Effectiveness of financial incentives for long-acting injectable antipsychotic adherence in patients with psychotic and bipolar disorders: a systematic review protocol

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Review question: The question of this review is: what is the effectiveness of financial compensation for receiving a dose of long-acting injectable antipsychotic medication on the rate of medication adherence in adult patients with psychotic and bipolar disorders in an outpatient/community setting?

Keywords Adherence; antipsychotics; compensation; compliance; mental disorders

Introduction

Schizophrenia is a lifelong psychotic disorder (PD) and it is associated with recurrent relapse, high rates of hospital readmissions, poor physical health, suicide and violent behaviors.¹ Psychotic disorders are mental illnesses that affect how people think, feel and behave.²,³ Worldwide, PDs affect approximately 3% of the population.⁴ Poor medication adherence is common in people with PDs, with an estimated 60% of PD patients having difficulty with adherence over time.⁵,⁶ This leads to negative stigmas, social isolation, unemployment, drug abuse and homelessness, which all decrease quality of life (QOL) and chances for positive outcomes.⁶,⁷

Bipolar disorders (BD) are chronic mental illnesses that cause extreme fluctuations in mood, including intermittent episodes of mania, depression, hypomania or mixed states.⁸ The disorder usually starts in adolescence and affects about 4% of adults worldwide.⁹ As a result of poor medication adherence, people with BDs are at risk for repeated relapse, high utilization of mental health services, persisting disability, increased mortality, increased risk for suicide and decreased QOL.⁸,¹⁰ Adherence is estimated to be between 37% and 50% for people with BDs.¹¹ The impact of untreated BDs can be devastating and financial implications are estimated to be £5.2 billion annually in England alone.⁸,¹²

Antipsychotic medications are the cornerstone of treatment for people with PD and BD.¹⁰ Long-acting injectable (LAI) antipsychotics, also known as depot medications, were developed to address medication nonadherence in patients with chronic mental illness.⁵,¹³ The intramuscularly administered depot medications ensure sustained drug delivery for a specific period of time, thereby eliminating questions about whether medication has been taken as prescribed.¹³,¹⁴ The clinical advantage of LAI antipsychotics is that dosing is required weekly or once or twice monthly. Less frequent dosing eliminates the adherence demands of daily dosing, which may pose a challenge to patients with impaired thinking, memory difficulties and lack of illness insight.⁸,¹³,¹⁴ Additionally, clinicians are immediately aware if medication is missed, thus active measures can be taken to prevent relapse.⁸ Despite these advantages, an estimated 25–51% of patients with a PD or BD eventually become non-adherent to LAI antipsychotic regimens, against clinical advice.¹⁴,¹⁹

Medication adherence can be defined as the extent to which a patient’s medication taking habits matches that prescribed by the clinician.¹⁵ A wide range of alternative terms has been used to describe medication adherence, including medication compliance, nonadherence, and fidelity; but adherence is
The issue of poor medication adherence is not a new concept for mental illness, yet the development and application of appropriate interventions to improve this has proven challenging. \(^\text{11}\) Increases in hospital admissions due to poor medication adherence cost an estimated USD100 billion per year in the United States alone. In Ethiopia, costs for PD and BD relapse cases are four times higher than that of non-relapse cases.\(^\text{7,18}\) Suboptimal medication adherence is strongly associated with reduced functional status, increased relapse rates, longer duration of inpatient treatment and decreased QOL among patients with PD and BD.\(^\text{11,16}\) Quality of life as an outcome has been studied in nursing for many years. De Lima et al.\(^\text{17}\) defines health-related QOL as “the value assigned to life as altered by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy”.\(^\text{[p.832]}\) Factors that lead to poor medication adherence involve lack of illness awareness and the direct impact of illness, including depression, cognitive impairment, and positive and negative symptoms.\(^\text{7}\) Social isolation, comorbid substance abuse and the increasing fragmentation of mental health services also contribute to poor adherence in many countries.\(^\text{15}\)

Behavioral interventions, cognitive approaches, electronic reminders, motivational interviewing, and psychosocial and psychoeducational enhancement programs have all been used in attempts to improve medication adherence in people with PD and BD; yet, it is still unclear as to which interventions are most effective for improving adherence to LAI antipsychotics.\(^\text{11,20,21}\) One promising intervention, demonstrated to be successful in two pilot studies, is the provision of financial incentives.\(^\text{22,23}\)

Financial incentives are monetary benefits offered in the form of cash, check, gift cards or vouchers to encourage behaviors that might not otherwise take place.\(^\text{19,24}\) Priebe et al.\(^\text{24}\) reported findings from a randomized controlled trial conducted in the United Kingdom on financial incentives to improve adherence to LAI antipsychotic maintenance treatment. Average compliance to LAI antipsychotics was considerably higher in subjects receiving financial incentives (85% [Standard Deviation (SD) 15]) than subjects in the control group (71% [SD 22]) after one year. The calculated adjusted estimated effect was 11.5% (95% CI 3.9–19.0; \(p = 0.0003\)).\(^\text{24}\) In a related trial piloted in the Netherlands, Noordraven et al.\(^\text{19}\) randomly allocated 169 subjects to a group to receive financial incentives or the control group. The primary outcome was the Medication Possession Ratio (MPR), defined as the number of LAI antipsychotics received divided by the total number of LAI antipsychotics prescribed during the one-year trial period.\(^\text{19}\) The average MPR was better in subjects receiving financial incentives (94.3% [SD 11.3%]) than subjects in the control group (80.3% [SD 19.1%]) after one year. The calculated adjusted difference was 14.9% (95% CI 8.9–20.9%; \(p < 0.0001\)); with the difference being sustained throughout a six-month follow-up period.\(^\text{19}\)

