OROS-methylphenidate to reduce ADHD symptoms in male prisoners aged 16–25 years: a RCT

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Scientific summary

OROS-methylphenidate for ADHD symptoms in male prisoners

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Scientific summary

Background

The National Institute for Health and Care Excellence and the Scottish Intercollegiate Guidelines Network recommend methylphenidate as the first line in the treatment of attention deficit hyperactivity disorder (ADHD). However, there is uncertainty about the effects in young adult offenders who present with an array of mental health and drug use problems, as these may better explain states of inattentive, overactive and impulsive behaviour or interfere with the treatment response. There was a previous open label trial in young adult offenders with ADHD investigating the effects of osmotic release oral system (OROS)-methylphenidate, an extended release preparation of methylphenidate, which showed significant reductions in ADHD symptoms. A small ($n = 30$) randomised controlled trial of OROS-methylphenidate in a prison population found a large effect, with a standardised mean difference of 2.1 in improvement of ADHD symptoms after 5 weeks of treatment.

Objectives

Primary objective

What is the efficacy of OROS-methylphenidate in reducing inattention and hyperactivity/impulsivity in young male prisoners meeting diagnostic criteria for ADHD [according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5)]?

Secondary objective

What is the efficacy of OROS-methylphenidate in reducing secondary outcomes that are key indicators of behavioural and functional impairments used in the management of young male prisoners in the UK? These include emotional dysregulation, antisocial behaviour in the prison, violent attitudes (a measure linked to aggression) and reports of behaviour from prison staff.

Tertiary objective

Are improvements in secondary behavioural outcomes mediated by improvements in ADHD symptoms or emotional dysregulation?

Methods

Study design

This was designed as a Phase IV, 8-week, parallel-arm, double-blinded, randomised, placebo-controlled trial of OROS-methylphenidate compared with placebo. After 8 weeks of treatment, we compared the two trial arms on outcomes for ADHD symptoms and 13 secondary outcomes.

Setting

Her Majesty's Prison and Young Offender Institution Isis (London, England), a category C prison defined as suitable for prisoners who cannot be trusted in open conditions but who are unlikely to try to escape, and Her Majesty's Young Offender Institution Polmont (Falkirk, Scotland), a holding facility for young offenders in Scotland aged 16–21 years with sentences ranging from 6 months to life.

Participants

Participants were young male prisoners aged 16–25 years who met the DSM-5 criteria for ADHD.

Inclusion criteria

- Male.
- Aged 16–25 years at the time of consent for screening.
- English-speaking.
- Able to provide informed consent.
- Meets the DSM-5 criteria for ADHD.

Exclusion criteria

- Lacked capacity to give informed consent.
- Intelligence quotient of < 60.
- Serious risk of violence to the researcher.
- Current major depression, psychosis, mania or hypomania.
- Past history of bipolar disorder or schizophrenia.
- Medical contraindications to the use of stimulants.
- Drug-seeking behaviour or craving.
- Currently prescribed ADHD medication.

Randomisation

Participants were randomised to 8 weeks of treatment with OROS-methylphenidate or placebo. A total of 200 participants were randomised and allocated in a 1 : 1 ratio to either the drug or placebo, stratified by prison.

Blinding to trial arm

Blinding was maintained for all trial investigators, including the on-site researchers, pharmacy staff and trial manager. The statistical team remained blinded to trial arm allocation until the planned analyses had been completed. Investigator-rated outcome measures were obtained by an assessor who was not involved in the titration procedures.

Trial intervention

Participants received either 18-mg overencapsulated OROS-MPH or placebo capsules.

Titration procedure

Treatment with OROS-methylphenidate or placebo started at one capsule for 1 week. The number of capsules increased weekly over 5 weeks to a maximum dose of four capsules. Titration upwards was stopped if all 18 ADHD symptoms were scored as negligible, if there were unacceptable adverse events or if a participant objected to an increase. A stable dose was maintained for the final 3 weeks.

Primary outcome

The primary end point was the level of ADHD symptoms measured on the investigator-rated Conners' Adult ADHD Rating Scale-Observer at 8 weeks post treatment initiation.

