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

Nathan Hodson ,[1] Madiha Majid,[1] Ivo Vlaev ,[2] Swaran Preet Singh [1]

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[1]Mental Health and Wellbeing, Warwick Medical School, Coventry, UK
[2]Warwick Business School, Coventry, UK

Correspondence to
Dr Nathan Hodson;
nathan.hodson@warwick.ac.uk

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 for 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.

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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%.[1] 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.[2] There is tentative evidence that eHealth technologies such as SMS reminders and smart pill containers may improve adherence to oral antipsychotics.[3 4] Depot preparations offer another means of increasing antipsychotic adherence as treatment events are less frequent and covert nonadherence 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.[5 6] Cohort studies have, however, provided evidence supporting the use of long-acting injectable antipsychotics to prevent relapse and hospitalisation.[7 8] 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.[9] For some individuals stabilised on depot treatment, however, relapse has been associated with side effects such as tardive dyskinesia and functional decline.[10] 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 abuse,[24 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

Box 1 Overview of theory of change

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.[71 72] 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.[73]

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:

i. $A + \partial B_u$

ii. $A - D + \partial B_t$

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). ∂ 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.[74 75] If future utility is valued at 40% of present utility, then ∂ is 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. One problem with this is that ∂ may be very small for people facing other immediate adversity which would give D excessive weight simply because it is experienced in the present.[76]

Linking an incentive to treatment augments this model:

i. $A + \partial B_u$

ii. $A+C - D + \partial B_t$

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.[61] 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

Continued

Box 1 Continued

makes assumptions about rationality, effective organisation and functional prospective memory which may not apply to all patients under all circumstances.

through listing and tabulation. In phase 2, papers examining ethical, practical or conceptual considerations were analysed. Inductive thematic analysis was conducted by NH and MM. The coding framework drew on the four principles of medical ethics, plus an additional topic 'consideration of relationships', which is absent from Beauchamp and Childress's model.[33] This process generated a typology of ethical and practical issues. In phase 3, papers reporting experiences of patients and frontline staff were analysed by NH and MM. The typology of issues generated in phase two was used as a framework. The data from papers reporting the experiences of patients and frontline staff was analysed according to which practical and ethical issues were addressed. Any new issues emerging from these papers were added to the typology. Any evidence bearing on the practical and ethical issues was described. This generated a comprehensive list of issues in financial incentives for antipsychotics grouped by the current state of the evidence around this issue. The robustness of the synthesis was assessed discursively, drawing particularly on the critical appraisal of primary studies, their heterogeneity and strength of conclusions drawn. Critical appraisal was performed by NH. Pilot studies and protocols were not subjected to critical appraisal. Raw scores were reported.

Data extraction was preplanned for study type, number of participants in each arm, demographics, patient exclusion criteria, type of antipsychotic, mental disorders being treated, incentive regime, measure of adherence, adherence level, measure of clinical outcome and clinical outcomes. Additional extraction was performed for practical and ethical issues identified, economic outcomes, and experiences of patients and clinicians. Given the small number of RCTs specifically measuring change in adherence, our protocol dictated that meta-analysis was not performed. This systematic review was funded via NH and MM's National Institute for Health and Care Research (NIHR) fellowships.

Patient and public involvement

Research papers reporting the experiences of people offered incentives were searched for, included and synthesised in this review. Few people have been offered incentives for adherence so formal involvement of the relevant group was not possible.

RESULTS

General results

A total of 872 results were obtained through HDAS searches after deduplication. One additional paper was

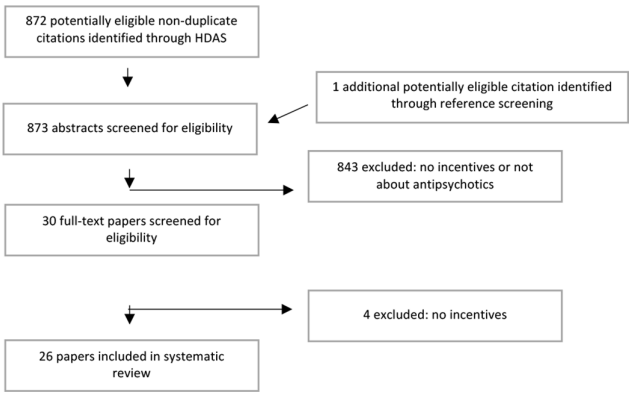

Figure 1 PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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).[4 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.[37] 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.[4 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 discontinuation of 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

