ACMD

Advisory Council on the Misuse of Drugs

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Rt Hon Chris Philp MP
Minister for Crime, Policing and Fire
2 Marsham Street
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27th March 2024

Dear Minister,

RE: ACMD Report – 'Acyl Piperazine Opioids, Including 2-Methyl-AP-237'

Thank you for your letter of 19th June 2023, where you requested the Advisory Council on the Misuse of Drugs (ACMD) to review the harms and consider control of 2-methyl-AP-237. This was obliged following the 66th session of the United Nations Commission on Narcotic Drugs (CND), where 2-methyl-AP-237 was added to the relevant Schedule 1 of the Single Convention on Narcotic Drugs of 1961.

The ACMD is pleased to enclose its report which considers the harms and control of 2-methyl-AP-237 and closely associated acyl piperazine opioids. The report includes recommendations on appropriate domestic controls under the Misuse of Drugs Act 1971, the 2001 Regulations and the Misuse of Drugs (Designation) Order 2015 following a thorough review of the evidence available. The ACMD is grateful to national and international experts who provided their expertise to this review.

The following conclusions were reached after review of acyl piperazine opioids by the ACMD Working Group:

1. There is a substantial risk that the recent Taliban ban on growing opium poppy for heroin production in Afghanistan will result in an increase in the appearance of new synthetic opioids, such as the acyl piperazines, in the UK illicit drug market.

2. Acyl piperazines are μ opioid receptor agonists that penetrate the central nervous system. They are therefore likely to cause dose-dependent adverse effects, including potentially fatal respiratory depression.

3. Repeated use of acyl piperazine opioids are likely to display abuse liability and have the potential for addiction and dependence, similar to that of heroin and synthetic opioids under international control.

4. In the UK, the involvement of acyl piperazines in non-fatal overdose cases may not yet be recognised because detailed sample analysis is not a component of standard clinical care. Similarly, the association of acyl piperazines in fatal drug overdose cases may be missed if the presence of these drugs is not tested for routinely.

5. The potential emergence of these potent opioid agonists in the UK demonstrates the importance of a fully functioning UK-wide forensic early warning system.

6. In some instances, the opioid antagonist naloxone has been used and demonstrated subsequent clinical improvement. This is consistent with experimental evidence, indicating that it antagonises the behavioural effects of acyl piperazine opioids, as it does those of established opioids.

7. The ACMD has reviewed the current evidence available and considered four options for control in the report, including listing compounds by name and generic controls. Specifically listing currently identified compounds for control is the simpler approach, but risks being overtaken in the future by the development of further variants, an observation seen among other families of novel psychoactive substances (NPS). The acyl piperazine compounds that have been identified are as follows:

   (i) AP-237 (bucinnazine), 2-methyl-AP-237, para-methyl-AP-237
   (ii) AP-238
   (iii) Azaprocin, para-nitroazaprocin

8. The ACMD advises that control of 2-methyl-AP-237 and closely related acyl piperazine compounds via the Misuse of Drugs Act 1971 is necessary. Due to the likelihood of further increases in their prevalence and the potential health and social harms associated with specific acyl piperazines, listing in Class A is recommended. In addition, listing in Schedule 1 of the Misuse of Drugs Regulations is recommended, given that 2-methyl-AP-237 and closely related acyl piperazine compounds have no medicinal use in the UK. AP-237 is licensed as a medicine in China so, following listing in Schedule 1, those legitimately prescribed AP-237 in that country would need an appropriate license to bring it into the UK.

9. The risk that substituted acyl piperazine compounds, other than those listed in paragraph 7 above, may be developed, and misused in the UK is unknown. In the absence of a generic control, these new compounds would not be classified under the Misuse of Drugs Act 1971, but examples with

demonstrated psychoactive activity would be captured by the Psychoactive Substances Act 2016.

10. The ACMD consulted with an external stakeholder to check the proposed generic definition against a comprehensive chemical database, to assess the scope and likely impact of the statement. The returned hit rate result from the substructure search was minimal, suggesting that the potential impact and risk of this proposed generic causing any unintended impact on the pharmaceutical and chemical industry is likely to be low. Nevertheless, the Home Office would need to undertake a thorough consultation with the research community and industry stakeholders, should the generic definition be introduced.

Based on the evidence available, the ACMD has made the following recommendations:

Recommendation 1

The following named compounds which have appeared on the international illicit drug scene, should be added to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids.

As these materials have no medicinal use in the UK, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, to which Section 7(4) of the Misuse of Drugs Act 1971 applies. The control of the compounds should extend to include any stereoisomeric forms, any salts of such compounds and any preparation or product containing such compounds.

