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Editorial

Methylphenidate for prison inmates with ADHD: yes or no?

Samuele Cortese

Summary

In a double-blind randomised controlled trial by Asherson et al., involving prisoners with attention-deficit hyperactivity disorder (ADHD), the rates of response to osmotic-release oral system methylphenidate (OROS-methylphenidate) and placebo were very similar (~50%). I critically discuss this trial against other international literature, highlighting the key issues in the field in terms of clinical practice and research.

Keywords

Methylphenidate; attention-deficit hyperactivity disorder; prisoner; randomised controlled trial; forensic mental health services.

Samuele Cortese is Professor of Child and Adolescent Psychiatry at the University of Southampton and an Honorary Consultant in child and adolescent psychiatry for Solent NHS Trust, UK. His research aims to inform clinical decision-making, with a particular focus on neurodevelopmental disorders, via advanced evidence-synthesis approaches and analysis of large datasets.

Stimulants, including methylphenidate and amphetamines, are generally recommended as the first-line pharmacological option in current national and international clinical guidelines on the management of attention-deficit hyperactivity disorder (ADHD).[1] More specifically, the 2018–2019 National Institute for Health and Care Excellence (NICE) guidelines recommend methylphenidate as the first-line medication for children aged 5–18, and methylphenidate or lisdexamfetamine as the first option in adults (https://www.nice.org.uk/guidance/ng87). These recommendations are supported by meta-analytic evidence based on randomised controlled trials (RCTs) pointing to a clear separation of methylphenidate from placebo in terms of efficacy (i.e. reduction of ADHD core symptom severity), with an estimated effect size that can be defined as high (s.m.d. = 0.78, 95% CI 0.62–0.93) in children and moderate (s.m.d. = 0.49, 95% CI 0.35–0.64) in adults, based on clinicians' ratings.[1]

As ADHD is estimated to affect at least 20% of prison inmates,[1] gaining insight into the effects of methylphenidate in this specific population is crucial.

The study by Asherson and colleagues

Asherson et al[2] conducted the largest double-blind RCT assessing the effects of methylphenidate in prison inmates with ADHD. The study included 200 participants aged 16–25 from two prisons (one in England and the other in Scotland), 101 randomised to osmotic-release oral system methylphenidate (OROS-methylphenidate) and 99 to placebo. At the study end-point (8 weeks), the authors observed what they defined as – and many in the field would agree – an 'unexpected' finding: there were no significant differences between participants randomised to OROS-methylphenidate and placebo on the primary (ADHD symptom severity on the observer-rated Conners' Adult ADHD Rating Scale, CAARS-O) and on any of the 13 secondary outcomes, including measures of emotion dysregulation, psychopathology, mind-wandering, attitudes towards violence, global impression of therapeutic effect, reports from prison and educational staff and the number of critical incidents and education sessions attended reported in prison records. Also, no significant differences were noted in terms of blood pressure and heart rate, which raises concerns on subjectively reported adherence. The lack of separation of methylphenidate from placebo is at odds with findings from a previous smaller double-blind RCT[3] showing a striking superiority of OROS-methylphenidate (Cohen's $d = 2.17$) in improving ADHD symptom severity on the CAARS-O in a group of 30 prison inmates, aged 21–61, from a high-security prison in Sweden.

Why did methylphenidate not separate from placebo?

Asherson and colleagues were very thorough in assessing possible reasons for these unexpected findings. As only 41.5% of those assigned to OROS-methylphenidate took the medication on at least 75% of the days on which it was prescribed, the authors performed a sensitivity analysis focused on those with high adherence; results did not change substantially. This highlights the challenge of increasing adherence, rather than the concerns about overuse/misuse of methylphenidate, in the prison setting.

Also, as a substantial proportion of participants presented with comorbid mental health conditions or substance use disorder, additional sensitivity analyses were conducted on the subgroup of participants without comorbid mental health or drug and alcohol use disorders, but again, methylphenidate did not separate from placebo. Furthermore, borderline personality disorder, childhood trauma, and reactive and proactive aggression did not significantly moderate the response to the medication. Additionally, the final medication dose, self-reported drug use and diagnostic certainty were not significantly associated with medication response. The Hawthorne effect, i.e., in this case, the possibility that prison inmates could have reported improvements in symptoms to please the assessors, was ruled out by non-significant findings when considering ratings from educational and prison staff.

Should prison inmates with ADHD be treated with methylphenidate?

So, should this large and well-conducted trial lead to the conclusion that response to methylphenidate in prisoners with ADHD is poor and this medication should not be recommended in this population? In my view, the answer is no.