Table 1 Published designs for implementation of financial incentives for depot antipsychotic treatment

	Setting	Participants	Allocation	Payment regime	Outcome measures
Classen *et al* pilot[34]	Assertive outreach in East London in 2003–2004	Formerly non-adherent patients (n=5)	All offered payment	Between £five and £15 per depot depending on frequency of depot	Patient agreement to payment, change in adherence, change in hospital admissions
Staring *et al* pilot[35]	Assertive community team in Rotterdam in 2008–2009	Schizophrenia or schizoaffective disorder, spending 1 year under ACT, non-adherence (level not specified) and admission in the last year (n=6)	All offered payment	£10–£20 for each depot	Patient agreement to payment, change in adherence and change in hospital days, experiences of patients, clinicians and relatives.
Priebe *et al* FIAT trial[4]	ACT or community mental health teams in England and Wales over a 12 month period	Schizophrenia, schizoaffective disorder or bipolar affective disorder, with 75% or less adherence to antipsychotic drugs and under the team for the last 4 months. (141 patients from 73 teams)	Cluster randomised trial with 1:1 allocation at the level of the treatment team to intervention (78 patients from 37 teams) or treatment as usual (63 patients from 36 teams)	£15 for each depot	Adherence (doses received divided by doses prescribed), binary measure of adherence over 95%, clinical global improvement, QOL, hospital admissions, suicide attempts and violence, time spent in work, training or education.
Noordraven *et al* Money for Medication trial[36]	Three secondary mental healthcare centres in Rotterdam and the Hague.	Patients with psychotic disorder (no adherence limit) (n=169)	Patients randomised to intervention (n=84) or treatment as usual (n=85)	7.5–30 Euros per depot based on maximum of 30 euros per month for full adherence	Difference in change in adherence, difference in change in attitude to medication, clinical outcomes
Financial Incentives to Improve Acceptance of Antipsychotic Injections (Protocol only)[37]	St. Michael Hospital's Assertive Community Treatment team in Toronto aiming to run from 2020 to December 2021 lasting 18 months	Patients with schizophrenia, schizoaffective disorder or Bipolar I Disorder (n=20)	Patients randomised cross over study (10 v 10)	$C15	Difference in adherence levels, global clinical improvement, hospital admission/ER visits, criminal justice encounters, suicides, physical violence, rehabilitation programme work, QOL

ACT, Assertive Community Team; QOL, quality of life.

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).[51–58] 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.[51 52] Subsequent papers were able to explore the experience of patients

Table 2 Characteristics of FIAT and MfM participants

	FIAT (2013)[4]	MfM (2017)[36]	Combination
Study type	Cluster RCT	Open-label RCT with stratified randomisation for sex, substance use, baseline compliance,	Controlled trial randomised at cluster and individual level
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.	Intervention participants included: 155 Intervention randomisation units included: 116 Control participants included: 137 Control randomisation units included: 115
Demographics	Ix v Control Age: 44 vs 43 Male: 76% vs 73% White: 63% vs 57% Black 22% vs 23% Asian: 6% vs 7% Married: 10% vs 16% Employed: 4% vs 2% Duration of illness: 8.6 vs 8.5 years >1 admission in last year: 26% vs 20% CTO: 4% vs 7%	Intervention vs Control Male: 73% vs 78% Substance use disorder: 57% vs 54% Dutch: 35% vs 41% Surinamese: 20% vs 26% CTO equivalent: 37% vs 31% Mean duration of illness: 11.5 years vs 12.9 years Median previous psychiatric admissions: 2 (0–4) vs 1 (0–3) Length of admissions: 71 (0–161) vs 18 (0–103)	Weighted avg: Male: 74% vs 76% White: 51% vs 47% CTO equivalent: 22% vs 22% Duration of illness: 10.2 vs 11.2
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 v Control: Schizophrenia: 78% vs 82% Schizoaffective dx: 12 % vs 12% Bipolar disorder: 8% vs 2%	Ix v 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[34]		4	'Non-adherent'					'Improved'		
Starling *et al* 2010[35]		5	44%					100%		
Priebe et al 2013 intervention group[4]	FIAT	72	69%					85%		
Priebe *et al* control group[4]	FIAT	55	67%					71%		
Priebe *et al* 2016 intervention group[38]	FIAT								70%	68%
Priebe *et al* 2016 control group[38]	FIAT								77% (0=0.078)	74% (p=0.130)
Pavlickova *et al* 2015 intervention group[39]	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[39]	FIAT		67%	65%	67%	74%	79%			
Noordraven *et al* 2017 intervention group[36]	MfM	78	76.0%					94.3%	83.4%	
Noordraven *et al* 2017 control group[36]	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

