Evidence-based Synthesis Program Systematic Review Protocol

**Project Title:** Interventions to Improve Pharmacological Adherence among Adults with Psychotic-Spectrum Disorders, Bipolar Disorder, and Posttraumatic Stress Disorder

I. **Background**

Non-adherence to medication is a serious problem in the United States, and is related to increased risk of emergency department (ED) visits and hospitalizations,1-6 higher costs of care,1,5,6 and mortality.7,8 For patients with serious mental illnesses such as schizophrenia and other psychotic spectrum disorders, bipolar disorder, and posttraumatic stress disorder (PTSD), adherence to psychopharmacological and/or non-psychopharmacological medications are important concerns. While some similarities exist, in general, these three 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 medication is the primary course of treatment.9 Research estimates adherence to antipsychotic medication among people with schizophrenia to be between roughly 25%10,11-50%,12 with a study of patients with schizophrenia or schizoaffective disorder in the Veterans Affairs (VA) system reporting an adherence rate of 60%.13 Wide variation exists in reported adherence rates, and largely depends on the length of time examined and the method used to measure adherence.14 Factors related to non-adherence in individuals with psychotic spectrum disorders may include patient-level factors such as lack of awareness and insight into illness, negative attitudes towards medication,14,15 comorbid substance use, and cognitive impairment; demographic factors such as younger age, male gender, and lower socioeconomic status (SES); 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.15 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,16 and another study using VA data reporting a higher rate of non-adherence to oral hypoglycemic medications among veterans with schizophrenia than without.17

Similar to individuals along the psychotic spectrum, psychopharmacological medications (often antipsychotics) are the first line of treatment for patients with bipolar disorder,18 with reported rates of adherence between 30%-57%,19-21 and a study of patients in the VA reporting an adherence rate of 51.9%.15,22 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, having more suicide attempts, and receiving less intensive psychopharmacologic treatments.22

For individuals with PTSD, exposure-based psychotherapy is often the first line of treatment.23 Pharmacologic treatment for PTSD include antidepressants, adrenergic agents such as beta-blockers and prazosin, second-generation antipsychotics, and anticonvulsants.23 For patients with PTSD, in addition to pharmacologic treatment for symptoms related to PTSD, 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.24,25 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, and another 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.\textsuperscript{25,26}

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, administrative claims, and blood plasma concentrations; with subjective measures including patient report, self-reported scales, patient diaries, reports by caregivers or case managers, and clinician’s views on adherence based on therapeutic response.\textsuperscript{27-29}

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 and motivational interviewing, shared decision-making, customized adherence enhancement, and family supervised treatments. Provider-level interventions include provider education and training in motivational interviewing. System-level interventions include financial incentives; methods related to information and communication technology (e.g., phone follow-up, electronic reminder systems, e-Health interventions, refill reminders); reducing economic barriers (e.g., 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.\textsuperscript{30} While this review did examine interventions for medication adherence in patients with depression, it did not include other serious mental illnesses. Thus, the purpose of this review is to examine the effectiveness of interventions to improve medication adherence in patients with psychotic spectrum disorders, bipolar disorder, and PTSD, and their related harms, costs, and patient outcomes.

II. Key questions and inclusion/exclusion criteria

The research questions for this systematic review were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature, and consultation with internal partners, investigators, and stakeholders. Figure 1 provides our analytic framework. See Table 1 for PICOTS.

**KQ1. In adults with Psychotic Spectrum disorders:**
- a. What are the effects of medication adherence interventions on \textit{psychopharmacological} adherence?
- b. What are the effects of medication adherence interventions on \textit{long-acting injectable (depot) psychopharmacological} adherence?
- c. What are the effects of medication adherence interventions on \textit{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 \textit{psychopharmacological} adherence?
- b. What are the effects of medication adherence interventions on \textit{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:**

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?
Figure 1.

**Analytic Framework: Interventions for Medication Adherence in Adults with Psychotic Spectrum Disorders, Bipolar Disorder, and PTSD**

- **Interventions for Medication Adherence:**
  - Psychopharmacological Interventions
  - Depot Psychopharmacological Interventions
  - Non Psychopharmacological Interventions

- **Medication Adherence**
  - Objective Outcome Measures
  - Validated Subjective Measures

- **Patient Outcomes**
  - Intermediate 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

- **Harms and Costs**

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Table 1. The following table specifies the key questions (KQs) along with the relevant patient, intervention, comparator, and outcome criteria for each question.

