Can incentives improve antipsychotic adherence in major mental illness? A mixed-methods systematic review

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ABSTRACT

Objectives Incentives have been effectively used in several healthcare contexts. This systematic review aimed to ascertain whether incentives can improve antipsychotic adherence, what ethical and practical issues arise and whether existing evidence resolves these issues.

Design Systematic review of MEDLINE, EMBASE and PsycINFO. Searches on 13 January 2021 (no start date) found papers on incentives for antipsychotics. Randomised controlled trials (RCTs), cohort studies, qualitative research and ethical analyses were included. Papers measuring impact on adherence were synthesised, then a typology of ethical and policy issues was compiled, finally the empirical literature was compared with this typology to describe current evidence and identify remaining research questions.

Results 26 papers were included. 2 RCTs used contingent financial incentives for long-acting injectable antipsychotic preparations. Over 12 months, there were significantly larger increases in adherence among the intervention groups versus control groups in both RCTs. There were no consistently positive secondary outcomes. 39 ethical and practical issues were identified. 12 of these are amenable to empirical study but have not been researched and 7 the current evidence is mixed.

Conclusions In keeping with other areas of healthcare, antipsychotic adherence can be increased with financial incentives. Payments of 2.5 times minimum wage changed behaviour. The typology of issues reported in this systematic review provides a template for future policy and ethical analysis. The persistence of the effect and the impact of incentives on intrinsic motivation require further research.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A large number of papers were included.
⇒ Diverse methodologies have been synthesised to enable in-depth analysis of incentives for antipsychotics.
⇒ Meta-analysis was not possible as a too few randomised controlled trials were identified.
⇒ All objections were taken at face value, rather than subjected to philosophical analysis, so weak objections may have been included.

BACKGROUND

Some people prescribed medications do not take them. Indeed, this is the case for antipsychotics. Incentives may overcome this reluctance, but would have extensive ramifications for patients, healthcare workers, and health systems. Adherence to antipsychotic treatment entails taking oral preparations or accepting injectable preparations as they are prescribed. A systematic review of patients with schizophrenia and bipolar affective disorder found that on subjective measures antipsychotic adherence ranges from 60% to 81%. Poor adherence often means undertreatment of psychotic illness.

Interventions have been designed to improve adherence to antipsychotics. Approaches such as adherence therapy and family therapy have had mixed results. There is tentative evidence that eHealth technologies such as SMS reminders and smart pill containers may improve adherence to oral antipsychotics. Depot preparations offer another means of increasing antipsychotic adherence as treatment events are less frequent and covert non-adherence is prevented. Earlier systematic reviews found that depot treatment did not increase adherence compared with oral treatment and that there was no difference in relapse rates in randomised controlled trials (RCTs) comparing long-acting injectable to oral preparations. Cohort studies have, however, provided evidence supporting the use of long-acting injectable antipsychotics to prevent relapse and hospitalisation. A more recent systematic review incorporating cohort studies and pre–post studies in addition to RCTs, indicated that long-acting injectable antipsychotics are consistently more favourable in reducing risk of relapse or hospitalisation when compared with oral antipsychotics. For some individuals stabilised on depot treatment, however, relapse has been associated with side effects such as tardive dyskinesia and functional decline. Consistently improving adherence to antipsychotics may...
reduce relapse so other interventions to increase adherence should be considered.

Incentives may improve health behaviours including medication adherence.11 Financial incentives have been used in a wide range of healthcare settings: asthma, diabetes, HIV, weight loss and smoking cessation.12-16 A systematic review of 16 RCTs found that incentives were around 1.5–2.5 times more effective than other interventions at promoting a range of health behaviours.16 Other studies of financial incentives have found no effect or even negative effects.13 Incentives can be designed with a guaranteed sum or a lottery.17 They may motivate participants with the possibility of financial gains or the risk of loss.18 Rewards may be vouchers or cash, magnitudes vary and arrangements may change over the course of the intervention.19 20 Either the healthy behaviour or the healthy outcome can be rewarded.21

Governments around the world are interested in using incentives to improve health. The UK government recently announced plans for an Office for Health Improvement and Disparities, aiming to replicate the success of the Singaporean Health Promotion Board which has used financial incentives to increase behaviours including exercise and healthy eating.22 Unlike the Health Promotion Board, the UK’s Office for Health Improvement and Disparities will have a special remit for promoting mental health, suggesting financial incentives could enter mainstream mental healthcare in the UK over coming years.

Antipsychotic pharmacotherapy is an area where financial incentives are worth considering, not least because of the limited success of other interventions to improve adherence to antipsychotics.23 Much of the research into financial incentives in mental healthcare has examined positive financial incentives for substance abuse24 25 although there have been small studies exploring treatment of other conditions such as depression.26 Antipsychotics are the mainstay of treatment for schizophrenia, a chronic condition with a lifetime morbid risk of 7.2 per 1000 and a median age of onset in the mid-20s.27 28 Preventing psychotic relapse should be a policy priority because of its human and health economic cost. Annually, 35.8 people are hospitalised with psychosis per 100,000 population and the cost of relapse is estimated at tens of thousands of dollars.29 30 However, it is important that ethical and public policy issues are also taken into consideration beyond any mental health benefits of incentives.

Whether an incentive changes behaviour is best ascertained with RCTs. Appraising whether an incentive improves care in the complex setting of mental health provision entails considering the whole biopsychosocial programme of care including its impact on relapse risk, relationships, other patients, staff and the wider health system.

Aims

This systematic review aims to investigate how far current evidence supports a policy of using incentives to increase antipsychotic adherence. Specifically, the paper asks three questions:

1. Do incentives improve antipsychotic adherence?
2. What are the potential ethical and practical issues in offering incentives for antipsychotic adherence?
3. Does existing evidence clarify any ethical and practical issues identified?