	Respect for autonomy	Beneficence	Non-Maleficence	Justice	Relationships	Others
Szmukler 2009[40] (JBI*=5)	Not coercion. Fixing a sum which is 'non-coercive' may be difficult because of 'ackground 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)		Dignity: selling something which should not be sold. (5.1)
Priebe *et al* 2013[41] (JBI*=3)	Dignity: devaluing or denigrating patients' decisions about what they think is best. (1.3)		'Denigration of treatment' (3.3)	Risk of increased marginalisation among those with SMI (4.3)		Dignity: like selling a child. (5.1)
Kendall 2013[42] (JBI*=5)	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)
Marteau *et al*[43] (JBI*=4)	Informed consent may be undermined if side-effects are down-played. (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)	Alters a relationship otherwise based on trust. (5.6) Means of improving population health (4.1) The impact of side-effects may be downplayed resulting in impact on doctor–patient relationship where patient 'blames' the physician (3.5) Exchange between doctor-patient becomes financial, and not based on trust - Impact on this relationship requires further research (5.6)	Incentives may reduce intrinsic motivation. (5.2)
Guinart & Kane 2019[44] (JBI*=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)		No information about other types of incentive. (5.3) There may be other behavioural economics aspects to explore such as loss aversion (5.3)

Continued

Table 4 Continued

	Respect for autonomy	Beneficence	Non-Maleficence	Justice	Relationships	Others
Guinart & Kane 2020[45] (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 nd Decisions 2019[46] (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[47] (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[48] (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. (3.1) 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-adherence 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

Table 4 Continued

	Respect for autonomy	Beneficence	Non-Maleficence	Justice	Relationships	Others
FIAT Protocol 2009[49] (JBI*=n/a)	Avoid financial dependence. Payments should not impair access to other benefits. (1.2)	Some patients may discover adherence is not as bad as they thought. (2.5) Anticipated benefits: improved QOL, reduced compulsory admissions, patients see the benefit of adherence and later take it without incentive (2.2)	Difficulty eventually withdrawing incentives. (3.6) Patients may spend money on drugs. (3.2)	Difficulty in engaging a range of individuals; 'the target group of this study are very difficult to engage in care and often even more difficult to engage in research trials' (4.4)		Risk patients demand more money over time. (5.4) Reduced harm to others from crime. (5.4)
MfM Protocol 2014[50] (JBI*=n'a)	Avoid financial dependence. (1.2)	Even partial non-adherence can be harmful. (2.2) Compliant patients may also benefit. (2.4)	Patients may spend money on drugs.(3.2)	Incentives should be as low as is efficient. (4.1)		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.

and clinicians involved in trials of financial incentives either through qualitative research or through analysis of quality of life and motivation questionnaires.[53–58] Two papers[53 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 5 A table describing any evidence supporting or opposing the established objections to the use of incentives for antipsychotic adherence

