

ACMD

Advisory Council on the Misuse of Drugs

Novel Benzodiazepines

A review of the evidence of use and harms of Novel Benzodiazepines

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1. Introduction

- 1.1. The ACMD reviewed etizolam and a group of previously uncontrolled benzodiazepines in December 2016, prompted by concerns of the abuse potential of etizolam and its involvement in several deaths across the UK [ACMD, 2016a]. That report recommended that etizolam and 15 other previously uncontrolled benzodiazepines (listed in Annex A) should be controlled under Class C of the Misuse of Drugs Act 1971 (MDA) and placed under Schedule 1 of the Misuse of Drugs Regulations 2001 (MDR) [ACMD, 2016b]. These controls came into force in May 2017.
- 1.2. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) collates information about novel psychoactive substances identified from participating countries in seizures, test purchasing and forensic testing, and records this information on the European Database on New Drugs (EDND). Since the publication of the ACMD (2016) report there have been notifications of 9 benzodiazepines detected in seizures across Europe and reported to the EMCDDA, and the ACMD have identified a further 4 benzodiazepines listed on the EDND. These 13 benzodiazepines are not currently classified under the MDA. Although some of these compounds were originally developed as medicines in the 1960s and 1970s and some are currently licensed medicines in other countries, they are considered to be novel psychoactive substances in the context of drug misuse.
- 1.3. This report examines the UK prevalence and available evidence of harm of these 13 benzodiazepines and makes recommendations about inclusion of some of these substances in the MDA and MDR. For the purposes of this report, the term *novel benzodiazepines* refers to this list of 13 substances.
- 1.4. Limited information is available about the health and social harms of newly emerging benzodiazepines, although in view of their closely related chemical structure and pharmacology, these are likely to be similar to those of other established benzodiazepines. Some of the newer versions are highly potent with the potential of producing harm at low dose. This report therefore includes a summary of the evidence of health and social harms associated with benzodiazepine misuse in general.

2. Legal control of benzodiazepines

- 2.1. In the UK, benzodiazepines licensed as medicines are largely controlled as Class C drugs under the MDA and listed in Schedule 4 Part 1 of the MDR. Temazepam, flunitrazepam and midazolam are regulated under Schedule 3 of the MDR because of their misuse potential and increased risk of diversion. Benzodiazepines that are not licensed as medicines have been controlled as

Class C drugs and are listed in either Schedule 1 (no recognised medicinal use in the UK) or Schedule 4 part 1 of the MDR as detailed in Annex A.

- 2.2. Benzodiazepines that are not currently classified under the MDA are likely to be captured by the Psychoactive Substances Act 2016 (PSA). Benzodiazepines that are licensed as medicines internationally but not in the UK may be regarded as medicinal products for the purpose of the 'medicinal products' exemption to the PSA. For this exemption to apply, the product must meet the definition of medicinal product in Regulation 2 of the Human Medicines Regulations 2012. The Medicines and Healthcare products Regulatory Agency (MHRA), which is an executive agency of the Department of Health and Social Care (DHSC), decides what satisfies the definition of a medicinal product for the purposes of the 2012 Regulations.
- 2.3. In the UK, benzodiazepines are controlled under the MDA by the listing of individual substances – rather than by the use of a generic definition. The ACMD believe this remains an appropriate model of control as the analogue variation of benzodiazepines is proportionally low compared to other drugs groups such as synthetic cannabinoids or fentanyl. As a result of the infrequent rate with which illicit use of benzodiazepines is displaced to novel analogues, substances that become problematic can be addressed individually. Germany has developed a generic control for benzodiazepines [Federal Republic of Germany, 2019] due to concerns regarding a significant increase in seizures of 'designer' benzodiazepines across Europe in 2016. Of particular concern was the extreme potency of some of these new compounds. For example, flubromazolam (one of the 16 benzodiazepines that were controlled in the UK in 2017) is effective at doses well below 1 mg.
- 2.4. The German generic definition was designed to ensure all established and novel analogues of this drug group were brought within the scope of their Narcotics Act. Their generic definition is based on the use of a series of structural diagrams of 16 different benzodiazepine cores, together with a defined range of modifications, coupled with a limit on the molecular weight of the materials controlled. This allows control of specific benzodiazepine sub-groups (i.e. 1,4-benzodiazepines, 1,5-benzodiazepines, lopraxolam derivatives, etc.) while limiting control to the small, pharmacologically active, analogues. It would be challenging to implement this type of expansive generic definition within UK legislation, where only descriptive text is used and the clarity of the definition would be lost in rendering the many core structural diagrams into text. Instead, the UK can utilise legislation such as the PSA - which prohibits the manufacture and supply of all psychoactive substances - to enable general benzodiazepine control. For this reason, the approach of utilising a generic definition is not recommended by the ACMD to encompass benzodiazepines under the MDA.