Secondary outcomes

The secondary outcomes addressed questions about the effects of trial treatment on comorbid symptoms and behavioural impairments at 8 weeks. These included measures of emotional dysregulation (using the Wender–Reimherr Adult Attention Deficit Disorder Scale), irritability (using the Affective Reactivity Index-Self), spontaneous mind-wandering (using the Mind Excessively Wandering Scale), attitudes towards violence (using the Maudsley Violence Questionnaire), common psychopathological symptoms (using the Brief Symptom Inventory), overall therapeutic effect (using the Clinical Global Impression Scale), current psychological distress (using the Clinical Outcomes in Routine Evaluation – Outcome Measure), prison officer and educational staff ratings of behaviour (using behaviour report cards from each) and aggression (using Modified Overt Aggression Scale-Prison officer and Modified

Overt Aggression Scale-Educational staff), engagement with the educational programme (i.e. proportion of scheduled sessions attended) and the number of critical incidents reported in the prison records. In total, we analysed 13 secondary outcomes.

Adverse events

At each assessment, common adverse events were captured using a rating scale, and pulse and blood pressure were checked.

Moderators

Baseline scores from the Zanarini Rating Scale for Borderline Personality Disorder, the Childhood Trauma Questionnaire and the Reactive–Proactive Aggression Questionnaire were used as moderator variables.

Mediators

Putative mediators of the number of critical incidents and prison officer-rated behaviour report cards were ADHD symptoms using the Conners' Adult ADHD Rating Scale-Observer hyperactive/impulsivity and inattention subscores, and the Wender–Reimherr Adult Attention Deficit Disorder Scale for emotional dysregulation after 5 weeks.

Sample size calculation

A single-arm, open-label pilot study of OROS-methylphenidate in young prisoners with ADHD showed a mean decrease of 25.0 points on the Conners' Adult ADHD Rating Scale-Observer, with a standard deviation of 9.1 (Asherson P, Evans C, Young S. *A Pilot Study of Concerta XL in Adult Offenders with ADHD*. 2018. URL: www.clinicaltrialsregister.eu/ctr-search/trial/2012-000517-37/results). It was assumed that 20% of this effect might be attributed to the medication. On this basis, this study was powered to detect a standardised effect of $d = 0.55$. For 90% power at 5% significance, 142 participants are required. Inflating for 25% loss to follow-up, a minimum of 190 participants are required, with the final target set at 200.

Statistical analyses

The primary trial analysis was conducted according to a statistical analysis plan developed by the statisticians in collaboration with the Trial Management Group and approved by the Trial Steering Committee. Analyses followed the intention-to-treat principle by including all participants who were randomised. We found that withdrawal from treatment was predictive of missing primary outcome data. To accommodate such a missing-at-random process, we used multiple imputation, including an imputation and analysis step. For the primary outcome, we used a regression model that contained the Conners' Adult ADHD Rating Scale-Observer score at 8 weeks as the dependent variable, and we used trial arm, Conners' Adult ADHD Rating Scale-Observer score at baseline and prison site as explanatory variables. For secondary outcomes, similar generalised linear models were used. Binary secondary outcomes, such as any aggressive events reported by prison staff, were analysed using logistic regression, and count outcomes, such as critical incidents, were analysed using a negative binomial model. For each outcome variable, the imputation step of the procedure followed standard guidelines to achieve congeniality. The primary trial analysis also contained planned moderator and mediator modelling and a set of prespecified sensitivity analyses. After completion of the statistical analysis plan analyses and unblinding of the research team, post hoc analyses were conducted in an attempt to further investigate the findings of this trial.

Results

A total of 1183 prisoners consented to be screened: 585 screened negative on the Barkley ADHD Self-rating Scale and 52 did not meet eligibility criteria. A total of 546 were then considered for further assessment using the Diagnostic Interview for ADHD in Adults 2.0. Of these, 153 did not meet

diagnostic criteria for ADHD, 86 failed to attend the assessment, 28 were excluded because of a high risk of early release and six did not meet one of the other eligibility criteria. This left 273 who met diagnostic criteria for ADHD and were invited to complete consent for the trial, 54 of whom declined the invitation. Of the 219 who signed consent, three were no longer willing to participate, two were assessed after the trial had completed recruitment and 14 did not meet the eligibility criteria, leaving 200 participants who were randomised.