First, it would be unexpected for a single study to drive clinical recommendations. We would need additional double-blind RCTs from other research groups and ideally meta-analytic evidence. It would be important for possible future meta-analyses to assess the effect of substance use disorder and psychiatric comorbidities, which are highly prevalent in this clinical population.

Second, even though RCT is the preferred design to test the effects of an intervention, it does have limitations, and data from RCTs should be considered alongside evidence from observational studies that include outcomes that are rarely included in RCTs. Although observational studies are hampered by the lack of randomisation, a particular design, referred to as within-individual design, has been successfully used in the field of ADHD pharmacotherapy to control for at least some of the bias related to the lack of randomisation. In this design, outcomes of interest are compared during periods on and off medication in the same person, thus controlling for confounding of indication. One such study (summarised in Faraone et al[1]) included 25 656 Swedish individuals, aged 15 or older, with ADHD. Around 54% of them had taken ADHD medications (including methylphenidate, the stimulant most commonly used in Sweden) and 37% had been convicted for at least one crime during follow-up in the study period (2006–2009). The authors found that, compared with non-medication periods, the rate of criminal acts was decreased by 32% (stratified Cox regression hazard ratio 0.68; 95% CI 0.63–0.73) for men and 41% (hazard ratio 0.59; 95% CI 0.50–0.70) for women when on medication. The public health relevance of these data should not be overlooked.

Third, the maximum dose of OROS-methylphenidate used by Asherson and colleagues (72 mg/day; final mean dose 54 mg/day) may not have been enough to effectively tackle ADHD symptoms. It is also possible that the use of illicit drugs by a substantial proportion of the sample may have increased resistance to usual doses of methylphenidate, but this hypothesis should be empirically tested. Of note, currently the British National Formulary (bnf.nice.org.uk/drug/methylphenidate-hydrochloride.html) recommends a maximum of 108 mg/day of OROS-methylphenidate in both adults and children, even though the maximum licensed dose in children in the UK is 54 mg/day. Overall, the issue of possible advantages in using doses beyond the licensed ones, and even beyond the maximum recommended ones, is far from clear and requires rigorous testing in future studies. This seems to be particularly important in relation to the use of ADHD medications in prison inmates.

Fourth, the conclusion that participants in the Asherson et al study had a poor response to methylphenidate does not seem to be accurate. Nearly half of them (48.3%) responded to OROS-methylphenidate, when defining response as a reduction of 20% in the CAARS-O score. Rates of response to OROS-methylphenidate vary across previous RCTs, in part owing to different thresholds to define response (ranging from 20% to 50% reduction, more commonly 30%). The rate of response in the Asherson et al RCT is somehow lower than the figure (~60%) reported in another trial of methylphenidate in adults with ADHD using the same threshold to define response.[4] However, the main problem is that, in the Asherson et al study, the percentage of participants who responded to placebo (47.8%) was very close to the rate of response to OROS-methylphenidate. This is in contrast to previous RCTs in which response to placebo has generally been smaller compared with the rates of response to methylphenidate (and other stimulants). Interestingly, placebo and nocebo effects have been assessed for other agents (e.g. antidepressants) in psychiatry, but are less well understood for ADHD medications. However, a recent meta-analysis[5] of 128 RCTs, encompassing 10 578 children/adolescents and 9175 adults, found that, when considering a rating of 'improved' or 'very much improved' on the Clinical Global Impression (CGI) scales, the pooled estimate of response was 60% for stimulants, 47% for non-stimulants and 25% for placebo. Of note, except for self-ratings of ADHD symptom severity, each of the other scales (clinician-rated, parent-rated and teacher-rated) showed a statistically significant positive correlation between the baseline-to-end-point placebo effect and the baseline-to-end-point active medication effect. These correlations suggest that the active drug effect is accounted for by the improvement specifically due to the active drug plus the improvement related to placebo effects. Therefore, psychosocial contextual factors such as those related to expectation of benefit may contribute to the beneficial effects of the placebo as well as of the active drug. The question then arises as to why the placebo effect was so high in the trial by Asheron and colleagues. The authors thoughtfully speculated that 'in an environment impoverished of meaningful interactions with others in a caring role, there was an enhanced placebo effect contributing to the outcome of this study'. Future RCTs on ADHD medications, in the general population of individuals with ADHD as well as in prison inmates with the disorder, should endeavour to better understand the factors underlying placebo effects.

Conclusions

Like many other studies, the well-conducted RCT by Asherson et al. raises more questions than answers. I believe that the main value of the study, rather the directly and unequivocally informing clinical practice, is to raise the need for additional rigorous studies on the role of the psychosocial context in influencing medication effects.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Samuele Cortese, School of Psychology, Centre for Innovation in Mental Health (CIMH), Faculty of Environmental and Life Sciences, University of Southampton, UK; Solent NHS Trust, Southampton, UK; Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, New York, USA; and Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, UK

Correspondence: Samuele Cortese. Email: samuele.cortese@soton.ac.uk

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References

1 Faraone SV, Banaschewski T, Coghill D, Zheng Y, Biederman J, Bellgrove MA, et al. The World Federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. *Neurosci Biobehav Rev* 2021; **128**: 789–818.