No definitive empirical answer		
Increase in autonomy	No empirical evidence	Not amenable to empirical research
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.[34] The question of coercion was raised in 24/25 focus groups in Preibe *et al*.[52] Noordraven *et al*[55] 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 possible coercive nature of the intervention.[34]	Mixed evidence that people thought it could be coercive; may not be amenable to empirical research.
Exploiting power dynamic over unwell	No empirical evidence.	No evidence; not amenable to definitive empirical research.
Disrespect 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'.[52]	No evidence of disrespect; may not be amenable to empirical research.
Impact on patient dignity	No research	Not amenable to definitive empirical research.
No evidence		
Improved outcomes	There was no difference in hospitalisation rate in either the FIAT or MfM trials.[4 36]	No significant evidence.
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.[52]	No evidence of significantly reduced hospital admissions.
May benefit compliant 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*.[34] Several participants in Priebe *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.[52] Henderson *et al* found no significant difference in differences of health costs before and during the intervention, comparing the arms of the MfM trial.[57] Noordraven *et al* found no statistically significant difference in health costs or criminal justice costs.[58] Henderson *et al* found that the average spent directly on incentives was around £300 per participant.[59]	No evidence of large costs of wider health system.
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.
Difficulty setting appropriate payment levels	No empirical evidence comparing different payment levels. All studied payment levels have been £5–20 per depot injection.[4 34–36]	Not studied.
Transparency and personalisation	No empirical evidence.	Not studied.
Increased demand for psychopharmacology	This matches comments by psychologists in Priebe *et al* that the medical model is wrongly dominant.[52] Highton-Williams *et al* found clinicians reported that 6/73 patients asked to receive their depot more frequently.[54] 12/73 patients asked for a dose to be given early, but often in a joking tone. In the Staring *et al* pilot 2/5 patients asked for doses early.[35]	Not studied; evidence that it is plausible.
Reduced attention to adverse effects	Participants in Preibe *et al*'s focus groups feared that patients would not mention adverse effects if they were receiving incentives.[52] Staring *et al* illustrated that the incentives did not disguise adverse effects, but made them tolerable, with the quote "money makes it better".[35]	Not studied.
Mixed evidence		
Penalises good adherence	Highton-Williams *et al* found that clinicians reported 22 patients not in the trial who asked why they were not being paid.[54] Many participants in Priebe 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".[52] Noordraven *et al* found that 62% of patients and 71% of staff thought other patients would be jealous of those receiving incentives.[55] On the other hand, many perceived it as rewarding good adherence.	Mixed evidence.
Inculcating a sense of entitlement	Arguably some evidence from Highton-Williams *et al* where patients treated it as "pay day".[54] Also some evidence of increased pro-social attitudes.	Mixed evidence.
Increased drug and alcohol use	Highton-Williams *et al* found clinicians reported that incentives were spent on tobacco and drugs by 21 and 17 out of 73 patients, respectively.[54] The authors also found that some patients improved their engagement with drug and alcohol services during the course of the trial. Several clinicians told the authors that the patient may have accessed drugs and alcohol without the incentive money. In Staring *et al*.'s pilot, at least one patient spent some of the incentive money on cannabis.[35]	Mixed evidence and unclear direction of effect. Further research needed.

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*.[56] 62% of patients agreed that money for depots helped patients 'get into a positive flow'.[56] 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=0.078).[4 36 38]	Mixed evidence of habit formation and further research needed
Improvement in quality of life	Priebe *et al* found increased quality of life in the intervention group.[4] Noordraven found no difference between groups.[36] Moran *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.[53]	Mixed evidence.
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.[34] Highton-Williams *et al* found that clinicians reported improved ability to care for 53/73 patients and improved relationships with 21/73 patients including improved trust and more contact time.[54] 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.[55]	Mixed evidence.
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.[55] Highton-Williams *et al* found clinicians reported improved insight in 10/73 patients.[54]	Mixed evidence.
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%.[4] 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%.[36] The Classen *et al* and Starling *et al* pilots also reported improved adherence.[34 35]	The evidence supports the claim that financial incentives increase antipsychotic depot 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.[54] Patients were proactive in making contact with team, increased engagement with team (and other services such as substance misuse), allowing for monitoring physical health.[54] 77% of patients had improved management.[54] Classen identified improved social circumstances: fewer problems with neighbours and police.[34]	The evidence supports better engagement with the wider treatment plan when financial incentives are in place for antipsychotics.
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.[52] 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.[54] In the Staring *et al* pilot and the Classen *et al* pilot no other patients asked for money for adherence.[34 35]	Some evidence of the potential for perverse incentives; further research needed.
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.[54]	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.[55]	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.[55]	Evidence shows many patients identified this benefit.
Discomfirmatory 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.[34] 16% of patients and 17% of clinicians in the MfM study agreed that withdrawing incentives would mean patients stop adhering.[55] See also, Habit Formation and Tolerance.	Little evidence of difficulty withdrawing incentives, but mixed evidence of reduced adherence after withdrawal.
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.[52] No evidence on patient stigmatisation.	No evidence of 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.[55] Highton-Williams *et al* identified that dependence on financial incentives was a risk.[54]	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.[4 36]	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.[36] 6 months after discontinuation only 17% reported having little motivation for or resistance to their current treatment.[36] A patient in the Staring *et al* pilot put it this way: "the money keeps me motivated".[35] Noordraven *et al* found large majorities of patients and clinicians (72% and 82%) agreed that money for depots 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.[55]	Preliminary evidence suggesting no change in intrinsic motivation.