- 2.5. At the international level, the World Health Organization's Expert Committee on Drug Dependence (WHO ECDD) continues to review particular emerging compounds of concern. At their 42nd meeting in October 2019 [WHO 2019b], WHO ECDD recommended that flualprazolam (currently not classified under the MDA or scheduled under the MDR, but considered in this report) and etizolam (currently Class C of the MDA and Schedule 1 or the MDR) should be brought under international control by the addition of these compounds to Schedule IV of the 1971 Convention on Psychotropic Substances. The United Nations Commission on Narcotic Drugs (CND) voted in favour of the WHO ECDD recommendation at their 63rd Session held in March 2020. As a result, both substances have now been added to Schedule IV of the 1971 Convention on Psychotropic Substances, where the benzodiazepines alprazolam and triazolam are currently also scheduled [CND, 2020].

3. Benzodiazepine chemistry and pharmacology

- 3.1. Benzodiazepines are sedative and anxiolytic drugs that have been in clinical use since the 1960s for the treatment of anxiety, insomnia, muscle spasms, spasticity and epilepsy. They are also used as premedication for anaesthesia and as adjuncts for withdrawal from alcohol and other substances [Farias *et al*, 2017; Hayhoe & Lee-Davey, 2018; Moosmann & Auwärter, 2018]. Commonly prescribed benzodiazepines include diazepam, temazepam, chlordiazepoxide and lorazepam - but there are many other benzodiazepines licensed as medicines in the UK (Annex A) and further examples are licensed in other countries (e.g. etizolam, phenazepam).
- 3.2. Benzodiazepines work as central nervous system depressants by enhancing the actions of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain and spinal cord. This neurotransmitter has an inhibitory ('calming') effect on many functions of the brain, inducing sedation and sleep [EMCDDA, 2018]. The (GABA)-A receptor, a ligand-gated chloride-selective ion channel, modulates the action of GABA. Benzodiazepines act as positive allosteric modulators to the (GABA)-A receptor, meaning they bind to the receptor to amplify any effects [Griffin *et al*, 2013].
- 3.3. In the brain there are multiple types of GABA-A receptors, made up from different combinations of protein subunits and benzodiazepines can vary in pharmacological effect depending on the type of GABA-A receptors they interact with. Sedation and sleep induction result primarily from interactions with GABA-A receptors containing the $\alpha 1$ subunit [McKernan *et al*, 2000]. The anxiolytic effects appear to be mediated through the $\alpha 2$ and $\alpha 3$ subunit-containing receptors [Atack, 2010], whilst interaction with the $\alpha 5$ subunit may contribute to improvement of mood and cognition [Jacob, 2019].

- 3.4. The diversity in chemical structures of benzodiazepines affects their lipid solubility, and this affects how they are handled in the body, including the duration of their psychoactive effects. [EMCDDA, 2018]. Benzodiazepines can be categorised as:
- short-acting agents, with half-lives of less than 6 hours (e.g. midazolam, triazolam);
 - intermediate-acting agents, with half-lives of 6 to 24 hours (e.g. temazepam, alprazolam);
 - long-acting agents, with half-lives of over 24 hours (e.g. diazepam).
- 3.5. Adverse effects of benzodiazepines include drowsiness, psychomotor impairment, unsteadiness and incoordination, memory loss and confusion. Higher doses may cause loss of consciousness and respiratory depression, especially if used in combination with alcohol or other sedatives [White & Irvine, 1999; CDC, 2014]. Toxicity arising from overdose or use in combination with other central nervous system depressants is a relatively frequent Emergency Department presentation [EMCDDA, 2018]. Death arising from the use of benzodiazepines is thought to be uncommon in otherwise healthy people, unless other drugs or alcohol have also been used. Data provided by the National Programme on Substance Abuse Deaths (NPSAD) showed that in England between 2006 and 2015 there were 5740 benzodiazepine related deaths. Of these 5740 deaths, 207 (3.6%) recorded benzodiazepines as the only compounds implicated in the cause of death.
- 3.6. Benzodiazepine use is common in people who use opioids, such as heroin, and this combination is particularly hazardous, with each drug exacerbating the respiratory depression caused by the other, resulting in an increased risk of death. There is a reversal agent for benzodiazepine toxicity, flumazenil, which acts as a competitive antagonist at the benzodiazepine-binding site on the GABA-A receptor. Use of this can improve consciousness level but may precipitate seizures, especially if drugs that lower seizure threshold have also been taken [Seger, 2004; An & Godwin, 2016].