<table>
<thead>
<tr>
<th>Key Question</th>
<th>KQ1. In patients with Psychotic Spectrum disorders:</th>
<th>KQ2. In patients with Bipolar Disorder:</th>
<th>KQ3. In patients with Posttraumatic Stress Disorder:</th>
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<tr>
<td></td>
<td>a. What are the effects of medication adherence interventions on <strong>psychopharmacological</strong> adherence?</td>
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<td>b. What are the effects of medication adherence interventions on <strong>long-acting injectable (depot)</strong> <strong>psychopharmacological</strong> adherence?</td>
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<th>Populations</th>
<th>Adults with Psychotic Spectrum Disorders</th>
<th>Adults with Bipolar Disorder</th>
<th>Adults with Posttraumatic Stress Disorder</th>
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<tr>
<th>Intervention</th>
<th>Include: Studies where the primary outcomes include medication adherence, including:</th>
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<td></td>
<td>- Patient-level interventions specifically designed to address medication adherence, such as: compliance or adherence therapy, adherence skills training, psychosocial interventions (e.g., psychoeducation, behavioral interventions, motivational interviewing, 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 motivational interviewing or - Systems-level interventions specifically designed to address medication adherence, such as: financial incentives, information and communication technology (e.g., follow-up by phone, electronic reminder systems), reduction of economic barriers to adherence (e.g., 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 (e.g., assertive community treatment, nurse-facilitated enhanced-treatment)</td>
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<th>Comparator</th>
<th>• Other active interventions</th>
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<tbody>
<tr>
<td></td>
<td>• No intervention</td>
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<td></td>
<td>• Usual care</td>
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Portland Evidence-based Synthesis Program
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<th>Outcomes</th>
<th>Medication adherence:</th>
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<td>- Measured objectively (e.g., medication container with electronic monitoring [e.g., MEMS], pill counts, biological markers, observed intake, medication possession ratio, medication plasma level, electronic ingestible event marker)</td>
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<td>- Measured subjectively by a validated patient self-report scale or measure (e.g. Morisky Medication Adherence Scales [MMAS-8, MMAS-4 or MAQ]).</td>
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<td>Patient outcomes:</td>
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<td>Costs</td>
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<td><strong>Exclude:</strong> Medication adherence is 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</td>
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<th>Timing</th>
<th>Short- and long-term outcomes</th>
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| Study design | RCTs; Methodologically rigorous observational studies (case control/cohort studies) that adjust for important confounders |
III. Literature search strategies

Search strategies will be developed in consultation with a research librarian. The search strategy will be peer reviewed by a second research librarian using the instrument for Peer Review of Search Strategies (PRESS). We will conduct a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the key questions. To identify relevant articles, we will begin by searching MEDLINE®, PubMed, PsycINFO®, Embase®, CINAHL®, 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). We will further evaluate the bibliographies of included primary studies and any systematic or nonsystematic reviews that are identified. To identify studies not published in peer-reviewed journals, we will search ClinicalTrials.gov, the World Health Organization’s International Clinical Trials Registry Platform (ICTRP), ISRCTN Registry, Conference Papers Index, and Dissertations & Theses Global.

Using pre-specified inclusion/exclusion criteria, at the title and abstract stage, two independent reviewers must agree on a final inclusion/exclusion decision for 10% of the search yield, with the remaining 90% decided by a single reviewer. Titles and abstracts will be reviewed using Abstrackr. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision for all articles, with a third reviewer reading a full-text article for inclusion/exclusion if coding discrepancies cannot be resolved between the first two reviewers. Articles meeting eligibility criteria will be included for data abstraction.

IV. Data abstraction

Data from published reports will be abstracted into a customized database by one reviewer and over-read by a second reviewer. From each study, we will abstract 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.

V. Assessment of methodological quality of individual studies

Two reviewers will independently assess the quality of each study using pre-defined criteria based on guidance and tools developed for the Agency for Healthcare Research and Quality’s (AHRQ) Evidence-based Practice Centers (EPC), which allows for the assessment of risk of bias for a wide range of study designs. Disagreements will be resolved through discussion. Each trial will be given an overall summary assessment of low, medium, high, or unclear risk of bias.

VI. Data synthesis

We will summarize the primary literature by abstracting relevant data and qualitatively synthesizing the literature for each key question. We will determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis) to estimate summary effects depending on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of results reported by included studies.
VII. Assessing the overall body of evidence

We will assess the overall strength of evidence for outcomes using a method developed for AHRQ’s EPCs. 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:

- 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, i.e., 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.

VIII. Timeline

Project start: November 2014
First call with Technical Expert Panel: January 2015
Abstract review due: March 2015
Internal draft report due: May 2015
Anticipated draft report due: June 2015
Reviewer feedback: July 2015
Anticipated final report submitted: September 2015

IX. Stakeholders and Technical Experts

Topic Nominator:
Anthony Morreale, PharmD, MBA, BCPS, FASHP
Assistant Chief Consultant for Clinical Pharmacy Services and Healthcare Services Research
Office of Pharmacy Benefits Management Services

Technical Experts:
- Bean, Jennifer R.
- Cramer, Joyce A.
- Depp, Colin A.
- Gellad, Walid
- Houser, Jennifer
- Hudson, Teresa
- Hyatt, Judith
- Semla, Todd
• Sajotovic, Martha
• Valenstein, Marcia
• Velligan, Dawn
• Voils, Corrine
• Wells, Daina L.
• Zeber, John E.

X. Citations


35. Viswanathan M, Berkman N, Dryden D, Hartling L. *Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank.*