MATERIAL AND METHODS

Search strategy and selection criteria

Search strategy

A systematic search of heterogeneous research was performed by NH and MM. MEDLINE, EMBASE and PsycINFO were searched for papers addressing financial or non-financial incentives in antipsychotics. Searches included a term related to antipsychotics and a term related to incentives (see online supplemental file 1). References were screened. RCTs and observational studies were included per the protocol; qualitative research and ethical analyses were also included because they covered perspectives which would otherwise be missed. Papers published up to 13 January 2021 were included. There was no start date. Trials in populations aged under 18 or over 70 were excluded to avoid compounding any ethical objections to financial incentives. No articles were translated and it was not necessary to contact study authors. The protocol adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statements (see online supplemental file 2 and 3).

Study selection

Searches were carried out on 13 January 2021. Search results were stored on Healthcare Databases Advanced Search (HDAS) and duplicates were removed automatically. (Population, Intervention, Comparison, Outcomes and Study Design (PICOS) table given in online supplemental file 4). Further deduplication was carried out by NH. Remaining studies were screened by title and abstract by both NH and MM. All disagreements were discussed and resolved. Each paper was read in full and data extraction was carried out by NH and MM. Data extraction varied by paper type. The Joanna Briggs Critical Appraisal Tools for Qualitative Research, Economic Analysis, RCTs, and Text and Opinion were used to assess the quality of the methodology sections of the relevant included papers.31

Analysis

Results were analysed sequentially by paper type. It was anticipated that evidence regarding implementation would include a diverse range of papers and accordingly a narrative synthesis was planned following Popay et al’s methodology.32 A theory of change was developed by NH and SS building on the literature around present bias (see box 1). In phase 1, a preliminary synthesis of the impact of incentives on adherence was developed by NH.
We use the standard economic assumption that people’s preferences have financial equivalents; most pleasant experiences have a maximum amount of money any given person would pay to experience it. This simply means that in general people would willingly accept a given unpleasant experience in exchange for a large sum of money but not a small sum of money, and it stands to reason that there is a cut-off point which represents the minimum amount of money a given person would be willing to accept to experience it. People also make trade-offs whereby pleasant experiences for which one would pay the same amount of money could be exchanged with one another, or where one accepts an unpleasant pleasant experience of a lesser equivalent value in order to gain a pleasant experience.

These values can be estimated experimentally across groups. Although infrequently used in front-line healthcare, they provide a helpful way to think about patients’ preferences and choices. These values also allow bundles of qualitatively different goods to be combined and compared. Under treatment as usual the decision whether or not to adhere to an antipsychotic can be modelled as a choice between option i and option ii. The values of the constituent parts of options i and ii can be given this way:

\[
\begin{align*}
\text{i. } A + \partial B_t \\
\text{ii. } A - D + \partial B_u
\end{align*}
\]

In this model, A is some level of baseline well-being, D balances out the cost of the discomfort and inconvenience caused by the depot treatment, or the equivalent payment they would accept to accept such an experience. B is the expected change in future utility which is influenced by whether mental illness is untreated (B_u) or treated (B_t). \(\partial\) represents the time discount factor. People value future well-being less than they value present well-being and a great deal of evidence shows that immediate discomfort is often overweighted in decisions bearing on future well-being. If future utility is valued at 40% of present utility, then \(\partial = 0.4\). (As we only consider one future time point, we need not consider different models of discounting over time.)

This shows that under treatment as usual a rational actor would choose option ii if they expect B_u to exceed B_t by more than D after temporal discounting plus the incentive.

Linking an incentive to treatment augments this model:

\[
\begin{align*}
\text{i. } A + \partial B_t \\
\text{ii. } A + C - D + \partial B_u
\end{align*}
\]

In this model, the incentive (with an equivalent value of C) and the treatment occur immediately and future well-being is, as above, discounted. Now the rational actor would accept the depot antipsychotic if C cancels out D (less the discounted amount by which B_t exceeds B_u) after taking into account the different weighting of losses and gains described by prospect theory. That is, if the discomfort or inconvenience of the depot is smaller than the expected benefit of the treatment after temporal discounting plus the incentive.

Based on this model we believe contingent incentives can change behaviour. Whether or not other regimes of incentives can change behaviour would require more detailed consideration of the evidence. We doubt that patients generally believe that their long run well-being is harmed by antipsychotic treatment, but if they acknowledge only a small benefit and this is discounted by present bias then the immediate inconvenience and discomfort of adherence may outweigh adherence. We anticipate that the value of an immediate incentive could outweigh the immediate inconvenience and discomfort, meaning that many patients would change behaviour. We recognise that this model makes assumptions about rationality, effective organisation and functional prospective memory which may not apply to all patients under all circumstances.
identified through references. 30 papers were assessed at full paper and 26 papers were included in the final analysis (see figure 1 and online supplemental file 5).34–58 All included papers addressed financial incentives; no papers discussed non-financial incentives. All papers studied depots including long-acting injectable preparations and weekly oral penfluridol for schizophrenia, schizoaffective disorder or bipolar affective disorder. Although our protocol stated that pilots would be excluded, two pilots were included because they also presented qualitative data.34 35 Ten included papers provided analysis but no new empirical data, among which were two RCT protocols.

Phase 1: change in adherence

Financial incentives for depot antipsychotic therapy have been implemented in five studies. In the UK and the Netherlands, there have been two pilot studies and two RCTs using immediate contingent incentives (as opposed to lotteries or deposit contracts).4 34–36 There is one short protocol for an ongoing and unpublished Canadian trial.35 Table 1 shows the characteristics of these studies. The results of the completed RCTs have been published across several papers so all high-quality evidence of efficacy comes from the FIAT trial and the Money for Medication (MfM) trial. Table 2 gives the similarities and differences between the participants in the RCTs. Both have quality scores of 9 out of 13, limited specifically by lack of blinding.

