Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics: cluster randomised controlled trial

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STUDY QUESTION

Does offering modest financial incentives to patients with psychotic disorders improve adherence to maintenance treatment with antipsychotics?

SUMMARY ANSWER

Offering modest financial incentives is an effective method in improving poor adherence to maintenance treatment with antipsychotics.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Good evidence suggests that financial incentives have a beneficial effect on adherence to a range of healthcare treatments. Adherence to treatment was significantly higher for those receiving financial incentives than those in the control group.

Design

In a cluster randomised controlled trial mental health teams were allocated to the intervention or control arm. Patients from teams in the intervention group were offered £15 (€17; $22) for each depot injection of antipsychotic over a 12 month period (intervals between injections ranging from 1-4 weeks). Clinicians gave the incentives in cash to patients after each injection. Patients from teams in the control condition received treatment as usual.

Participants and setting

Mental health teams providing care for patients with psychotic disorders in the community. Eligible adults were those under the care of the team for at least four months; aged between 18 and 65; with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; poor adherence to long acting treatment with antipsychotics (received ≤75% of prescribed drugs over the four months before screening).

Primary outcome

The primary outcome was the percentage of prescribed depots that patients received in the community within the 12 month trial period.

Main results and the role of chance

73 teams with 141 consenting patients were randomised, and outcomes were assessed for 131 patients (93%). Average baseline adherence was 69% in the intervention group and 67% in the control group. During the 12 month trial period adherence was 85% in the intervention group and 71% in the control group. The adjusted effect estimate was 11.5% (95% confidence interval 3.9% to 19.0%, P=0.003). A secondary outcome was an adherence of ≥95%, which was achieved in 28% of the intervention group and 5% of the control group (adjusted odds ratio 8.21, 95% confidence interval 2.00 to 33.67, P=0.003). Although differences in clinician rated clinical improvement between the groups failed to reach statistical significance, patients in the intervention group had more favourable subjective quality of life ratings (β=0.71, 95% confidence interval 0.26 to 1.15, P=0.002). The number of admissions to hospital and adverse events were low in both groups and did not show substantial differences.

Adherence levels to depot antipsychotics (percentage of prescribed injections that were received)

	Intervention group		Control group	
Period	No of patients	Adherence % (SD)	No of patients	Adherence % (SD)
Baseline	72	69 (16)	55	67 (16)
Intervention	75	85 (15)	56	71 (22)

Bias, confounding, and other reasons for caution

Several protocol violations occurred and data on depot drugs were missing during the baseline or study period. Blinding of clinicians, patients, and researchers was not possible, and less than 50% of the final sample had patient reported outcomes.

Generalisability to other populations

The sample was confined to those patients receiving depot injections so may not be generalisable to those receiving other formulations.

Study funding/potential competing interests

This trial was funded by the National Institute for Health Research Health Technology Assessment programme (project No 07/60/43). ASD received personal fees from Janssen Cilag and Eli Lilly. TB has received lecture fees from Janssen and Otsuka.

Trial registration number

ISRCTN77769281.

Autoimmune, neurological, and venous thromboembolic adverse events after vaccination of adolescent girls with quadrivalent human papillomavirus in Denmark and Sweden: cohort study

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STUDY QUESTION

Is there an increased risk of serious adverse events after immunisation with quadrivalent human papillomavirus (qHPV) vaccine?

SUMMARY ANSWER

Adolescent girls receiving the qHPV vaccine were not at higher risk of a diagnosis of autoimmune, neurological, or venous thromboembolic conditions than those not vaccinated.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Vaccines against HPV have been available since 2006. This study in almost one million adolescent girls found no evidence to support an association between exposure to qHPV vaccine and autoimmune, neurological, or venous thromboembolic adverse events.

Participants and setting

997 585 adolescent girls aged 10-17 in Denmark and Sweden between 2006 and 2010. 296 826 received a total of 696 420 qHPV vaccine doses.

Design

Register based nationwide cohort study. The outcome measure was incidence rate ratio with 95% confidence interval according to qHPV vaccine exposure.

Main results and the role of chance

Among the 53 assessed outcomes, 29 fulfilled the criterion for further analysis (≥5 vaccine exposed cases within the predefined risk periods after vaccination). Whereas the rate ratios for 20 of 23 autoimmune events were not significantly increased, exposure to the qHPV vaccine was significantly associated with Behcet's syndrome, Raynaud's disease, and type 1 diabetes. On further assessment, however, these three associations were weak and not temporally related to vaccine exposure. The rate ratios for the five analysed neurological events were not significantly increased and there were inverse associations with epilepsy and paralysis. There was no association between qHPV vaccine exposure and venous thromboembolism. The findings need to be interpreted in light of the multiple outcomes assessed, as chance could have influenced the significant associations observed in initial analyses.