Continued

Table 5 Continued

No definitive empirical answer		
May not help forgetful people	Highton-Williams *et al* found that clinicians reported that 12/73 patients made additional effort to attend on time, such as calling ahead to check the time and day.[54]	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.[54] After the Staring *et al* pilot, all five patients said they thought the incentive should be higher, but none complained during the pilot.[35] In Classen *et al*'s pilot one patient requested for the amount to be increased.[34] No threats or demands for larger incentives.	No evidence of fraud or serious demands for more money.
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.[54] In the Staring *et al* pilot both mothers interviewed were in favour of the intervention.[35] Classen *et al*.'s pilot reported improved social relationships.[34]	Preliminary evidence of improved social networks.
Logistics of monitoring compliance	Highton-Williams *et al* found that the additional time involved in the incentive programme was a problem for clinicians of 5/73 patients.[54]	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.[52] In the Staring *et al* pilot patients said they preferred a cash incentive to a non-financial incentive.[35] The two mothers interviewed agreed.[35] 7/70 AOT managers in Classen *et al*'s survey reported using non-financial rewards for adherence but not directly as incentives.[34] Noordraven *et al* found that 68% of patients and 47% of staff thought it was good to give financial incentives.[55]	Preliminary evidence suggests less effective.

AOT, Assertive Outreach Team; MfM, Money for Medication.

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.[61] This reveals that most people who miss their antipsychotic depot 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.)[62 63] These findings should be taken into consideration in future ethical analyses of autonomy in this area.

The incentives were linked to a positive behaviour (depot acceptance) not a complex health outcome (such as not relapsing). Fryer found that incentive programmes were more effective when linked to actions rather than outputs.[21] Indeed depot administration is well-suited for incentivisation because it is binary and easily monitored. Among oral psychiatric medications, the next appropriate area might be a tablet with routine monitoring of levels (such as clozapine or lithium). The studies included in this review also targeted patients with low adherence. This is in keeping with Mitchell *et al*'s finding that the effect of incentives on daily steps was more marked among adults with a low baseline.[64]

Whether the change in adherence persists remains uncertain. Some have argued that incentives erode intrinsic motivation such that the removal of incentives means target behaviour falls below baseline, but this review found some evidence of preserved intrinsic motivation. Others have argued that incentives can drive habituation meaning positive changes persist after withdrawal of incentives although a systematic review of incentives for exercise found post-intervention physical activity generally returned to baseline.[11 65]

Titmus proposed that paying people to give blood could theoretically reduce donations by 'crowding out' the intrinsic motivation and Frey and Oberholzer-Gee have shown that financial incentives crowded out motivation enough to reverse some people's preferences, but in the context of healthcare there is a lack of clear evidence of crowding out.[66 67] This systematic review found evidence that self-reported intrinsic motivation was not reduced by incentives, but the unclear results regarding post-intervention adherence leave open questions about whether revealed motivation may differ from reported motivation.[67]

Previous authors have been wary of financial incentives because of apparent ethical issues. This is in keeping with Promberger *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.[68 69] Halpern *et al* summarised five ethical issues regarding incentives in healthcare.[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.

Twitter Nathan Hodson @nathanhodson

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ORCID iDs
Nathan Hodson http://orcid.org/0000-0001-6022-2260
Ivo Vlaev http://orcid.org/0000-0002-3218-0144
Swaran Preet Singh http://orcid.org/0000-0003-3454-2089

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Supplemental material:

1. **Search terms**

	Database(s)	Search Term
1	Medline	(antipsychotic).ti,ab
2	Medline	(major tranquilizer).ti,ab
3	Medline	exp "ANTIPSYCHOTIC AGENTS"/
4	Medline	exp MOTIVATION/
5	Medline	exp REWARD/ OR exp "DELAY DISCOUNTING"/
6	PsycINFO	exp "NEUROLEPTIC DRUGS"/
7	PsycINFO	exp INCENTIVES/ OR exp REWARDS/ OR exp MOTIVATION/
8	PsycINFO	exp "MONETARY REWARDS"/ OR exp "MONETARY INCENTIVES"/
9	EMBASE	exp "NEUROLEPTIC AGENT"/
10	EMBASE	(incenti*).ti,ab
11	EMBASE	(rewar*).ti,ab
14	PsycINFO	(7 OR 8)
15	EMBASE	(10 OR 11)
17	PsycINFO	(6 AND 14)

