ACMD

Advisory Council on the Misuse of Drugs

Chair: Professor Les Iversen
Secretary: Zahi Sulaiman
1st Floor (NE), Peel Building
2 Marsham Street
London
SW1P 4DF
Tel: 020 7035 1121
ACMD@homeoffice.gsi.gov.uk

Minister of State for Crime Prevention
Home Office
2 Marsham Street
London
SW1P 4DF

31 March 2015

Dear Minister,

I am writing to recommend that you lay a temporary class drug order (TCDO) pursuant to section 2A of the Misuse of Drugs Act 1971 on a number of methylphenidate-based NPS: ethylphenidate, 3,4-dichloromethylphenidate ('3,4-DCMP'), methylnaphthidate ('HDMP-28'), isopropylphenidate ('IPP' or 'IPPD') and propylphenidate.

Methylphenidate-based NPS

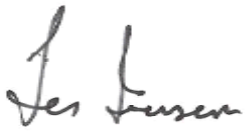
Methylphenidate is a licensed stimulant pharmaceutical and is controlled in the UK as a Class B controlled drug. The methylphenidate-related materials being marketed as NPS have psychoactive effects so similar to the parent compound that they can be expected to present similar risks to users.

Although ethylphenidate is by far the most widely available of this group, other variants are already in the market place. In the short term, to address the widespread availability of methylphenidate-based NPS and the associated problems which are being reported, the ACMD has considered the evidence on methylphenidate-based NPS and recommends control of these NPS by means of a TCDO.

The attached report contains the ACMD's consideration of the evidence concerning methylphenidate-based NPS.

In providing this advice, I would like to convey my thanks to Police Scotland, the National Programme on Substance Abuse Deaths (npSAD) and UK Focal Point.

Yours sincerely,



Professor Les Iversen
ACMD Chair

Cc
Home Secretary
Jane Ellison, Parliamentary Under Secretary of State for Public Health
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Methylphenidate-based NPS: A review of the evidence of use and harm

Background

1. Several materials which are very closely related to methylphenidate but which are uncontrolled are being marketed as NPS (see Annex A). Ethylphenidate is currently the most common, although the effects are similar. These are all materials which had been described in pharmaceutical research literature published in the late ‘90s and early 2000s, which explored structure-activity relationships in chemical variants of methylphenidate.

Methylphenidate

2. Methylphenidate was developed as a central nervous system (CNS) stimulant in the 1960s. It acts primarily as a re-uptake inhibitor for dopamine and norepinephrine and has found widespread application in the treatment of Attention Deficit Hyperactivity Disorder (ADHD), as the symptoms of this condition are believed to be linked to depressed levels of these neurotransmitters. Methylphenidate formulations include tablets containing 5, 10 or 20 mg of the active ingredient and slow-release tablets containing up to 40 mg.

3. Methylphenidate is listed within the 1971 UN Convention on Psychotropic Substances as a Schedule II material. In the UK, it is controlled as a Class B material and as a Schedule 2 substance under the Misuse of Drugs Regulations.

Methylphenidate-based NPS

4. **Ethylphenidate**, (Ethyl 2-phenyl-2-(piperidin-2-yl)acetate) is the simple homologue of methylphenidate. It first appeared as an NPS in the UK in 2011 and has now become one of the most commonly encountered stimulant NPS. Ethylphenidate was confirmed as being on sale on UK-based websites by the UK Forensic Early Warning System (FEWS) in 2011.

5. **3,4-Dichloromethylphenidate (‘3,4-DCMP’)**, the halogenated derivative of methylphenidate appeared in the UK as an NPS in 2013. It is claimed to be several times more potent than the parent compound, with a slower onset of action and longer duration.

6. **Methylnaphthidate (‘HDMP-28’)**, the naphthyl analogue of methylphenidate, became available in the UK as an NPS in late 2014. In addition to acting as a re-uptake inhibitor for dopamine and norepinephrine, it also acts at the serotonin receptor, and is therefore a triple re-uptake inhibitor, reminiscent of

cocaine. It is claimed to have several times the potency of methylphenidate, but with a shorter duration of action.