Bias, confounding, and other reasons for caution

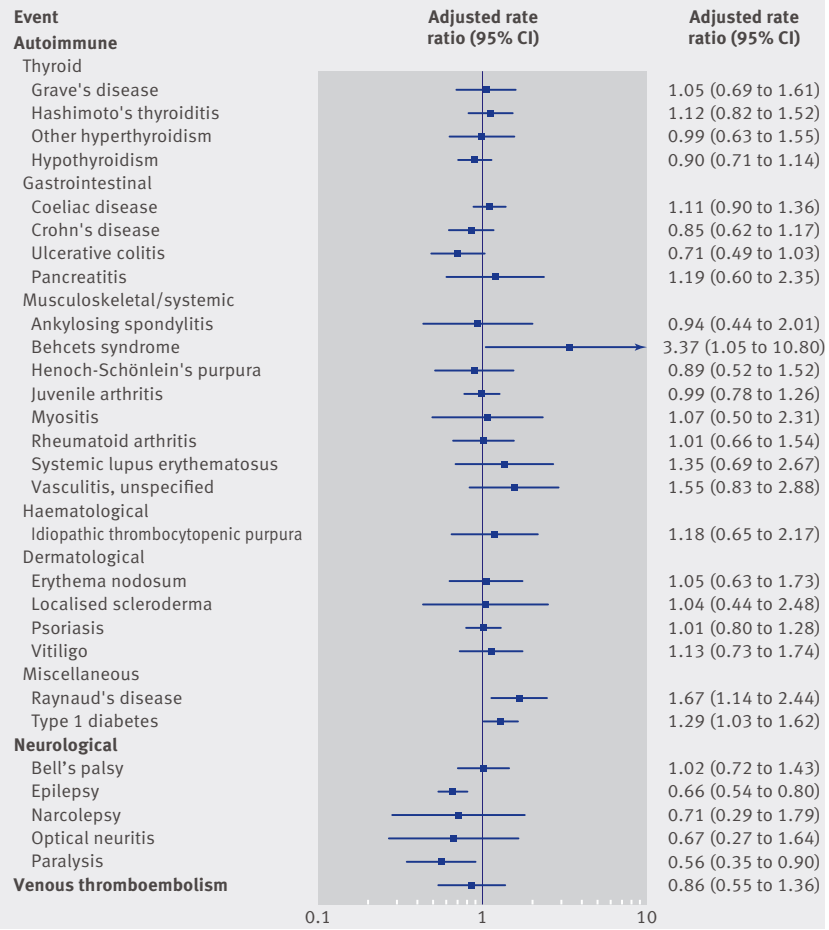
Although this study identified no safety signals for autoimmune, neurological, or venous thromboembolic events after the qHPV vaccine, the findings need to be confirmed. Further monitoring of HPV vaccine safety is warranted, with longer follow-up time and in other populations with increasing coverage.

Generalisability to other populations The results from this study may be generalisable to comparable populations of similar age but not directly extrapolated to adults.

Study funding/potential competing interests

This study was supported by a grant from the Swedish Foundation for Strategic Research and the Danish Medical Research Council. The funders had no role in the study design; the collection, analysis, and interpretation of the data; the writing of the article; and the decision to submit it for publication. All authors are independent from the funding agencies. LAD and PS are and have been involved in other studies with unconditional grants from GlaxoSmithKline, Sanofi Pasteur MSD, and Merck.

Rate ratios are adjusted for country, age in two year intervals, calendar year, and parental country of birth, parental education, and paternal socioeconomic status



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- Clinical Review: Developing role of HPV in cervical cancer prevention (*BMJ* 2013;347:f4781)
- Research: Comparing bivalent and quadrivalent human papillomavirus vaccines: (*BMJ* 2011;343:d5775)
- Observations: Warts and all at last (*BMJ* 2011;343:d7779)

Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management)

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STUDY QUESTION

Does targeting antibiotic use for acute sore throat—according to clinical score or rapid antigen testing used according to clinical score—improve symptom control or antibiotic use compared with delayed antibiotic prescription?