Table 3 compares data from the four implementations of financial incentives for antipsychotic depot therapy, illustrating baseline, intervention period and postintervention adherence where available. Over the 12 months of the FIAT trial and the MfM trial, the intervention groups’ adherence increased by 16 and 18 percentage points, respectively, and the control groups’ adherence only increased by 4 and 2 percentage points, respectively.34 36 Both these differences were statistically significant and support the hypothesis that incentives increase adherence. Pavlickova et al explored how the FIAT trial data varied over the four quarters of the trial period, revealing that adherence in both groups increased over time but that adherence in the intervention group was higher at all stages.39 This shows incentives are effective throughout the first 12 months.

Results of follow-up differed between the trials. In the FIAT trial no difference was found between the intervention and control group after the incentives were withdrawn. From the final quarter of the intervention to the first 6 months after incentives the intervention group’s adherence fell from 90% to 70% and the control group’s adherence fell from 79% to 77%.38 The difference between 70% and 77% was not significant at the 0.05 level (p=0.078).38

The MfM study found that in the first 6 months after incentives were withdrawn adherence fell from 94.3% to 83.4% in the intervention group, and also fell from 80.3% to 76.0% in the control group. The difference between the two groups after the incentive was withdrawn was significant at the 0.05 level (p=0.047).36

The FIAT trial followed patients until 24 months after incentives were withdrawn. During this period, adherence fell in both groups to 68% and 74% in the intervention and control groups respectively (p=0.130).38 The consistent finding is that the incentives increase adherence while they are in place, but after they are withdrawn it is not clear whether the difference persists, disappears or even reverses.

Secondary outcomes from the RCTs revealed few significant differences. Both FIAT and MfM measured overall clinical state (FIAT through clinician global rating and MfM through the Positive and Negative Symptoms Scale (PANSS)), suicide attempts, psychiatric hospital admissions and quality of life with FIAT using a structured communication between patient and clinician (known as DIALOG) and MfM using Manchester Short Assessment of Quality of Life (MANSA).4 36 59 60 The MfM trial included measures of substance misuse (Composite International Diagnostic Interview (CIDI) and Addiction Severity Index (ASI) scores), psychosocial functioning (Health of the Nation Outcome Scale (HoNOS) total) and medication side effects (Acute Stress Checklist (ASC) scores). The FIAT trial measured criminal justice contact and violent incidents and also published follow-up 6 months and 24 months after the trial period ending describing suicide attempts, violent incidents and police arrests. Among these secondary outcomes almost all had insignificant results. The exception was that the FIAT trial’s DIALOG scores differed significantly (p=0.002) in favour of the intervention group, although the MANSA score in the MfM study did not differ (p=0.36).4

Phase 2: ethical and practical issues

The search identified 11 papers including 2 RCT protocols which analysed ethical and practical considerations in financial incentives and antipsychotics without using original data (see table 4).40–50 These papers are important because they interrogate concepts with a level of depth not possible in empirical research. All but one paper...
scored over 50% on the Joanna Briggs Institute critical appraisal.

Table 4 shows the themes from these papers and indicates which theme they were assigned. A coding framework listing all the issues emerging from these papers was created (see online supplemental file 6). Themes connected to respect for autonomy ranged from risk of coercion (1.1) through to less restrictive option (1.6) and increase in autonomy (1.7). Beneficence covered elements of effectiveness including increasing adherence (2.1), limited flexibility (2.6) and who might benefit (2.4 and 2.6). Non-maleficence themes included a range of possible harms caused by incentives such as perverse incentives (3.1) and increased substance abuse (3.6) Only five themes were connected to justice and included fairness between patients (4.1 and 4.4), patients’ perception of fairness (4.2 and 4.5) and the risk of an exploitative power dynamic (4.3). Seven codes fell outside of the four principles and went beyond relational issues, covering abstract concepts such as dignity (5.1), intrinsic motivation (5.2), greed (5.4) and trust (5.6) as well practical implementation considerations (5.3, 5.5 and 5.7).