4. Benzodiazepine misuse

- 4.1. Medicinal use of benzodiazepines became popular by the mid-1970s, but evidence subsequently emerged of benzodiazepine tolerance and dependence and the development of severe withdrawal symptoms after use for more than a few weeks [Hayhoe & Lee-Davey, 2018; PHE, 2019a]. Subsequently, the potential for benzodiazepine misuse became increasingly recognised [Moosmann & Auwärter, 2018].

- 4.2. Benzodiazepines can be misused in a variety of ways, often in the context of polydrug use [Schmitz, 2016]. They may be used with other sedatives to potentiate their effects, or they may be used to ‘come down’ after stimulant use. They are also sometimes used by injection to produce heroin-like effects, and benzodiazepines such as alprazolam (‘Xanax’) are sometimes found mixed into heroin as ‘extenders’.
- 4.3. In the past, misuse has arisen from diversion of medicinal benzodiazepines [Hayhoe & Lee-Davey, 2018], but synthetic processes for benzodiazepine manufacture are now freely available, and many illicitly manufactured benzodiazepines have been encountered in recent years [Moosmann *et al*, 2015]. These can evade local (national) drug misuse legislation, at least initially, and can often be bought in bulk, usually via the internet.
- 4.4. Prescribing of benzodiazepines by General Practitioners in the UK has been discouraged and has fallen progressively in recent years. Prescription items issued in primary care in England fell from 16.3 million in 2015-16 to 14.9 million in 2018-19 [NHSBA, 2020]. Following their launch, there was increased prescribing of the related so-called ‘Z-drugs’ (zopiclone, zolpidem and zaleplon) [Hayhoe & Lee-Davey, 2018] but this started to reverse in 2014. In 2017-18, there were 1.4 million adults in England and Wales who received one or more benzodiazepine prescriptions. Of those prescribed a benzodiazepine in 2015, 5% received this continuously for at least 12 months and 120,000 people received continuous benzodiazepine prescribing between April 2015 and March 2018. Long-term benzodiazepine use was associated with low income and the use of benzodiazepines that are short-acting agents [PHE, 2019a].
- 4.5. In contrast to the prescribing data, deaths where a benzodiazepine was implicated have increased over the past decade across the UK (Figure 1), consistent with an increased role of illicitly manufactured benzodiazepines. There is evidence of this in Scotland, where ‘street’ or unlicensed benzodiazepines were involved in 85% of the 792 deaths in 2018 where a benzodiazepine was implicated, while medicinal ‘prescribed’ benzodiazepines were reported in only 30% [NRS, 2019].