Post-randomisation losses

A total of 184 participants provided primary outcome data at the end of the trial. During the trial, five participants were released and four were deported or transferred to an inaccessible prison. Six participants withdrew from the study entirely. One participant refused trial medication and assessment, but allowed prison record data to be accessed. A total of 24 participants stopped taking the trial medication, but continued with the trial assessments, and a further two were transferred to accessible prisons where the week 8 outcome measures were completed, but medication had to be stopped.

Baseline characteristics

Participants had a mean age of 20.7 years at randomisation; 62.5% were white and 37.5% were from black and minority ethnic groups, which was representative of the prison populations. The mean intelligence quotient score was 89.4. A total of 39.5% had no educational qualifications and most participants left school before the age of 16 years; 66.5% were unemployed. A total of 76.5% had not previously received ADHD medication.

Participants were moderately ill according to the Clinical Global Impression scale. Criteria for coexisting antisocial personality disorder were met by 149 (74.5%) participants, criteria for possible problem alcohol use were met by 149 (74.5%) participants and criteria for illicit drug use were met by 194 (97%) participants. However, additional analyses showed that few participants met the criteria for high risk of problem drug use, with only three reporting problem opiate users, 12 problem cannabis users, four problem cocaine/methamphetamine users and no problem spice users identified who met this criterion. Other mental health disorders were less common, including any type of anxiety disorder [$n = 38$ (19%)], any type of mood disorder [$n = 38$ (19%)] and antisocial personality disorder [149 (74.5%)]. High levels of childhood trauma were reported on the Childhood Trauma Questionnaire.

Missing data handling

Follow-up rates were very high, so the results are not expected to be heavily affected by assumptions regarding the missing data generation process. At week 8, 184 out of 200 participants completed the primary outcome, leaving 16 (8%) participants with missing values. We found that withdrawal from treatment ($p < 0.001$) and employment status ($p = 0.08$) predicted missing primary outcome at 8 weeks. These variables were included as predictors of missing values in the imputation step of the multiple imputation procedure.

Primary outcome measure

There was a greater estimated reduction in the Conners' Adult ADHD Rating Scale-Observer scores in the OROS-methylphenidate arm than in the placebo arm at 8 weeks [difference 0.57, 95% confidence interval −2.41 to 3.56). The effect on the Conners' Adult ADHD Rating Scale-Observer score was very small (0.06) when standardised. The difference was not statistically significant and was smaller than the difference that the trial was powered to detect.

To investigate the responder rate, we applied the operational definition of a responder as a 20% reduction in the baseline Conners' Adult ADHD Rating Scale-Observer score. The percentage of responders was 48.3% for the OROS-methylphenidate arm and 47.9% for the placebo arm.

Secondary outcome measures

Small improvements between the active and placebo arms were seen for the Wender–Reimherr Adult Attention Deficit Disorder Scale, Mind Excessively Wandering Scale, Maudsley Violence Questionnaire, Brief Symptom Inventory and Clinical Global Impression Scale, but deteriorations were seen for the Affective Reactivity Index-Self and Clinical Outcomes in Routine Evaluation – Outcome Measure. None of the secondary outcomes showed improvement differences between the OROS-methylphenidate and placebo arms. In all cases, the standardised difference was very small and non-significant.

Regarding education at baseline, almost all participants had some form of education scheduled. At 8 weeks, the number of education sessions scheduled was similar in the two trials arms (34 for the OROS-methylphenidate arm and 32 for the placebo arm). Of those, the mean proportions attended were 0.80 and 0.82 for the OROS-methylphenidate arm and placebo arm, respectively. The median ratings of aggressive behaviour by education staff were zero (no aggression) at baseline and at 8 weeks in both groups.

Regarding prison officer-rated behaviour at baseline, 50 out of 200 (25%) participants had the minimum score of 6 for the prison officer-rated behaviour report cards and 143 out of 200 (71%) had a score of zero for the Modified Overt Aggression Scale-Prison officer at baseline, indicating low levels of reported aggression. The median scores were similar for both trial arms at baseline and at 8 weeks for both measures, with no significant trial arm differences detected.