**Phase 3: experience**

Eight papers included data on the experience of staff and patients in their analysis of financial incentives (see online supplemental file 7). Throughout the pilots and trials of financial incentives, researchers studied the lived experience of relevant stakeholders. Early papers sought the perspectives of stakeholders on feasibility of and challenges around using financial incentives. Subsequent papers were able to explore the experience of patients...
| **Table 2** Characteristics of FIAT and MfM participants |
|----------------|----------------|----------------|
| **Study type** | Cluster RCT | Open-label RCT with stratified randomisation for sex, substance use, baseline compliance, |
| **No of participants in each arm** | 75 intervention patients in 35 clusters: 71 patients from 32 clusters were included. 56 control patients from 31 clusters: 52 from 30 teams were included. | 84 received MfM, 85 received treatment as usual. |
| **Demographics** | Ix vs Control | Intervention vs Control | Weighted avg: |
| | Age: 44 vs 43 | Male: 73% vs 78% | Male: 74% vs 76% |
| | Male: 76% vs 73% | Substance use disorder: 57% vs 54% | White: 51% vs 47% |
| | White: 63% vs 57% | Dutch: 35% vs 41% | CTO equivalent: 22% vs 22% |
| | Black 22% vs 23% | Surinamese: 20% vs 26% | Duration of illness: 10.2 vs 11.2 years |
| | Asian: 6% vs 7% | CTO equivalent: 37% vs 31% | |
| | Married: 10% vs 16% | Mean duration of illness: 11.5 years vs 12.9 years | |
| | Employed: 4% vs 2% | Median previous psychiatric admissions: 2 (0–4) vs 1 (0–3) | |
| | Duration of illness: 8.6 vs 8.5 years | Length of admissions: 71 (0–161) vs 18 (0–103) | |
| | >1 admission in last year: 26% vs 20% | | |
| | CTO: 4% vs 7% | | |
| **Patient exclusion criteria** | Baseline adherence above 75%, lack capacity, LD, insufficient English | Cognitive impairments, insufficient Dutch | Lack of language skills |
| **Type of antipsychotic** | Of the 131 patients with primary outcome data, three (2%) were prescribed an injection every week (two in the intervention group, 3%; one in the control group, 2%) during the 1-year study period. Eighty (61%) were prescribed an injection every 2 weeks (n=51, 68%; n=29, 52%), seven (5%) every 3 weeks (n=4, 5%; n=3, 5%) and 31 (24%) every 4 weeks (n=13, 17%; n=18, 32%). For 10 (8%) patients the prescription cycle varied (n=5, 7%; n=5, 9%). | Depot antipsychotics, including IM typical and atypical antipsychotics, and oral penfluridol.Ix vs control: First generation antipsychotics: 73% vs 76% Second generation antipsychotics: 26% vs 21% >50% adherence: 80% vs 80% Names of antipsychotics not given | Combination not possible |
| **Mental disorders being treated** | Ix vs Control: Schizophrenia: 78% vs 82% Schizoaffective dx: 12% vs 12% Bipolar disorder: 8% vs 2% | Ix vs Control Paranoid Schz: 55% vs 60% Schizoaffective dx: 12% vs 9% Psychotic disorder not otherwise specified: 14% vs 15% Schz disorganised type: 5% vs 8% Other schizophrenic disorder: 14% vs 15% | Schizophrenia: 75.8% v 82.6% Schizoaffective dx: 12% vs 10.1% Bipolar disorder: 3.7% vs 0.8% Psychotic disorder NOS: 7.6% vs 9.3% |

CTO, Community Treatment Order; IM, Intra Muscular; LD, Learning Disability; MfM, Money for Medication; NOS, Not otherwise specified; RCT, randomised controlled trial.
### Table 3  Adherence at different time points across all programmes of financial incentives for depot antipsychotics

| Linked study | n  | Baseline adherence | Adherence effect at 12 months | Adherence at 18 months (6 months after incentive discontinued) | Adherence at 36 months (7–24 months after incentive discontinued) |
|--------------|----|--------------------|-----------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Classen et al 2007 | 4 | ‘Non-adherent’ | ‘Improved’ | | |
| Starling et al 2010 | 5 | 44% | | 100% | |
| Priebe et al 2013 intervention group | FIAT | 72 | 69% | 85% | |
| Priebe et al control group | FIAT | 55 | 67% | 71% | |
| Priebe et al 2016 intervention group | FIAT | | | 70% | 68% |
| Priebe et al 2016 control group | FIAT | | | 77% (p=0.078) | 74% (p=0.130) |
| Pavlickova et al 2015 intervention group | FIAT | Baseline | 0–3 months | 4–6 months | 7–9 months | 10–12 months |
| | | 69% | 78% | 81% | 86% | 90% |
| Pavlickova et al 2015 control group | FIAT | 67% | 65% | 67% | 74% | 79% |
| Noordraven et al 2017 intervention group | MfM | 78 | 76.0% | 94.3% | | 83.4% |
| Noordraven et al 2017 control group | MfM | 75 | 77.9% | 80.3% | | 76.0% (p=0.047) |

MFM, money for medication.
## Table 4  Ethical issues and outstanding concerns identified in theoretical analysis papers

| Issue                                                                 | Respect for autonomy | Beneficence | Non-Maleficence | Justice | Relationships | Others |
|----------------------------------------------------------------------|----------------------|-------------|-----------------|---------|---------------|--------|
| Not coercion. Fixing a sum which is ‘non-coercive’ may be difficult because of ‘backdrop threat’. (1.1) | Not coercion. Fixing a sum which is ‘non-coercive’ may be difficult because of ‘backdrop threat’. (1.1) | Financial incentive in exchange for medications can be effective in enhancing compliance (1.1) Goal is to achieve a ‘commonly accepted good’ and as the financial incentives are small, not considered exploitation (1.2) | Legal implications with development of side effects as a result of taking medications following incentive (3.5) Possibility of harm to identity, personhood (3.4) Unclear when incentive would be terminated during treatment (3.6) | Risk of high costs. (4.1) Risk of penalising good adherence. (4.2) Risk that this is an NHS cost-saving exercise. (4.1) Risk of exploitation—those with SMI disadvantaged (4.3) Unclear who incentives would be offered to: all patients or non-compliant patients or those at risk to others? (4.4) Incentives mutually advantageous to both patients and health system (4.1) | | |
| ‘Denigration of treatment’ (3.3) | | | | Risk of increased marginalisation among those with SMI (4.3) | | Dignity: like selling a child. (5.1) |
| Failing to take steps to prevent relapse may lead to (more) restrictive treatment (1.6) | Failing to take steps to prevent relapse may lead to (more) restrictive treatment (1.6) | Other treatments are more effective when people are adherent to antipsychotic treatments. (2.3) Size of financial incentive may influence efficacy (2.1) Treatment adherence leads to an improved QOL (2.2) Adherence not necessarily linked to reduced relapse or admissions (2.2) | Stigma and negative media representation of incentives (3.3). | Incentive dependent on patient context including severity and chronicity of illness (4.4) Threatens the doctor-patient relationship (5.6) Doctor-patient relationship is already subject to financial incentives and influence (5.3) Issues with honesty and possibility of fraud (5.4) Impact on internal reward mechanisms (5.2) | | |
| Informed consent may be undermined if side-effects are downplayed. (1.4) Incentives enhance autonomy (1.7) Incentives are less restrictive than legislation (1.6) Libertarian paternalism (1.6) | Informed consent may be undermined if side-effects are downplayed. (1.4) Incentives enhance autonomy (1.7) Incentives are less restrictive than legislation (1.6) Libertarian paternalism (1.6) | Incentives shown to have improved health outcomes—drug misuse and smoking cessation (2.1) | Risk of diabetes, weight gain—threats may be downplayed due to financial incentive (3.5) | Risk that incentives work differently on different groups, impacting equity. (4.4) May encourage an ‘entitled to incentives’ attitude (4.5) | | |
| Payments should not reach a level of ‘financial aid’. (1.2) Financial incentives reduce ‘presence bias’ and improved long term outcomes (1.7) Incentives should be personalised and offered to patient in a ‘tailored’ manner with clear and predefined procedures (1.5) | Payments should not reach a level of ‘financial aid’. (1.2) Financial incentives reduce ‘presence bias’ and improved long term outcomes (1.7) Incentives should be personalised and offered to patient in a ‘tailored’ manner with clear and predefined procedures (1.5) | Effect may not last after incentive withdrawn. (2.5) RCTs conducted have many issues; have focused on injectable drugs; inclusion criteria includes already non-adherent patients; range needed; no blinding Longer follow-up needed. (2.1, 2.2) | Must avoid perverse incentives. (3.1) Unsustainable; poor adherence once financial incentives stopped (3.6) | Balance; Incentive should not function as financial aid but should influence desired response (5.5) | | |