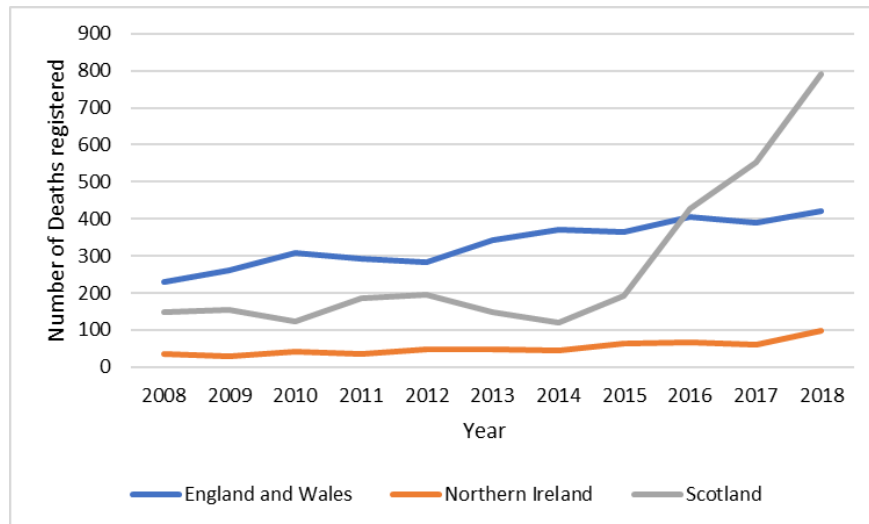


Figure 1: Number of Benzodiazepine-related deaths by year of death registration for England and Wales [ONS, 2019], Northern Ireland [NISRA, 2020] and Scotland [NRS, 2019]. The ONS and NISRA definition of benzodiazepine-related death refers to death where any benzodiazepine was mentioned on the death certificate. The NRS definition of Benzodiazepine-related death covers deaths which any benzodiazepine was implicated in, or which potentially contributed to the cause of death.

- 4.6. Benzodiazepine misuse is more common in those with underlying medical or psychiatric conditions (including anxiety, panic disorder or agoraphobia, chronic sleep disorder, co-morbid psychiatric disorders and substance use disorders [Guina & Merrill, 2018]), and people with lower educational or socio-economic status are also at increased risk of misuse. A systematic review in the US found that women were more likely to display stronger associations between psychiatric distress and benzodiazepine misuse [Votaw *et al*, 2019].
- 4.7. Younger adults (18-29 years) [Kurtz, 2011; 2017] often source and misuse legally prescribed benzodiazepines and may also purchase illegally obtained benzodiazepines and their analogues. The under-18 substance misuse treatment statistics for England in 2018-19 demonstrated a 53% increase in young people reporting a problem with benzodiazepines than reported in 2017-18 and a 3-fold increase against what was reported in 2016-17 [PHE, 2019b]. A recent study found that young people who obtained benzodiazepines from multiple sources, legal and illegal, were also more likely to have a substance use disorder [McCabe *et al.*, 2018].

Benzodiazepine use with opioids

- 4.8. Individuals with concomitant opioid disorders report using benzodiazepines to enhance the effects of the opioid-based drug and this in turn is a strong predictor of a more severe polysubstance use problem (including more harmful patterns of use of benzodiazepines) [Vogel *et al*, 2013].

Benzodiazepines may also be used to combat the effects of opioid withdrawal [Stein *et al*, 2016; Vogel *et al*, 2013]. Overdoses associated with the ingestion of benzodiazepines are more likely to occur with concomitant use of opioids. Results from two studies which considered overdose in people with opioid use disorders and injecting use highlighted that benzodiazepine use was associated with higher rates of mortality, including overdose deaths [Pavarin, 2015; Riley *et al*, 2016]. An increased risk of mortality has also been identified in patients with concurrent opioid and benzodiazepine prescriptions [Sun *et al*, 2017]. Furthermore, patients taking a combination of prescribed opioids and benzodiazepines were found to take higher opioid doses and for longer periods [Kay *et al*, 2019].

Social harms of benzodiazepine use

- 4.9. Social harms and harms to others associated with benzodiazepine use include criminal activity, aggression and violence, risk-taking behaviours, suicide ideation/attempts and concurrent substance use disorders.
- 4.10. Benzodiazepines can cause paradoxical reactions such as disinhibition, excitement, irritability, hostility and violence, arguments and inappropriate sexual behaviour. Whilst all benzodiazepines have the propensity to cause aggressive behavioural reactions, there is evidence that alprazolam is of particular concern [Jones *et al*, 2011; Albrecht *et al*, 2014]. Several studies have found that individuals who use alcohol and alprazolam can show increased signs of aggression and anger compared to those who use the substances individually. Whilst the drugs may induce increased feelings of relaxation, they also decrease an individual's ability to regulate their feelings and behaviour and may increase impulsivity. However, this may depend on the proportions of alcohol and drug ingested. Three of the novel benzodiazepines considered in more detail in this report (flualprazolam, flunitrazolam and clobromazolam) are structurally related to alprazolam.
- 4.11. Criminal activity associated with benzodiazepine usage includes offences against the person, sexual offences and burglary, and the risk is increased for highly potent substances. Qualitative studies have highlighted that some perpetrators reported that using benzodiazepines lowered their inhibitions and increased their self-confidence prior to the committing of offences. Supply of such materials from illicit manufacturing facilities may also lead to unpredictable dosages and unintended overdosing [Votaw *et al*, 2019].
- 4.12. In a Norwegian study, which considered blood concentrations of 'designer' benzodiazepines in a population of drugged drivers and other offenders, blood results indicated the presence of one or more designer benzodiazepines