7. **Isopropylphenidate ('IPP' or 'IPPD')** became available in the UK as an NPS in 2015. In 2013, it had been described in the scientific literature as having a greater effect on dopamine levels than norepinephrine when compared with methylphenidate and as being more resistant to metabolism, resulting in a longer-lasting effect.

8. **Propylphenidate** has also begun to be advertised in the UK as an NPS in 2015. Little is known of its neurochemical properties, but these can be expected to be similar to isopropylphenidate.

Chemistry and Pharmacology

9. Ethylphenidate is the ethyl homologue of methylphenidate.

10. Reports from human users indicate that ethylphenidate is an amphetamine-like stimulant (Police Scotland reports).

11. The neurochemical profiles of ethylphenidate, methylphenidate and cocaine are compared in terms of their ability to inhibit dopamine (DA) uptake, norepinephrine uptake and serotonin (5-HT) uptake in Table 1:

*	Cocaine	±methylphenidate	±ethylphenidate
Dopamine uptake EC_{50} (nM)	250	20	95
Norepinephrine uptake – EC_{50} (nM)	392	51	480
5-HT uptake – EC_{50} (nM)	253	>10,000	>10,000

*Data from, +Willard *et al*., 2007.

Table 1 Uptake inhibition data for cocaine, methylphenidate and ethylphenidate. EC_{50} = drug concentration for 50% inhibition of uptake (smaller values indicate a higher potency).

12. Willard *et al.*, 2007 also reported that both methylphenidate and ethylphenidate stimulated motor activity in mice, with ethylphenidate having a somewhat smaller effect than methylphenidate.

13. Ethylphenidate and methylphenidate are both potent inhibitors of dopamine (DA) uptake, and both inhibit norepinephrine (NE) uptake, although ethylphenidate is almost 5 times less potent against NE than DA, while methylphenidate is less selective (Table 1). Both compounds stimulate motor behaviour in mice, which is consistent with their profiles as psychostimulants.

Prevalence of use

14. Ethylphenidate has been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by the UK (2011, 2013, 2014), Luxembourg (2014), Slovenia (2014), Croatia (2014), Italy (2014), Lithuania (2013), Hungary (2013), France (2013), Denmark (2013), Spain (2013), Finland (2012) and Sweden (2012).

15. Ethylphenidate is widely available on NPS websites and has been routinely identified in FEWS surveys since 2011. Ethylphenidate is sold by Internet suppliers as a replacement for cocaine. It is being marketed both as a single substance ‘research chemical’ and as a component of ‘branded’ products such as ‘Gogaine’, ‘Nopaine’, ‘Fake cocaine’, ‘Banshee Dust’ and ‘Evoke’. The single substance can be purchased as powder, crystals (which command a slightly higher price) or ‘pellets’ (tablets) containing up to 50 mg per tablet.

16. Typical prices of ethylphenidate are of the order of £15 per gram for powder, £20 per gram for ‘crystal’ and £1 per 50 mg tablet. However, significant price reductions are offered for bulk purchases. Ethylphenidate can also be found as a component of branded products: mixed with other stimulants (often MPA) or mixed with serotonin-releasing agents (MDAI, 2-AI).

17. **3,4-Dichloromethylphenidate (‘3,4-DCMP’)** is being marketed as a powder (£35 per gram) or as tablets of 5 or 10 mg (£3 to £5 each).

18. **Methylnaphthidate (‘HDMP-28’)** is being sold as a powder at a cost of £25 per gram and as ‘pellets’ (tablets) containing 10 mg of methylnaphthidate.

19. **Isopropylphenidate (‘IPP’ or ‘IPPD’)** is now available on several UK NPS websites at a cost of around £20 per gram.

20. **Propylphenidate** is being offered by a small number of UK websites at around £20 per gram.

Polysubstance use

21. Samples taken by WEDINOS have found the following substances in combination with Ethylphenidate: Methiopropamine, 5-MeO-DALT, Phenacetin, 2-aminoindane, Phenylethylamine, Ephedrine, Caffeine, Lidocaine, Benzocaine and Mannitol.