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Continued
| **Table 4** Continued | Respect for autonomy | Beneficence | Non-Maleficence | Justice | Relationships | Others |
|------------------------|----------------------|-------------|----------------|---------|---------------|--------|
| **Guinart & Kane 2020**<sup>46</sup> (JBI*=5) | Incentivisation is not coercion. (1.1) Incentivisation serves the same goals as persuading an individual to undertake a desirable health behaviour (1.3) | The goal is to help the patient garner the benefits of necessary treatment. (2.2) Allows ‘continued dialogue and treatment flexibility’, for example, reduced doses (2.6) | Not all patients who accept incentives are in ‘need’ (4.4) Need to carefully choose patients for incentives, (4.4) Implementation challenge lies in identifying patients who would benefit (4.4) More research needed with different drug formulations, duration and clinical settings to evaluate efficacy of incentives (4.4) | | | |
| **Peterson-Dana and Decisions 2019**<sup>46</sup> (JBI*=4) | Coercion seems unavoidable because motivated by money have some financial need. (1.1) | Shared decision-making would be more effective than incentives. (2.8) Risk of patients adhering despite side effects. (3.5) Side effects of medications — metabolic, tardive dyskinesia; drugs can be reduced or discontinued under psychiatric care—continued dialogue with prescribers more important than incentivising (3.5) Treatment is multifaceted. Medication is part of the treatment in addition to psychosocial factors; focus should therefore not just be on medication adherence (3.4) | | Family involvement in decisions is better than incentives. (5.7) | |
| **Burns 2007**<sup>17</sup> (JBI*=6) | Opposition to payments is overly paternalistic. (1.6) Our language of ‘coercion’ is inadequate. (1.1) Transparent—what is being offered is clear; patient can make a choice. There is a ‘respectful and equal exchange’ (1.5) Financial incentive seen as being better than compulsory admissions (1.6) | RCTs exploring financial incentives in patients with physical health problems have shown good results; less controversy (2.1) The money is not exchanged for anything improper (2.1) Financial incentive is for the benefit of patients, not for an ‘improper purpose’ (2.2) | Concerns as to how the patient will spend their money despite ‘sums being modest’ (3.2) Voluntary adherence may disappear’ (3.6) | Relatively small inducements do not seem unjust. (4.1) Financial incentive reduce costs and outcomes of non-compliance (admissions, relapse etc) (4.1) | Decisions in healthcare often influenced by patient, their families and healthcare professionals. ‘Negotiation a constant reality in mental healthcare’ (5.7) | Mental healthcare already involves reinforcement. (5.3) ’rewards’ are not a new concept in healthcare—healthcare professionals involved in ‘rewarding and shaping behaviours’ (5.3) |
| **Shaw 2007**<sup>48</sup> (JBI*=4) | It is coercion ‘by carrot’ (1.1) No help to people who are forgetful or chaotic. It will not tip ‘the necessity-concerns’ equation. (2.7) Financial incentives does not address other causes of non-adherence which may impact on decision making and behaviour; non-adherence may not be intentional and therefore financial incentives may not be helpful for example, forgetfulness, difficulty understanding instructions (2.7) | Creates perverse incentives, (2.1) Create impression drugs are bad for patient, (3.3) ‘Voluntary adherence would disappear’ (3.6) Patient demand for pharmacotherapy will increase, (3.4) | If non-adherenece is costly to society then payments are acceptable. (4.1) | | Undermines therapeutic alliance. (5.6) | Risk of fraud by patients. (5.4) Monitoring adherence ‘infringes personal privacy’. (5.1) Loss of personal dignity and privacy (5.1) Difficulty in monitoring compliance (5.1) |

Continued
and clinicians involved in trials of financial incentives either through qualitative research or through analysis of quality of life and motivation questionnaires.53–56 Two papers53 56 used validated tools to answer specific questions about the experience of participants while the others used unvalidated surveys or interviews.53 Among qualitative papers, quality varied greatly reflecting that some analyses were conducted ad hoc.

In combination with the papers reporting change in adherence, these papers shed light on the typology of themes identified in phase two. Table 5 details what is known about each issue.

Six new themes also emerged from the experience data. There is a safeguarding risk of exploitation in the community when people received regular cash payments, which unless monitored could in turn have implications for consent. Whether or not quality of life improves is a relevant policy consideration. The possibility of using non-financial incentives emerged. Patients perceived an inherent benefit to having more money available and there was evidence that the idea of rewarding good behaviour was salient. Finally, researchers have also considered the risk that financial incentives impair insight.