18	EMBASE	(9 AND 15)
19	Medline	(1 OR 2 OR 3)
20	Medline	(4 OR 5)
21	Medline	(19 AND 20)
22	Medline	(19 AND 20) [Human age groups Adult] [Humans]
23	EMBASE	(9 AND 15) [Human age groups Adult 18 to 64 years OR Aged 65+ years]
24	EMBASE	(9 AND 15) [Human age groups Adult 18 to 64 years] [Humans]
25	PsycINFO	(6 AND 14) [Human age groups Adulthood 18 Yrs + Older] [Population Human]

2. Prisma checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	n/a short abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P5-7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P7

Section and Topic	Item #	Checklist item	Location where item is reported
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	n/a
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	n/a
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	n/a
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P18
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P11
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1, 3, 4, and 5

Section and Topic	Item #	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table4 and suppl 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2 and 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P18
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Table 1, 4, and 5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P18
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P15
	23b	Discuss any limitations of the evidence included in the review.	P18
	23c	Discuss any limitations of the review processes used.	P18
	23d	Discuss implications of the results for practice, policy, and future research.	P18-19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	P7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P9
Competing interests	26	Declare any competing interests of review authors.	Title page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/a

3. ENTREQ Table

No	Item	Guide and description	Page
1	Aim	State the research question the synthesis addresses.	P7
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology *(e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis).*	P8
3	Approach to searching	Indicate whether the search was pre-planned (*comprehensive search strategies to seek all available studies)* or iterative (*to seek all available concepts until they theoretical saturation is achieved)*.	P7-8
4	Inclusion criteria	Specify the inclusion/exclusion criteria *(e.g. in terms of population, language, year limits, type of publication, study type).*	P7
5	Data sources	Describe the information sources used (e.g. *electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists)* and when the searches conducted; provide the rationale for using the data sources.	P7
6	Electronic Search strategy	Describe the literature search *(e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits).*	P7
7	Study screening methods	Describe the process of study screening and sifting *(e.g. title, abstract and full text review, number of independent reviewers who screened studies).*	Fig 1, p8
8	Study characteristics	Present the characteristics of the included studies *(e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions).*	Table 1 and 2 and suppl 6
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion *(e,g, for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications t the research question and/or contribution to theory development).*	Fig 1

10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings *(e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings).*	P18
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings *(e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope* [25]*; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting).*	P8
12	Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required.	P8
13	Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale.	P18 and table 4 and 7
14	Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? *(e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software).*	P8 and 9
15	Software	State the computer software used, if any.	P8 and 9
16	Number of reviewers	Identify who was involved in coding and analysis.	P8 and 9
17	Coding	Describe the process for coding of data *(e.g. line by line coding to search for concepts).*	P8
18	Study comparison	Describe how were comparisons made within and across studies *(e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary).*	P8 and 9
19	Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive.	P8 and 9
20	Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation.	Table 3
21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. *new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct).*	Table 4

4. PICOS Table

Population	People with serious mental illness requiring antipsychotic treatment
Intervention	Incentives
Comparison	No Incentives
Outcome	Adherence to antipsychotic treatment
Study type	No restrictions

5. List of included papers

1. Classen D, Fakhoury WK, Ford Rm Priebe S. Money for medication: financial incentives to improve medication adherence in assertive outreach. Psychiatric Bulletin (2007), 31, 4-7
2. Staring AB, Mulder CL, Priebe S. Financial incentives to improve adherence to medication in five patients with schizophrenia in the Netherlands. Psychopharmacol Bull. 2010;43(1):5-10.
3. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, David AS, O'Connell N, Forrest A, Burns T. Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics: cluster randomised controlled trial. BMJ. 2013 Oct 7;347:f5847. doi: 10.1136/bmj.f5847.
4. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AF, Staring AB, Mulder CL. Financial incentives for improving adherence to maintenance treatment in patients with psychotic disorders (Money for Medication): a multicentre, open-label, randomised controlled trial. Lancet Psychiatry. 2017 Mar;4(3):199-207. doi: 10.1016/S2215-0366(17)30045-7.
5. Financial Incentives to Improve Acceptance of Antipsychotic Injections. NCT03192631 Cochrane Central Register of Controlled Trials. 31 May 2018. Issue 5
6. Priebe S, Bremner SA, Pavlickova H. Discontinuing financial incentives for adherence to antipsychotic depot medication: long-term outcomes of a cluster randomised controlled trial. BMJ Open. 2016;6(9):e011673. Published 2016 Sep 21. doi:10.1136/bmjopen-2016-011673
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8. Szmukler G. Financial incentives for patients in the treatment of psychosis. J Med Ethics. 2009 Apr;35(4):224-8. doi: 10.1136/jme.2008.027151.