2 Asherson P, Johansson L, Holland R, Fahy T, Forester A, Howitt S, et al. Randomised controlled trial of the short-term effects of OROS-methylphenidate on ADHD symptoms and behavioural outcomes in young male prisoners with attention deficit hyperactivity disorder (CIAO-II). *Br J Psychiatry* 2019; **20**: 663.

3 Ginsberg Y, Lindefors N. Methylphenidate treatment of adult male prison inmates with attention-deficit hyperactivity disorder: randomised double-blind placebo-controlled trial with open-label extension. *Br J Psychiatry* 2012; **200**: 68–73.

4 Biehl SC, Merz CJ, Dresler T, Heupel J, Reichert S, Jacob CP, et al. Increase or decrease of fMRI activity in adult attention deficit/hyperactivity disorder: does it depend on task difficulty? *Int J Neuropsychopharmacol* 2016; **19**(10): pyw049.

5 Faraone SV, Newcorn JH, Cipriani A, Brandeis D, Kaiser A, Hohmann S, et al. Placebo and nocebo responses in randomised, controlled trials of medications for ADHD: a systematic review and meta-analysis. *Mol Psychiatry* 2022; **27**: 212–9.

Psychiatry in Theatre

Anna 'Asja' Lācis (1891–1979): drama, trauma and neuropsychiatry

George Ikkos

Pioneer female theatre director Asja Lācis was born in the Russian Empire's Livonia (Latvia) and gained a degree from neurologist and experimental psychologist Vladimir Bekhterev's (1857–1927) Institute of Psychoneurology in St Petersburg. She had sharp wit and excellent knowledge of Russian, German and French literature and in 1914 moved to Moscow to train at the Kommisarshevski Institute of Theatre Sciences. In 1917 she embraced the Bolshevik revolution and went on to make the most of its early commitment to gender equality and radical innovation in art.

Of interest to psychiatrists is Lācis' work as a children's theatre director. In *A Memoir* she recounts her experiences in Oryol (central Russia), where she was assigned in 1918. Here she found the *besprizorniki*, feral 'abandoned children … black faced boys … gangs of thieves – victims of world war and civil war', who repeatedly ran away from state help. When approached, they taunted and threatened her, but gentle perseverance was rewarded by lively engagement in her children's theatre workshop in a requisitioned aristocratic villa. She curtailed directorial authority, cherished their autonomy, cultivated their sensory acuity and trusted their psychological, moral and aesthetic development through collective production of performances by children for children.

Duties for the People's Commissariat for Enlightenment (Narkompros) took Lācis to Berlin in 1922, where she engaged with the city's flourishing artistic *avant-garde* and collaborated with theatrical genius Bertolt Brecht (1898–1956), who recognised her outstanding acting talent. She married second husband philosopher and theatre director Bernhard Reich (1894–1972), who followed her to the USSR. Daughter Daga's ill health took Lācis to Capri in 1924, where she had an affair with German critic Walter Benjamin (1892–1940). They collaborated intellectually and he acknowledged her profound impact on his work. Infatuated, he pursued her unsuccessfully over a decade in Berlin, Riga and Moscow.

Following a period of exhausting activity, Lācis was admitted to hospital in 1926. Concerned, Benjamin travelled to the USSR and *Moscow Diary*, the vivid memoir of his frustrating visit, refers to her 'mental breakdown'. In a posthumously published Russian-language autobiography *The Red Carnation* she wrote: 'when I got home, I wasn't feeling well: my body listed to one side, I saw everything double, I lost my balance'. She returned to Germany in the late 1920s and had a similar episode in 1929 at a time of emotional turmoil: 'my coordination of movement became disturbed. Benjamin took me to the famous neural surgeon, Kurt Goldstein. "I can't diagnose you in just a few minutes," Goldstein said and invited me to come to his Sanatorium in Frankfurt am Main for treatment'. Migraine? Functional neurological symptoms? Regardless, an attempted cohabitation with Benjamin was marred by constant arguments and lasted only 2 months. Both were moody, intense.

During 1938–1948 Lācis was exiled to a forced labour camp. Following release, she returned to Latvia and developed a theatrical ensemble of international reputation in Valmiera despite the Cold War (1947–1991). Her *Revolutionär im Beruf: Berichte über proletarisches Theater, über Meyerhold, Brecht, Benjamin und Piscator* was translated in French and Italian. She died in Riga aged 88.

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