Several of the themes raised had supporting evidence: better adherence, better efficacy of other treatments, risk of perverse incentives, having more money to spend, rewarding good behaviour and risk of exploitation. Meanwhile, there was evidence indicating several potential challenges had not materialised: financial dependence, forgetful patients, ineffectiveness, increased stigma, difficulty withdrawing incentives, reduced intrinsic motivation, fraud or demands for increased money, supplanting social networks or non-financial incentives being more appropriate.

Several topics require further research, some because existing evidence is mixed and some because there is no existing evidence. There was mixed evidence around habit formation, increased substance abuse, sense of entitlement, penalising good adherence, the impact on the clinician-patient relationship, quality of life and insight. Meanwhile there was no information regarding medication counselling, treatment personalisation, compliant patients’ attitudes, flexible payment arrangements, increased demand for medications, disinterest in adverse effects, inclusion criteria, links with other reinforcement techniques or changing payment levels. Importantly, there is no current evidence that hospitalisations reduce with financial incentives, meaning conclusions cannot be drawn regarding claims that incentives offer a less restrictive option or have better outcomes. In connection, the differences in healthcare system (and justice system) costs of financial incentives were not significant.57 58 The direct costs of financial incentives are small, costing hundreds of pounds per year, but the wider economic impact is unknown (see online supplemental file 8).

Finally, there were several domains which we did not believe could be definitively resolved with empirical data:

| Table 4 Continued |
|------------------|
| **Respect for autonomy** |
| **Beneficence** |
| **Non-Maleficence** |
| **Justice** |
| **Relationships** |
| **Others** |
| **FAT Protocol** |
| 2009 (JBI=**n/a**) |
| Avoid financial dependence. (1.2) |
| Even partial non-adherence can benefit. (2.2) |
| Some patients may discover adherence is not as bad as they thought. (2.5) |
| Patients may spend money on drugs. (3.2) |
| Risk intrinsic motivation will decrease. (5.2) |
| JBI Critical Appraisal Score (max 6).JBI, Joanna Briggs Institute; MfM, Money for Medication; QOL, quality of life; RCTs, randomised controlled trials. |

Finally, there were several domains which we did not believe could be definitively resolved with empirical data:
### Table 5  
A table describing any evidence supporting or opposing the established objections to the use of incentives for antipsychotic adherence

| No definitive empirical answer | No empirical evidence | Not amenable to empirical research |
|--------------------------------|-----------------------|-----------------------------------|
| Increase in autonomy | No empirical evidence | Mixed evidence of large costs of wider health system. |
| Risk of coercion | Classen et al’s survey of AOT leaders who had never used financial incentives found that 8% thought they could be coercive. Noordraven et al found that 36% of patients and 27% of staff in the MfM study endorsed the claim that depots would make patients feel forced to adhere. 8% of participants in Classen et al’s study raised the possibility of coercive nature of the intervention. | No research into incentives for patients whose compliance is already good. No evidence. |
| Exploiting power dynamic over unrewarded decisions | No empirical evidence. | No research into changing payment levels. No evidence. |
| Disregard for considered decisions | No empirical evidence, but mentioned in Preibe et al: ‘A core issue was whether the introduction of money would motivate patients to make decisions that may go against their beliefs on what was right for them’. | No evidence of disrespect; may not be amenable to empirical research. |
| Impact on patient dignity | No research | No evidence of large costs of wider health system. |
| No evidence | Improved outcomes | Mixed evidence; people thought it could be coercive; may not be amenable to empirical research. |
| Less restrictive option | Participants in Preibe et al’s focus groups held mixed views about whether incentives were more acceptable than detention and coercive treatment. No evidence of reduced hospital admission. | No evidence of significantly reduced hospital admissions. |
| May benefit complier patients | No research into incentives for patients whose compliance is already good. | No evidence. |
| Reduced counselling about treatment | No empirical evidence. | Not studied. |
| Costs/savings for wider healthcare system | 4/70 AOT leaders who had not used financial incentives raised concerns about the cost in Classen et al. Several participants in Preibe et al’s focus groups wondered whether spending on incentives would mean cuts to other areas, but others suspected incentives represented a government efficiency strategy. Henderson et al found no significant difference in differences of health costs before and during the intervention, comparing the arms of the MfM trial. Noordraven et al found no statistically significant difference in health costs or criminal justice costs. Henderson et al found that the average spent directly on incentives was around £1300 per participant. | No evidence of disrespect; may not be amenable to empirical research. |
| Inclusion criteria | No empirical evidence comparing different groups of inclusion criteria. | Not studied. |
| Relationship to existing reinforcement techniques | No empirical evidence combining incentives with other reinforcement techniques. | Not studied. |
| Limits of flexibility | No research into changing payment levels. | No evidence. |
| Transparency and personalisation | No empirical evidence comparing different payment levels. All studied payment levels have been £5–20 per depot injection. | No evidence. |
| Reduced attention to adverse effects | Participants in Preibe et al’s focus groups feared that patients would not report adverse effects if their | No evidence of large costs of wider health system. |
| Mixed evidence | Highton-Williams et al found that clinicians reported 22 patients not in the trial who asked why they were not being paid. Many participants in Preibe et al’s focus groups suggested that it was wrong to pay some patients to adhere and not others and could cause anger: “you’ve got a group of service users and some of them are being paid to take the medication and some aren’t, there’d be mutiny”. Noordraven et al found that 62% of patients and 71% of staff thought other patients would be jealous of those receiving incentives. On the other hand, many perceived it as rewarding good adherence. | Not studied. |