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11. Marteau TM, Ashcroft RE, Oliver A. Using financial incentives to achieve healthy behaviour. BMJ. 2009 Apr 9;338:b1415. doi: 10.1136/bmj.b1415. PMID: 19359291.
12. Guinart D, Kane JM. Use of Behavioral Economics to Improve Medication Adherence in Severe Mental Illness. Psychiatr Serv. 2019 Oct 1;70(10):955-957. doi: 10.1176/appi.ps.201900116.
13. Guinart D, Kane JM. Incentivizing Is Not Coercing: A Commentary. Psychiatr Serv. 2020 Jan;71(3)DOI:10.1176/appi.ps.201900543
14. Peterson-Dana C. Shared Decisions and Agency: Better Engagement Tools. Psychiatr Serv. 2019 Oct 1;70(10):857. doi: 10.1176/appi.ps.701002. PMID: 31570080.
15. Burns T. Is it acceptable for people to be paid to adhere to medication? Yes. BMJ. 2007 Aug 4;335(7613):232. doi: 10.1136/bmj.39286.399514.BE. PMID: 17673764; PMCID: PMC1939784.
16. Shaw J. Is it acceptable for people to be paid to adhere to medication? No. BMJ. 2007 Aug 4;335(7613):233. doi: 10.1136/bmj.39286.422639.BE.
17. Priebe S, Burton A, Ashby D, Ashcroft R, Burns T, David A, Eldridge S, Firn M, Knapp M, McCabe R. Financial incentives to improve adherence to anti-psychotic maintenance medication in non-adherent patients - a cluster randomised controlled trial (FIAT). BMC Psychiatry. 2009 Sep 28;9:61. doi: 10.1186/1471-244X-9-61.
18. Noordraven EL, Audier CH, Staring AB, Wierdsma AI, Blanken P, van der Hoorn BE, Roijen LH, Mulder CL. Money for medication: a randomized controlled study on the effectiveness of financial incentives to improve medication adherence in patients with psychotic disorders. BMC Psychiatry. 2014 Dec 2;14:343. doi: 10.1186/s12888-014-0343-3
19. Classen D. Financial incentives for antipsychotic depot medication: ethical issues. J Med Ethics 2007;33:189–193. doi: 10.1136/jme.2006.016188
20. Priebe S, Sinclair J, Burton A, et al. Acceptability of offering financial incentives to achieve medication adherence in patients with severe mental illness: a focus group study. *J Med Ethics*. 2010;36(8):463-468. doi:10.1136/jme.2009.035071
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23. Noordraven EL, Schermer MHN, Blanken P, Mulder CL, Wierdsma AI. Ethical acceptability of offering financial incentives for taking antipsychotic depot medication: patients' and clinicians' perspectives after a 12-month randomized controlled trial. BMC Psychiatry. 2017 Aug 29;17(1):313. doi: 10.1186/s12888-017-1485-x.
24. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Mulder CL. The effect of financial incentives on patients' motivation for treatment: results of "Money for Medication," a randomised controlled trial. BMC Psychiatry. 2018 May 24;18(1):144. doi: 10.1186/s12888-018-1730-y.

25. Henderson C, Knapp M, Yeeles K, Bremner S, Eldridge S, David AS, et al. (2015) Cost- Effectiveness of Financial Incentives to Promote Adherence to Depot Antipsychotic Medication: Economic Evaluation of a Cluster-Randomised Controlled Trial. PLoS ONE 10(10): e0138816. doi:10.1371/journal.pone.0138816
26. Noordraven EL, Wierdsma AI, Blanken P, Bloemendaal AFT, Mulder CL. Medical and social costs after using financial incentives to improve medication adherence: results of a 1 year randomised controlled trial. BMC Res Notes. 2018 Sep 10;11(1):655. doi: 10.1186/s13104-018-3747-1.

