotion |
| LGP | Life Goals Program |
| M | Mean |
| MAQ | Medication Adherence Questionnaire |
| MARS | Medication Adherence Rating Scale |
| MDN | Median |
| MEMS | Medication Event Monitoring System |
| MET | Motivational Enhancement Therapy |
| MI | Motivational Interviewing |
| MM | Med-eMonitor |
| NA | Not applicable |
| NRCT | Non-randomized controlled trial |
| NS | Not significant |
| PANSS | Positive and Negative Syndrome Scale |
| PICOTS | Population, interventions, comparators, outcomes, timing, and setting |
| PTSD | Posttraumatic stress disorder |
| QLF | Quality of Life Scale |
| RCT | Randomized controlled trial |
| ROB | Risk of Bias |
| SAI | Schedule for Assessment of Insight |
| SAI-C | Schedule for the Assessment of Insight - C |
| SAI-E | Schedule for Assessment of Insight- Expanded |
| SD | Standard deviation |
| SE | Standard error |
| SF-36 | Short Form Health Survey |
| SMS | Short message service |
| SOFAS | Social and Occupational Functioning Scale |
| SRDR | Systematic Review Data Repository |
| SWN | Subjective Well-being on Neuroleptic Treatment Scale |
| TIPS | Telephone Intervention Problem Solving for Schizophrenia |
| TRQ | Tablet Routine Questionnaire |
| VA | Veterans Affairs |
| VHA | Veterans Health Administration |
| WHOQOL-BREF | World Health Organization Quality of Life instrument – Abbreviated version |
| WSRT | Wilcoxon signed-rank test |
| YMRS | Young Mania Rating Scale |