Continued
Table 5  Continued

| No definitive empirical answer |
|--------------------------------|
| **Habit formation and tolerance** | 51% of patients and 33% of clinicians in the MfM study agreed that financial incentives reinforced that patients were doing well in Noordraven et al. 62% of patients agreed that money for depot helped patients 'get into a positive flow'. Priebe et al and Noordraven et al both revealed large reductions in intervention group adherence over the 6 months after the incentives were removed; in the MfM trial adherence remained higher in the intervention group than the control group (83% to 76%, p=0.047) and in the FIAT trial adherence in the intervention group was lower than the control group but did not differ significantly (70% to 77%, p=0.079). No definitive empirical answer |
| **Improvement in quality of life** | Priebe et al found increased quality of life in the intervention group. Noordraven found no difference between groups. Noordraven et al explored the concern that increased quality of life was associated with having more money, not with better adherence and improved health, finding no association with the amount of incentive given, only with the number of depot doses received, suggesting that better adherence drives the improvement. |
| **Impact on clinician-patient relationship** | 9% of Classen et al's AOT leaders who had never used financial incentives raised concerns about a negative impact on the clinician-patient relationship. Highton-Williams et al found that incentives improved ability to care for 53/73 patients and improved relationships with 21/73 patients including improved trust and more contact time. However clinicians for 10/73 patients reported worsening of relationships because of money becoming central to the relationship. Noordraven et al found only 16% of patients and 16% of staff in the MfM study endorsed the statement that money for medication was harmful to the therapeutic relationship. |
| **Risk of patient not gaining insight into problems** | Noordraven et al: Although few patients (23%) agreed with the idea that 'If someone receives money for his depot, he won’t gain insight into his problems’, more clinicians (35%) were worried about this possibility. Highton-Williams et al found clinicians reported improved insight in 10/73 patients. |
| **Confirmatory evidence** | increased adherence The FIAT trial found that the difference in adherence in the control group increased from 67% to 71% and in the intervention group from 69% to 85%. In the MfM trial the difference in adherence in the control group increased from 78% to 80% and in the intervention group from 76% to 94%. The Classen et al and Starling et al pilots also reported improved adherence. |
| **Increased efficacy of other treatments** | Highton-Williams et al found that clinicians stated 32/73 patients improved their participation in other areas of treatment during the trial. Patients were proactive in making contact with team, increased engagement with team (and other services such as substance misuse), allowing for monitoring physical health. 77% of patients had improved management. Classen identified improved social circumstances: fewer problems with neighbours and police. |
| **Risk of perverse incentives** | Some participants in Priebe et al’s focus groups suggested incentives should always be a last resort, but others noted the risk of perverse incentives. Highton-Williams et al found that one patient not in the trial missed a dose in protest and another patient threatened to miss his dose. In the Starling et al pilot and the Classen et al pilot no other patients asked for money for adherence. |
| **Safeguarding: Exploitation in the community** | Highton-Williams et al describe a clinician reporting that one participant had ‘hangers on’ who came to see him when he received his incentive. Preliminary evidence suggesting this is a serious risk. |
| **Rewarding good behaviour** | Noordraven et al found that 76% of patients endorsed the statement that it is good to reward good behaviour. Evidence confirms patients identified this pattern. |
| **Having more money to spend** | Noordraven et al found that 41% of patients spontaneously said that having more money was an advantage of the MfM trial. Only 6% of clinicians noted this. Evidence shows many patients identified this benefit. |
| **Disconfirmatory evidence** | Difficulty withdrawing incentives One AOT leader who had not used financial incentives mentioned that transferring to a new area where incentives are not in place could be difficult. 16% of patients and 17% of clinicians in the MfM study agreed that withdrawing incentives would mean patients stop adhering. See also, Habit Formation and Tolerance. |
| **Risk of stigmatisation of patient and antipsychotics** | Frontline clinicians who had not used financial incentives feared incentives would create the impression that antipsychotics were not desirable, as reported in Priebe et al’s focus groups. No evidence on patient stigmatisation. |
| **Risk of financial dependence** | Following the MfM trial, Noordraven et al found that roughly a third of participants and of clinicians agreed that some participants would become dependent on incentives. Highton-Williams et al identified that dependence on financial incentives was a risk. No evidence of financial dependence; some people involved have been concerned about this outcome. |
| **May not increase adherence** | FIAT and MfM trials suggest incentives are effective at increasing adherence. Evidence from two trials show that incentives have increased adherence. |
| **Impact on intrinsic motivation** | Noordraven et al found no difference between control and intervention groups in treatment-related intrinsic motivation during the trial or after 6 months of follow-up. 6 months after discontinuation only 17% reported having little motivation for or resistance to their current treatment. A patient in the Starling et al pilot put it this way: ‘the money keeps me motivated’. Noordraven et al found large majorities of patients and clinicians (72% and 82%) agreed that money for depot improves patient’s motivation to use depots, but 71% of clinicians felt that patients would be adhering for the money more than the treatment, compared with only 38% of patients. Preliminary evidence suggesting no change in intrinsic motivation. |
coercion, disrespect for decisions, increased autonomy, exploitation of a power dynamic and patient dignity.

**DISCUSSION**

**Summary of results**

In this systematic review, two RCTs provide moderate-quality evidence that patients with relatively low adherence will accept more depot antipsychotic doses when combined with financial incentives. There is no consistent evidence of improved secondary outcomes and it is unclear whether adherence is adversely impacted after withdrawal of incentives. An extensive typology of potential issues in financial incentives for antipsychotic adherence has been generated. This has been used to identify the questions which remain unanswered in financial incentives, including 12 areas which are suitable for empirical study where there is no current evidence, and 7 where the evidence is currently mixed.