Supplement 5: Coding Framework from Phase Two

1. **Respect for Autonomy**
   - 1.1. Risk of coercion
   - 1.2. Risk of financial dependence
   - 1.3. Disrespect for considered decisions
   - 1.4. Reduced counselling about treatment
   - 1.5. Transparency and personalisation
   - 1.6. Less restrictive option
   - 1.7. Increase in autonomy
2. **Beneficence**
   - 2.1. Increased adherence
   - 2.2. Improved outcomes
   - 2.3. Increased efficacy of other treatments
   - 2.4. May benefit compliant patients
   - 2.5. Habit formation and tolerance
   - 2.6. Limits of flexibility
   - 2.7. May not help forgetful people
   - 2.8. May not work
3. **Non-Maleficence**

3.1. Risk of perverse incentives

3.2. Increased drug and alcohol use

3.3. Risk of stigmatization of patient and antipsychotics

3.4. Increased demand for psychopharmacology

3.5. Reduced attention to adverse effects

3.6. Difficulty withdrawing incentives

4. Justice

4.1. Costs/savings for wider healthcare system

4.2. Penalizes good adherence

4.3. Exploiting power dynamic over unwell

4.4. Inclusion criteria

4.5. Inculcating a sense of entitlement

5. Others

5.1. Impact on patient dignity

5.2. Impact on intrinsic motivation

5.3. Relationship to existing reinforcement techniques

5.4. Greed, fraud and demand for more money

5.5. Difficulty setting appropriate payment levels

5.6. Loss of trust in doctor-patient relationship

5.7. Supplanting family and social support

Supplement 6: Research exploring financial incentives among people with relevant lived experience

Paper *(JBI critical appraisal score max 10)*	**Linked study**	**Method and aims**	**Participants (n)**
Classen et al 2007 (41) *(2)*	None	Questionnaires and pilot **Aims:** to investigate attitudes to and effective use of financial incentives	70 AOT leaders in England and 4 patients (7 teams had used non-financial incentives for engagement, none for adherence)
Classen 2007 (59) *(3)*	None	Analysis of free text answers for team leaders with objections **Aims:** to identify and classify major ethical concerns with money for medication.	Only the 53 of 70 team managers who had concerns
Priebe et al 2010 (60) *(8)*	No trial	25 focus groups **Aims:** to explore attitudes, concerns and opinions of relevant stakeholders	139 participants including 76 mental health staff, 27 patients, 16 carers and 20 other stakeholders eg trust NEDs health economics recruited via CMHTs, AOTs and staff
Staring et al 2010 (42) *(3)*	Staring et al pilot	A short questionnaire **Aims:** to test the feasibility of using financial incentives	All 5 patients, two mothers,

Moran & Priebe 2016 (61) *(n/a see FIAT RCT)*	FIAT	Regression models of trial data comparing adherence, money received and wellbeing **Aims:** to determine whether QOL increase was due to adherence or financial incentives	56 intervention group patients who completed DIALOG subjective QOL scores
Highton-Williamson et al 2015 (62) *(8)*	FIAT	Semistructured interviews at 6 months and 12 months and thematic analysis **Aims:** to explore clinicians' experiences of financial incentives	59 clinicians from the FIAT study
Noordraven et al 2017 (63) *(2)*	MfM	Structured interviews with 2 open questions and 19 statements to rate. **Aims:** to assess "attitudes and ethical considerations of" patients and clinicians in MfM trial	133 patients 97 clinicians (46% nurses)
Noordraven et al 2018 (64) *(n/a see MfM RCT)*	MfM	HoNOS (n=131) and TEQ (n=61) assessments of treatment motivation at 0, 12 and 18 months **Aims:** to assess impact of financial incentives on motivation	Participants from the MfM trial. At 6 months, 66 from intervention and 65 from control. At 18 months 60 and 49 respectively.

Supplement 7: Economic analyses of financial incentives for antipsychotic depot treatment

	Linked study	Included patients	Total health costs at baseline	Physical health costs during intervention	Mental health costs during intervention	Of which MH admissions during intervention	Total health costs during intervention	Social/criminal costs	Conclusion
Henderson et al (in GBP) (65)	FIAT	117/141							97.5% likelihood that "good adherence" can be achieved without these costs exceeding £27,800
Intervention		59	10088 (SD 1059)			3407 (SD 1101)	9350 (SD 1189)		
Control		78	10511 (SD 2004)			5105 (SD 1787)	8651 (SD 1890)		

Noordraven et al 2018 (in Euros) (66)	MfM	133/169	Not stated but "negligible" differences						No overall cost reduction
Intervention		69/		529.6 (SD2241.7)	1062.9 (SD3031.5)	613.3 (SD 2788.7)	1592.5 (SD 3700.7)	248.4 (SD856.2)	
Control		64/		484.0 (SD226.66)	788.8 (SD2379.3)	433.1 (SD 2379.3)	1272.8 (SD 3223.7)	229.3 (SD1477.4)	