(i) 2-Methyl-AP-237 (1-[2-methyl-4-[2E]-3-phenyl-2-propen-1-yl]-1-piperazinyl-1-butanone)
(ii) AP-237 (1-[4-([2E]-3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) (bucinnazine)
(iii) para-methyl-AP-237 (1-[4-[2E]-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl-1-butanone)
(iv) AP-238 (1-[2,6-dimethyl-4-[2E]-3-phenyl-2-propen-1-yl]-1-piperazinyl-1-propanone)

Leads: Home Office

Measure of outcome: The inclusion of the listed compounds in Class A of the Misuse of Drugs Act 1971, Schedule 1 of the Misuse of Drugs Regulations 2001 and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001.

Recommendation 2

Consistent with the classification of other potent opioids, the following compounds should be added to Class A of the Misuse of Drugs Act 1971 as a short-term approach, due to their potencies as μ agonists, relative ease of synthesis and potential to become drugs of misuse.

As these materials have no medicinal use in the UK, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, to which Section 7(4) of the Misuse of Drugs Act 1971 applies.

(i) Azaprocin (1-[3-[(E)-3-phenyl-2-propen-1-yl]-3,8-diazabicyclo[3.2.1]octan-8-yl]propan-1-one)
(ii) para-nitroazaprocin (1-[3-[(E)-3-(4-nitrophenyl)-2-propen-1-yl]-3,8-diazobicyclo[3.2.1]octan-8-yl)propan-1-one)

Leads: Home Office

Measure of outcome: The inclusion of the listed compounds in Class A of the Misuse of Drugs Act 1971, Schedule 1 of the Misuse of Drugs Regulations 2001, and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001.

Recommendation 3

The ACMD recommends that a consultation should be undertaken with stakeholders, including academia and the chemical and pharmaceutical industries on the introduction of a generic control to cover 2-methyl-AP-237-related variants, as new examples may be encountered and could present a serious risk of harm.

Following this consultation, materials covered by the generic should be added to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids.

As these materials have no medicinal use in the UK, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001, to which 7(4) of the Misuse of Drugs Act 1971 applies.

The proposed wording for the generic for addition to the Misuse of Drugs Act is as follows:

*AP-237 (bucinnazine) (*1-[4-([2E]-3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone*) and any compound structurally derived from bucinnazine by modification in any of the following ways:*

(i) By substitution to any extent by methyl in the piperazine or phenyl rings.

(ii) By replacement of the butyryl group by another acyl group containing three, four or five carbon atoms.
(iii) By substitution in the phenyl ring by a nitro group.
(iv) By addition of an ethylenic bridge across the piperazine ring

Leads: Home Office.

Measure of outcome: The inclusion of the generic definition in the Misuse of Drugs Act 1971, following appropriate consultation in addition to Schedule 1 of the Misuse of Drugs Regulations 2001 and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015.

Recommendation 4

Information should be provided in an appropriate format to the general public, including people vulnerable to drug related harms (such as through Frank) and to harm reduction services on the potential harms that acyl piperazines, such as 2-methy-AP-237, might cause if they become available on the illicit drug markets in the UK. This should include information on the potential health effects.

Leads: UK Health Security Agency (UKHSA), Office for Health Improvement and Disparities (OHID), Public Health Wales, Public Health Scotland, the Department of Health Northern Ireland and the Association of the Directors of Public Health.

Measure of outcome: Readily accessible information is available for the general public, including people vulnerable to drug-related harms, their families and the wider public.

Recommendation 5

In the view of the highly dynamic synthetic opioids landscape in the UK and the associated risks they present, responsible agencies in the devolved administrations should monitor for the appearance of acyl piperazines and other emerging new synthetic opioids in the opioid market across the UK. Adequate resources should be provided to facilitate the analysis of seized materials or submitted drug samples thought to contain opioids, as well as the analysis of patient toxicology and postmortem samples. These data should be collected, collated, and monitored by the relevant public health agencies in the UK and reviewed in a consistent and methodical manner by the UK Government, for example the newly established Synthetic Opioid Taskforce and the Early Warning System. To encourage ongoing collection of data, information about compounds appearing in the UK should be fed back to coroners / procurators fiscal and toxicology laboratories with, where necessary, information about analytical methods and access to appropriate analytical standards.

Leads: Office for Health Improvement and Disparities, Public Health Wales, Public Health Scotland, The Crown Office and Procurator Fiscal Service (COPFS), Public

Health Agency Northern Ireland, National Crime Agency, Home Office, and the Ministry of Justice.

Measure of outcome: Information on substances used to augment the UK opioid market provided to the ACMD by Government (Synthetic Opioid Taskforce) and Home Office.

We would welcome the opportunity to discuss this report in due course.

Yours sincerely,

Professor Owen Bowden-Jones

Chair of the ACMD

Professor Graeme Henderson

Acyl Piperazine Opioids Working Group Chair