SUMMARY ANSWER

Targeting with a clinical score improves symptoms and reduces antibiotic use. Rapid antigen testing used according to a clinical score provides similar benefits but no clear advantages over clinical score alone.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Antibiotics are still prescribed for most patients attending primary care with acute sore throat. Rapid antigen detection tests and clinical scores are commonly used to target antibiotic use in such patients but there is little robust trial evidence to support their use. Use of clinical score improves reported symptoms and reduces antibiotic use, but use of rapid antigen tests according to a clinical score provides no additional benefit to using a clinical score alone.

Symptom severity, antibiotic use, intention to consult in future (moderately likely or more likely), and reconsultations with sore throat (95% confidence intervals) in patients with sore throat according to randomised group

	Group 1 control (delayed prescription)	Group 2 (clinical score only)	Group 3 (clinical score + rapid antigen test)
Mean severity of sore throat and difficulty swallowing days on days 2-4 (7 point scale: 0 = no problem, 6 as bad as it could be):			
Crude mean (SD)	3.11 (1.49)	2.88 (1.52)	2.83 (1.62)
Adjusted mean difference*	—	−0.33 (−0.64 to −0.02; P=0.04)	−0.30 (−0.61 to 0.004; P=0.05)
Duration of symptoms rated moderately bad or worse (days):			
Median duration (IQR)	5 (3-7)	4 (2-6)	4 (2-7)
Hazard ratio*	1.00	1.30 (1.03 to 1.63; P=0.03)	1.11 (0.88 to 1.40; P=0.37)
Antibiotic use:			
Crude percentage	75/164 (46%)	60/161 (37%)	58/164 (35%)
Risk ratio*	1.00	0.71 (0.50 to 0.95; P=0.02)	0.73 (0.52 to 0.98; P=0.03)
Belief in need to see doctor in future episodes (slightly likely or less):			
Crude percentage	62/163 (38%)	54/155 (35%)	64/161 (40%)
Risk ratio*	—	0.97 (0.71 to 1.27; P=0.85)	1.03 (0.76 to 1.32; P=0.86)
Return within 1 month with sore throat:			
Crude percentage	17/207 (8%)	17/210 (8%)	13/212 (6%)
Risk ratio*†	1.00	0.91 (0.47 to 1.72; P=0.78)	0.74 (0.36 to 1.47; P=0.40)
Return after 1 month with sore throat (mean follow-up 0.73 years):			
Crude percentage	31/207 (15%)	26/210 (12%)	34/211 (16%)
Risk ratio*‡	1.00	0.79 (0.47 to 1.29; P=0.35)	1.06 (0.66 to 1.63; P=0.81)

IQR=interquartile range.
*All models adjusted for baseline symptom severity (of sore throat and difficulty swallowing) and fever during previous 24 hours
†Additionally adjusted for previous antibiotic use.
‡Additionally adjusted for previous attendance with sore throat and duration of follow-up.

Design

Open adaptive pragmatic parallel group randomised controlled trial. During the trial a preliminary streptococcal score (score 1; n=1129) was replaced by a more consistent score (score 2; n=631, features: fever during previous 24 hours; purulence; attends rapidly (within three days); inflamed tonsils; no cough/coryza; acronym FeverPAIN). Patients were randomised to targeted antibiotic use according to delayed antibiotics (the comparator group for analyses), clinical score, or antigen test used according to clinical score.

Participants

Patients aged 3 or over with acute sore throat in primary care (mean age 30).

Primary outcomes

Symptom severity on days two to four (primary outcome), duration of symptoms, and antibiotic use.

Main results and the role of chance

For score 1 there were no significant differences between groups.[t1] For score 2 symptom severity was documented in 80% (168/207 (81%) in the delayed antibiotics group; 168/211 (80%) in the clinical score group; 166/213 (78%) in the antigen test group). Severity was lower in the clinical score group (−0.33, 95% confidence interval −0.64 to −0.02; P=0.04), equivalent to one patient in three rating their sore throat a slight versus moderate problem, with a similar reduction for the antigen test group (−0.30, −0.61 to −0.00; P=0.05). Symptoms rated moderately bad or worse resolved significantly faster in the clinical score group (hazard ratio 1.30, 1.03 to 1.63) but not the antigen test group (1.11, 0.88 to 1.40). In the delayed antibiotics group, 75/164 (46%) used antibiotics. Use of antibiotics in the clinical score group (60/161) was 29% lower (adjusted risk ratio 0.71, 95% confidence interval 0.50 to 0.95; P=0.02) and in the antigen test group (58/164) it was 27% lower (0.73, 0.52 to 0.98; P=0.03).

Harms

There were no significant differences in complications or reconsultations.