Critical incidents were prison records of negative behaviours noted in the 8 weeks immediately before baseline and before the final 8-week time point. At 8 weeks, the median number of critical incidents was the same in both arms, at zero incidents.

Sensitivity analyses

Four sets of sensitivity analyses were conducted to check whether or not the results on the primary outcome were sensitive to collection of outcomes within the specified time window, starting treatment within the specified time, sufficiently high intelligence quotient confirmed by a standardised test or sufficient level of compliance with the treatment. The primary analysis was robust to all assumptions tested in these sensitivity analyses.

Of particular interest was the sensitivity analysis for adherence to trial medication. A total of 83 participants complied with trial medication according to our definition of compliance of taking some or all of their prescribed trial medication on at least 75% of the days for which it was prescribed. Thirty-four participants complied in the OROS-methylphenidate arm, and 49 participants complied in the placebo arm. The subgroup analysis of good compliers estimated a slight trial arm difference for the primary outcome, with a greater reduction in the placebo arm, which was not significant.

Moderator analyses

The following baseline variables were tested as possible moderators of treatment effect: borderline personality disorder (using the Zanarini Rating Scale for Borderline Personality Disorder), childhood trauma (using the Childhood Trauma Questionnaire), and reactive and proactive aggression (using the reactive and proactive subscales of the Reactive–Proactive Aggression Questionnaire). We did not find any evidence for effect modification by any of these variables.

Mediation analyses

We investigated the individual mediating effects of Conners' Adult ADHD Rating Scale-Observer hyperactivity/impulsivity subscores, Conners' Adult ADHD Rating Scale-Observer inattention subscores and Wender–Reimherr Adult Attention Deficit Disorder Scale emotional dysregulation scores as measured at 5 weeks, on the behavioural outcomes (measured using prison officer-rated behaviour report cards and the number of critical incidents) measured at 8 weeks. Mediation effects were negligible and not statistically significant.

Adverse events

Out of 336 adverse events reported at least once per participant, 184 were in the OROS-methylphenidate arm and 152 were in the placebo arm. Only one serious adverse event was reported and categorised as an important medical event unrelated to the trial medication. The numbers of participants reporting specific adverse events were broadly similar in the two trial arms. Exceptions showing greater reported adverse events in the OROS-methylphenidate arm than in the placebo arm were appetite loss (13 vs. 2 participants, respectively), depressed mood (12 vs. 4 participants, respectively) and dizziness (6 vs. 0 participants, respectively).

The Adverse Events Scale was administered at each visit. Symptoms of headache, dryness of mouth, sweating and appetite reduction appeared increased in the OROS-methylphenidate arm, compared with the placebo arm.

Blood pressure and heart rate were recorded at baseline, at each titration point during weeks 1–5 and at week 8. Body mass index (weight/height) was recorded at baseline, week 5 and week 8. There were no notable differences between trial arms at any point in the trial.

Receipt of trial medication

By week 8, 158 participants were continuing treatment (71 in the OROS-methylphenidate arm and 87 in the placebo arm). Participants in the OROS-methylphenidate and placebo arms took the treatment 56.3% and 70.5%, respectively, of the 56 days of the trial.

Conclusions

The trial targeted a sample that could be generalised to other prison populations of young males aged 16–25 years who meet the diagnostic criteria for ADHD, in the UK. The primary and secondary outcomes failed to show statistically significant differences between the OROS-methylphenidate and placebo arms, and any differences between the arms were negligible and not clinically meaningful. No significant safety risks were identified. Additional post hoc analyses found no explanation for the negative finding in this trial.

In conclusion, the study was robustly neutral and does not support the routine treatment of prisoners with ADHD. Future studies should ensure that adequate doses of medication are maintained and investigate non-pharmacological treatments, such as psychoeducation and structured psychosocial support, and early prevention and treatment of ADHD in the community.

Trial registration

This trial is registered as ISRCTN16827947 and EudraCT 2015-004271-78.

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