**Comparison with the literature**

The finding of effectiveness is broadly in keeping with the literature on financial incentives. This supports our theory of change and indicates that setting the value of C at around £15 was sufficient to outweigh the discomfort and inconvenience of treatment (valued at D) after taking into account the different treatment of losses and gains. This reveals that most people who miss their antipsychotic depot acceptance do so not because of deeply held or fixed values, but for reasons which are easily outweighed by a small incentive. (Note that £15 was roughly 2.5 times the top rate national minimum wage in the UK in 2013. Today that figure would be about £22.)

Some evidence suggests benefit to forgetful people.

Greed, fraud and demand for more money

Highton-Williams et al found clinicians reported that 6/73 patients requested more than £15 per depot, but that these requests were easily resolved. After the Staring et al pilot, all five patients said they thought the incentive should be higher, but none complained during the pilot. In Classen et al’s pilot one patient requested for the amount to be increased. No threats or demands for larger incentives.

Supplanting family and social support

Highton-Williams et al found that clinicians for 16/73 patients reported that their social functioning, including relationships and employment, had increased during the trial. In the Staring et al pilot both mothers interviewed were in favour of the intervention. Classen et al’s pilot reported improved social relationships.

Logistics of monitoring compliance

Highton-Williams et al found that the additional time involved in the treatment programme was a problem for clinicians of 5/73 patients. Preliminary evidence of logistical challenges.

Non-financial incentives instead

In the Priebe et al focus groups some participants suggested incentives were limited to therapeutic activities such as sport. In the Staring et al pilot patients said they preferred a cash incentive to a non-financial incentive. The two mothers interviewed agreed. 7/70 AOT managers in Classen et al’s survey reported using non-financial rewards for adherence but not directly as incentives. Noordraven et al found that 68% of patients and 47% of staff thought it was good to give financial incentives.

Coercion, disrespect for decisions, increased autonomy, exploitation of a power dynamic and patient dignity.

Previous authors have been wary of financial incentives because of apparent ethical issues. This is in keeping with Pronberger et al’s finding that members of the public generally felt health outcomes achieved through medication were more ethical than those achieved through
financial incentives, although any reasoning behind this instinct was unclear and there is diverse evidence regarding the acceptability of financial incentives in healthcare.\textsuperscript{68, 69} Halpern et al summarised five ethical issues regarding incentives in healthcare.\textsuperscript{70} The first was that they interfered with autonomy, but the authors argue that this is difficult to sustain given incentives do not close off any options to patients. In this study we have revealed a more complex relationship between incentives and autonomy, as incentives have improved many patients’ relationships with clinicians and have been viewed as a reward, not a constraint, by patients. The authors also suggested incentives could act as undue inducements, although this problem is unlikely in studies where each incentive is around £15. Similarly their fourth concern—monitoring invades privacy—was identified in this review but is irrelevant to depot treatment since covert non-adherence is impossible. Their third concern (crowding out) is actually a practical issue and has been addressed above. Finally there is a question of justice: why should those with low adherence be paid to do what other people do for free? This review has illuminated some relevant factors: few (but some) patients with good adherence complained about unfairness and nothing is known about the impact of incentives on high adherence patients. Given the low cost of incentives compared with the price of depots, future researchers should consider whether it is more efficient to reward those with good adherence as well. Altogether, this systematic review has bridged the ethical literature to the practical literature in order to identify which ethical issues remain outstanding, providing a template for future researchers exploring the ethics of financial incentives in this area.

**Strengths and limitations**

This review has taken an interdisciplinary approach. The authors include practising clinicians and behavioural scientists ensuring that the analysis has been informed by the realities of front-line practice and behavioural science research. It brings together a diverse set of evidence across 26 papers and is the first systematic review of financial incentives in the context of antipsychotic therapy. Studies using different methodologies and answering a range of research questions have been synthesised, providing a rich understanding of the intervention. This methodology has allowed us to advance the literature beyond the question of whether financial incentives increase antipsychotic depot adherence, by describing the relevant policy considerations and where conceptual issues remain unaddressed.

There have only been two published RCTs on financial incentives, the FIAT and MfM trials, and no meta-analysis has been performed. The other studies included in this systematic review were of mixed quality. The RCTs had low scores on critical appraisal tools because of a lack of blinding, but this did not impair external validity. However, some of the qualitative research was low quality due to a lack of preplanning and we would recommend that future studies embed qualitative assessment of acceptability in their protocol.

Another limitation is that in compiling a list of criticisms of financial incentives for antipsychotics we have not appraised whether these criticisms withstand rigorous theoretical analysis, rather comparing them with any available empirical data. This means our list of concerns may be overinclusive and may contain some weak criticisms. We identified several issues which we considered inappropriate for empirical study, but these conclusions could be proven wrong. Finally, we included pilot studies in this systematic review and both had positive results; this leaves the result open to publication bias but informal grey literature searches have failed to reveal any evidence of unpublished small studies with negative results.

**Implications for clinicians, researchers and policy-makers**

This review has generated a list of areas where further research is needed, some where the current evidence is mixed (such as substance abuse, entitlement to money, the clinician–patient relationship) and others where there is no evidence (whether incentives change medication consideration and counselling, how regimens can be altered or personalised and who should be included). It is also necessary to establish whether, on larger scale, financial incentives create a significant reduction in relapse and admission. If no reduction is identified, then it is important to ascertain whether that is because increased contact with services leads to more opportunities for admission, because of substance abuse, or because the wrong treatment is being used. This study failed to identify a knock-out ethical or practical argument against financial incentives for antipsychotic adherence, but ethicists should continue to explore how autonomy can be maximised where financial incentives are implemented.

We recommend that policymakers continue to pursue financial incentives as a viable means of helping patients improve their own mental health. This policy should involve larger studies of financial incentives for antipsychotic depots among low adherence patients with longer follow-up, and small studies including high adherence groups, different incentive magnitudes and daily tablet regimens. We have shown that, where implemented so far, financial incentives are an effective and acceptable way of increasing adherence to antipsychotics.

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