22. Consumers of ethylphenidate may not be aware that it is often mixed with a variety of other compounds.

Acute harm

23. As might be expected from a stimulant material which boosts dopamine levels, users report a strong urge to re-dose. One branded formulation, 'Burst', has been reported as causing particular problems in the Edinburgh area, including among injecting drug users, who report re-injecting repeatedly. There has recently been a report of an outbreak of *Staphylococcus aureus* and *Streptococcus pyogenes* infections in this area associated with NPS injecting, which is believed to involve ethylphenidate.

24. The majority of NPS-related presentations to Accident and Emergency in Edinburgh have been associated with use of 'Burst' (March to September 2014). Ethylphenidate-based products are a growing issue in Edinburgh and their use is associated with bizarre and violent behaviour.

25. Police Scotland reported that related practices include: communal injecting, users injecting each other due to rapid onset of effects and loss of fine motor control, needle sharing, injecting in unsanitary environments, high-risk injecting (in the neck and groin), and preparation with citric acid to improve water solubility, which additionally increases the corrosive nature of the substance *in vivo*.

26. These practices are likely to lead to a high risk of bacterial infection and local tissue damage. The injected contents are sometimes not fully solubilised and users will inject without filtering. Police Scotland has seen reports of the solution partially solidifying on injection.

27. Avon and Somerset and Devon and Cornwall Police have had similar reports. Throughout 2014 the market town of Taunton in Somerset has been hit with an epidemic of NPS injecting with all products originating from the one Head shop located in the main High Street. The injecting was happening in open public places including public toilets and users were abandoning their injecting works on the surrounding ground resulting on one occasion with a local 6-year old receiving a needle stick injury. In one clear up day in Taunton town centre,

over 200 needles were recovered. The injecting and resulting anti-social behaviour reached such a point that the communities set up their own Action Group (SWAG) and worked with the Police and Council to reduce the harms being caused. In December 2014 the Police applied for and achieved the closure of the Head shop under anti-social behaviour legislation. The products most commonly injected were Gogaine, Posh and Ching, all of which are Ethylphenidate-based.

28. The National Programme of Substance Abuse Deaths (npSAD) reported 5 cases in 2013-14, where ethylphenidate was found in post mortem toxicology. npSAD also reported 2 cases where ethylphenidate was implicated in the cause of death (2013-14 – see table 2).

Found in post mortem toxicology		**Implicated in cause of death**	
2013	2014	2013	2014
1	4	0	2

Table 2: Ethylphenidate entry on Deaths involving Novel Psychoactive and resurging substances reported to the npSAD.

29. The progress report of the UK Early Warning System (EWS) to the EMCDDA (*January to June 2014*) reported the detection of ethylphenidate.

30. There is one published case report of analytically confirmed acute ethylphenidate toxicity. This was a 26-year-old male who presented with anxiety, paranoia, visual disturbance, and chest pain following use of 500 mg ethylphenidate. On presentation to the Emergency Department (ED), he was restless, tachycardic and hypertensive.

Chronic harm

31. There is currently no data available on the potential for chronic harm associated with ethylphenidate or related analogues. However, with this frequent pattern of injecting, it is likely to lead to an increased risk of hepatitis C or HIV.

International data

32. Ethylphenidate is controlled in Denmark, Austria, Germany, Hungary, Portugal, Sweden, Jersey and Turkey. It is also classified under analogue scheduling in the US and Australia.

Legitimate use

33. The Medicines and Healthcare products Regulatory Agency (MHRA) has not found any evidence of any past or present legitimate medicinal use for methylphenidate-based NPS: ethylphenidate, 3,4-dichloromethylphenidate (‘3,4-DCMP’), methylnaphthidate (‘HDMP-28’), isopropylphenidate (‘IPP’ or ‘IPPD’) and propylphenidate.

Recommendation

34. The ACMD has reviewed the evidence and, pursuant to Section 2B(6) of the Misuse of Drugs Act 1971, it considers that, in the case of ethylphenidate, 3,4-dichloromethylphenidate (‘3,4-DCMP’), methylnaphthidate (‘HDMP-28’), isopropylphenidate (‘IPP’ or ‘IPPD’) and propylphenidate, these NPS are being, or are likely to be, misused, and that misuse is having, or is capable of having, harmful effects. The ACMD therefore recommends that ethylphenidate, 3,4-dichloromethylphenidate (‘3,4-DCMP’), methylnaphthidate (‘HDMP-28’), isopropylphenidate (‘IPP’ or ‘IPPD’) and propylphenidate be subject to a Temporary Class Drug Order (TCDO).