Bias, confounding, and other reasons for caution

This is an open trial that used an external generator for the randomisation code. Potential confounders were mostly well distributed between groups; where there were differences (such as fever at baseline) the analysis controlled for these. There was high retention (80%) and an intention to treat analysis was done without imputation. The trial was not powered for potentially important outcomes such as complications.

Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study

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- Editorial: Cytisine, the world's oldest smoking cessation aid (*BMJ* 2013;347:f5198)
- Editorial: Varenicline for smoking cessation (*BMJ* 2012;345:e7547)
- Feature: Electronic cigarettes: medical device or consumer product? (*BMJ* 2012;345:e6417)

STUDY QUESTION

Are patients prescribed the smoking cessation agents varenicline or bupropion at a higher risk of suicidal behaviour than patients prescribed nicotine replacement therapy (NRT)?

SUMMARY ANSWER

There is no evidence of an increased risk of suicidal behaviour with prescribed varenicline or bupropion compared with prescribed NRT.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

There have been ongoing safety concerns about varenicline and bupropion in relation to psychiatric adverse effects including suicide. With a larger sample size than in previous studies, this study included validated outcomes of fatal and non-fatal self harm by using linked data from the Office for National Statistics (ONS) and Hospital Episode Statistics (HES), and applied novel and conventional methods to assess the potential effect of confounding by indication.

Participants and setting

Patients aged 18 years and over, who were prescribed a smoking cessation product between 1 September 2006 and 31 October 2011 in English general practices in the Clinical Practice Research Datalink (CPRD).

Design, size, and duration

From 349 general practices, 81 545 patients were prescribed NRT (68.2%), 6741 bupropion (5.6%), and 31 260 varenicline (26.2%). Primary outcomes were incident episodes of treated depression (as measured by the initiation date of antidepressant therapy) and fatal and non-fatal self harm within three months of first prescription (determined from linkages with ONS mortality data (for suicide) and HES data (for hospital admissions relating to non-fatal self harm)). We undertook Cox multivariable regression models, propensity score matching, and instrumental variable analysis using physicians' prescribing preferences as an instrument.

Primary outcomes at three months in patients prescribed varenicline, bupropion, and NRT

Smoking cessation product	Total person time (person years)	No of events/ No of patients prescribed product	Adjusted model (hazard ratio (95% CI)
Fatal and non-fatal self harm			
NRT	19 196	69/78 407	1
Bupropion	1622	4/6568	0.83 (0.30 to 2.31)
Varenicline	7363	19/30 352	0.88 (0.52 to 1.49)
Treated depression*			
NRT	10 315	799/42 475	1
Bupropion	961	40/3910	0.63 (0.46 to 0.87)
Varenicline	4435	255/18 386	0.75 (0.65 to 0.87)

*Restricted to those with no previous antidepressant use.

Main results and the role of chance

We observed 92 cases of fatal and non-fatal self harm (326.5 events per 100 000 person years) and 1094 primary care records of treated depression (6963.3 per 100 000 person years). Adjusted models in Cox regression analyses accounted for sex; age; previous psychiatric illness or consultation; previous use of psychotropic drugs such as hypnotics, antipsychotics, and antidepressants; previous self harm; socioeconomic position; major chronic illness; number of general practice consultations in the year before the prescription; exposure to the drug before or after 2008; year of first prescription; and previous use of a smoking cessation product. We saw no evidence that people prescribed varenicline had higher risks of fatal or non-fatal self harm or treated depression than those prescribed NRT. We also saw no evidence that people prescribed bupropion had a higher risk of fatal or non-fatal self harm or treated depression than those prescribed NRT. Similar findings were obtained from propensity score methods and instrumental variable analyses.

Bias, confounding, and other reasons for caution

Observational pharmacoepidemiological studies have the potential for confounding by indication. We used three different methods to assess this confounding, including instrumental variable analysis, which attempts to mimic a randomisation process and should result in the equal distribution of measured and unmeasured confounders among the different treatment groups. Because this study was based on recording of prescriptions in primary care, we had no information on products bought over the counter or received from smoking cessation clinics in the United Kingdom's health service.

Generalisability to other populations

The population of the CPRD, including patients from the practices linked to the ONS and HES, is broadly representative of the UK population as a whole, and therefore findings should be generalisable to the UK and similar populations.

Study funding/potential competing interests

This study received support from the Medicines and Healthcare Products Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR) for the submitted work. KHT is funded by a NIHR doctoral fellowship. RMM is a member of the MHRA's independent scientific advisory committee for CPRD research and DG is a member of the MHRA's pharmacovigilance expert advisory group; both receive travel expenses and a fee for attending and preparing for meetings.