Prior systematic reviews have been conducted to evaluate the use of financial incentives on exercise, fitness, physical activity behaviors, and compliance to HIV and tuberculosis treatment, but none for LAI antipsychotic adherence.\(^\text{18,23–27}\) The primary objective of this research synthesis is to examine the effectiveness of financial incentives on LAI antipsychotic adherence in patients with PD and BD. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted in June 2018 and no current or underway systematic reviews on the topic were identified. This review is important because nonadherence remains a problem for people with PD and BD taking LAI antipsychotics.\(^\text{19,25}\) By finding an effective way to promote adherence to LAI antipsychotics, it may be possible to reduce psychiatric relapse and healthcare costs, and promote a better QOL for people with PD and BD.\(^\text{12,18}\)

### Inclusion criteria

#### Participants

This review will consider adults aged 18 years and over who are diagnosed with a PD or BD and are prescribed or have indication for LAI antipsychotic medication in an outpatient/community setting. Psychotic disorders or BD can be diagnosed using criteria from the Diagnostic and Statistical Manual for Mental Disorders or the International Statistical Classification of Diseases and Related Health Problems (e.g. schizophrenia, schizoaffective disorder, bipolar I disorder or another psychotic disorder). Long-acting injectable antipsychotic medications
may include, but are not limited to: aluphenazine, aripiprazole, aripiprazole lauroxil, fluphenazine deconate, haloperidol deconate, olanzapine pamoate, paliperidone, risperdal consta and penfluridol. Long-acting injectable antipsychotics can be administered weekly, monthly or bimonthly.

The review will exclude participants with cognitive impairments, intellectual disabilities and poor command of language that affects clinical communication and discussion.

**Intervention**
This review will consider studies that evaluate financial incentives of any amount, given to participants before or after receiving a LAI antipsychotic. Financial incentives may include, but are not limited to: cash, check, gift cards and vouchers.

**Comparator**
This review will consider studies that compare the intervention to no financial incentives for receiving a LAI antipsychotic.

**Outcomes**
This review will consider studies that include the primary outcome LAI antipsychotic adherence. The secondary outcome is QOL.

Medication adherence can be measured by the MPR or rate of adherence; calculated by the number, total or percentage of LAI antipsychotic medications taken as prescribed throughout the study.

Quality of life can be measured by the score from multiple validated tools including but not limited to the DIALOG scale, Manchester Short Assessment of QOL and the Client Satisfaction Questionnaire.

**Types of studies**
This review will consider both experimental and quasi-experimental study designs including randomized controlled trials (RCTs), non-RCTs, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion.

Studies published in English will be included. No date limit will be applied to ensure all applicable studies are included in the review.

**Methods**
The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence.28

**Search strategy**
The search strategy will aim to locate both published and unpublished studies. An initial limited search of PubMed and CINAHL was undertaken followed by analysis of the text words contained in the titles and abstracts, and of the index terms used to describe these articles. This informed the development of a search strategy which will be tailored for each information source. A proposed search strategy for PubMed is detailed in Appendix I. The search strategy, including all identified keywords and index terms will be adapted for each included information source. The reference list of all studies selected for critical appraisal will be screened for additional studies.

**Information sources**
The databases to be searched include: CINAHL, Embase, MEDLINE and PsycINFO.

The trial registers to be searched include: Cochrane Central Register of Controlled Trials, NIH Registry.

The search for unpublished studies will include: MedNar and ProQuest Dissertations and Theses

**Study selection**
Following the search, all identified citations will be collated and uploaded into EndNote X9 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that may meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute’s System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (Joanna Briggs Institute, Adelaide, Australia). The full text of selected citations will be retrieved and assessed in detail against the inclusion criteria by two independent reviewers. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results
of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

**Assessment of methodological quality**

Selected studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for studies used in the systematic review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

Following critical appraisal, studies of low methodological quality will be excluded. The following determination of quality will be used according to the number of “yes” answers:

- RCT’s: 11-13 = high; 7-10 = moderate; 1-6 = low.
- Quasi-experimental: 8-9 = high; 5-7 = moderate; 1-4 = low.
- Cohort: 9-11 = high; 6-8 = moderate; 1-5 = low.
- Analytical cross-sectional: 7-8 = high; 4-6 = moderate; 1-3 = low.
- Case control: 8-10 = high; 5-7 = moderate; 1-4 = low.

**Data extraction**

Data will be extracted from papers included in the review using the standardized data extraction tool available in JBI SUMARI by two independent reviewers. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objective. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

**Data synthesis**

Studies will, where possible, be pooled with statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) and weighted (or standardized) mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis.

Heterogeneity will be assessed statistically using the standard chi-squared and I² tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufanaru et al. 2015. Subgroup analyses will be conducted where there is sufficient data to investigate patient diagnosis, length of time on LAI antipsychotic medications, age and sex. Sensitivity analyses will be conducted to test decisions made regarding the effect of financial incentives on adherence to LAI antipsychotics. Where statistical pooling is not possible, the findings will be presented in narrative form, including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated within JBI SUMARI to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed, where appropriate.

**Assessing certainty in the findings**

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) will be created using GRADEPro GDT software (McMaster University, ON, Canada). The outcomes reported in the SoF will be: medication adherence and QOL.

**References**

Appendix I: Search strategy

Search conducted June, 2018

<table>
<thead>
<tr>
<th>Search</th>
<th>PubMed</th>
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<tbody>
<tr>
<td>#4</td>
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Year limited to 2007, language limited to English