35. The control of these compounds should extend to all stereoisomeric forms, and preparations or products.

36. The Council has found no evidence that ethylphenidate, 3,4-dichloromethylphenidate (‘3,4-DCMP’), methylnaphthidate (‘HDMP-28’), isopropylphenidate (‘IPP’ or ‘IPPD’) and propylphenidate have a recognised medicinal use and therefore advise that they are treated as Schedule 1 drugs in applying the provisions of the Misuse of Drugs Regulations (as amended).

References

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7) *EDND profile of ethylphenidate*
8) Submission received by the ACMD from Police Scotland (Superintendent Matt Richards and Sergeant Neil Wilson).
9) Submission received from Avon and Somerset Police
10) Casale J.J., Hays, P.A., *Ethylphenidate: An Analytical Profile: Microgram Journal, 8(2) 58-61*
11) Willard, R.L., Middaugh, L.D., Zhu, H.B., Patrick, K.S., *Methylphenidate and its ethanol transesterification metabolite ethylphenidate: brain disposition, monoamine transporters and motor activity*. Behavioural Pharmacology 2007 (18) 39-51
12) Report from the National Programme on Substance Abuse Deaths (npSAD) to ACMD on deaths involving novel psychoactive and resurging substances.
13) Submission received by the ACMD from Public Health Wales on WEDINOS information on ethylphenidate.
14) Bright GM. *Abuse of medications employed for the treatment of ADHD: results from a large scale community survey.* Medscape J Med, 2008, 10, 111.
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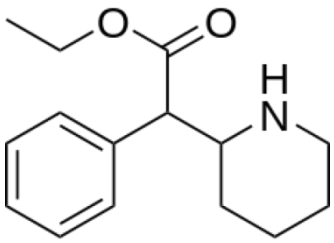
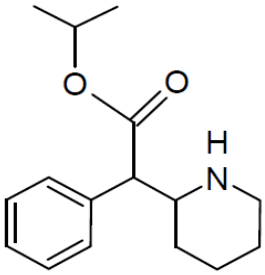
Annex A - Structures of Compounds recommended for control under a TCDO



Ethylphenidate



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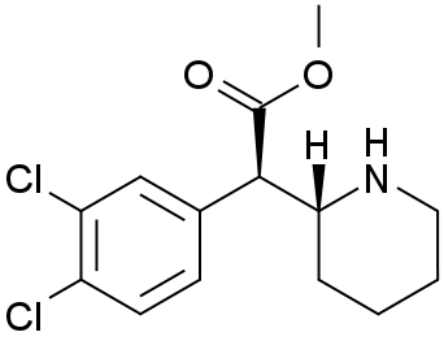
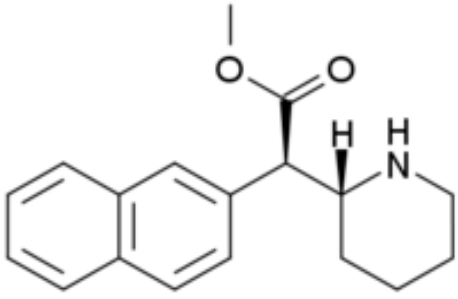
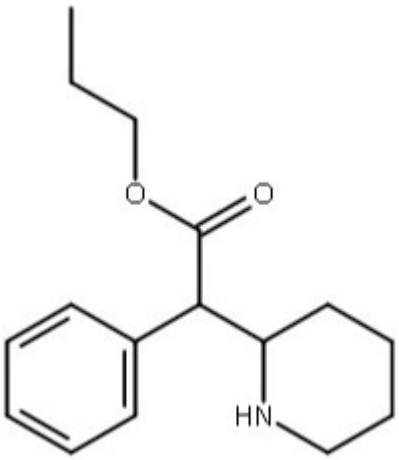


3,4-Dichloromethylphenidate



Methylnaphthidate ('HDMP-28')



Propylphenidate