(clonazolam, diclazepam, flubromazepam, flubromazolam or pyrazolam) in 77 cases over 3 years [Høiseth *et al*, 2016].

Suicide

- 4.13. There is a strong correlation between benzodiazepine use and suicide ideation in general populations [Schepis *et al*, 2018b] and sub-populations, for example adolescents [Juan *et al*, 2015] and those with alcohol dependence [Presuss *et al*, 2003] or opioid use disorders [Wines *et al*, 2004; Backmund *et al*, 2011]. Analysis of US general population data demonstrated that those with concomitant misuse of a benzodiazepine with another drug reported a higher rate of suicide ideation than reported for those with singular drug misuse problems [Schepis *et al*, 2018a]. Benzodiazepine intoxication, high-dose prescription of benzodiazepines and a diagnosis of depression are also considered significant risk factors in reported and completed suicides.

5. Prevalence and harm summaries of Novel Benzodiazepines

This section summarises the available evidence on pharmacology, identifications in the UK and reported evidence of harm for 13 benzodiazepines that have been notified to the EMCDDA but are currently not classified under the MDA.

The majority of these novel benzodiazepines are likely to have commensurate harms to benzodiazepines controlled under the MDA, as many are structurally related to previously controlled benzodiazepines. Most changes in the chemical structure involve either the substitution of a halogen atom with a different halogen or the addition of an extra halogen atom. In this text, substances in italics are benzodiazepines that are already controlled as Class C compounds under the MDA (listed also in Annex A). The chemical structures of the novel benzodiazepines discussed in this section are shown in Annex B, alongside the chemical structures of some examples of benzodiazepines that are already controlled via the MDA.

A consultation with the MHRA confirmed that there are no legitimate medicinal uses in the UK for any of these 13 substances.

1. Flualprazolam

IUPAC: 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

Flualprazolam (also known as Ro 11-5073/000, 2'-fluoro alprazolam, ortho-fluoro alprazolam or 'flualp') is a 1,2,4-triazolobenzodiazepine, where the diazepine ring is fused to a triazole ring. It is the 2-fluoro derivative of the benzodiazepine *alprazolam*. It is also structurally related to *triazolam*, differing by the replacement of the chlorine with fluorine at the 2-position (ortho position) on the phenyl ring, which is attached to the benzodiazepine moiety. It is also similar in structure to *flubromazolam*, which was brought under Class C control of the MDA in 2017.

Flualprazolam was patented in 1970 but was never marketed as a medicine. Methods of manufacture have been published [Fustero *et al*, 2006; WHO, 2019a]. No specific information is available on how the drug is handled by the body (pharmacokinetics), but properties are likely to be similar to those of alprazolam, which has a half-life of 9.5–12 hours [Garzone & Kroboth, 1989]. The onset of action of flualprazolam is reported to be 10–30 minutes after oral use, with a duration of action of 6–14 hours [Zawilska & Wojcieszak, 2019]. There is limited pharmacological information available about flualprazolam, but a study of triazolobenzodiazepines reported that substitution of chlorine or fluorine at the ortho position of the phenyl ring attached to the benzodiazepine moiety in a series of *alprazolam*-related substances, produced compounds with dramatically enhanced activity [Hester *et al*, 1971]. In pharmacological tests conducted on mice, flualprazolam was reported to be active at doses of less than 10 µg/kg [Orsolini *et al*, 2020].

As of March 2020, no studies of animal or human abuse or dependency potential have been published. Typical doses used in humans are in the range of 0.125 mg to 2.5 mg. Online user fora suggest similar effects from flualprazolam as those associated with *clonazepam* and *alprazolam*. These effects are consistent with preclinical studies described in the patent application demonstrating sedative/tranquilizer and muscle relaxant effects [WHO, 2019a].

Involvement of flualprazolam in the drug misuse markets was first notified to the EMCDDA EU Early Warning System by Sweden in November 2017, following a police seizure of a powder. Sales of the substance in powder form have been reported, advertised as flualprazolam. The EMCDDA issued a report on flualprazolam in March 2019, which noted that flualprazolam had been detected in Denmark, Finland, Germany, Slovenia, Sweden and Norway. More than 30,000 flualprazolam tablets were seized during 2018. Seizures reported by Sweden provided evidence that flualprazolam had been used to make falsified (fake) 'Xanax' and 'Xanor' tablets.

In this March 2019 report EMCDDA detailed deaths with confirmed exposure to flualprazolam have been reported by Sweden (24 deaths) and Finland (2 deaths). The cause of death was reported in 15 of these cases; in 8 of these

flualprazolam was cited as a contributing or possible contributing factor. Where additional toxicology information was available, other substances were detected in all cases.

There have been 42 flualprazolam reports on the United Nations Office of Drugs and Crime (UNODC) Early Warning Advisory on NPS Toxicology Portal (Tox-Portal), 40 from the US as well as 2 from Finland (which may be the same 2 cases reported to the EMCDDA). Five of these cases were post-mortem, 21 ante-mortem and the remainder were not classified.

Flualprazolam was considered causal to the event in 5 cases. There has also been a case report published from China describing the use of flualprazolam to sedate a victim for the purposes of robbery [Qian *et al*, 2020].

In the UK, several identifications of the compound have been reported from seizures and samples analysed by National Crime Agency (NCA), TICTAC Communications Ltd. and Welsh Emerging Drug & Identification of Novel Substances (WEDINOS) (see Annex C), as well as anecdotal reports of use from clients in receipt of treatment from Postscript360, a Bristol-based charity providing treatment solutions and referral pathways for people with benzodiazepine dependence. This indicates significant availability of this compound in UK markets. Of tablets sold as diazepam or alprazolam, analysis by WEDINOS has demonstrated the proportions containing flualprazolam to be 13% and 15%, respectively. The National Institute for Health Research (NIHR)-funded Identification of Novel Psychoactive Substances (IONA) study has analysed samples from 853 people attending a hospital with toxicity related to drug misuse since 2015. Although benzodiazepines were commonly detected (e.g. diazepam or a metabolite identified in 302 people), the only novel benzodiazepine identified so far has been flualprazolam, identified in 5 people between June 2019 and February 2020.

As of March 2020, there have been 12 flualprazolam-associated deaths in the UK recorded by regional statistical agencies (see Annex D). In October 2019, an unknown number of deaths were reported in Stockton-on-Tees where flualprazolam was the only psychoactive substance present.

2. Norfludiazepam

IUPAC name: 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one

Norfludiazepam (also known as norflurazepam, desalkylflurazepam or Ro 05-3367) is structurally related to *diazepam* and *4-chlorodiazepam* and can be used in the synthesis of *midazolam*. It is also a pharmacologically active metabolite of several other benzodiazepines including *midazolam*, *flurazepam*

and *fludiazepam* [Orsolini *et al*, 2020]. Norfludiazepam is a more potent inhibitor of 3H-flunitrazepam cerebellar or hippocampal membrane binding than diazepam [Sieghart, 1983]. It has a long elimination half-life (74 ± 24 hours) compared to *flurazepam* (2 hours) and has been shown to accumulate during prolonged administration of *midazolam*.

Norfludiazepam has been notified in the UK from a police seizure of 14 pale-blue tablets in March 2017 and one sample analysis by TICTAC in December 2017. Small-scale seizures of a mixture of tablets and powders have also been notified in Germany (2016), Sweden (2017), Norway (2018), and Denmark (2019).

Clients in receipt of treatment for benzodiazepine dependency via Postscript360 have also anecdotally reported either the use or purchase of norfludiazepam.

No deaths related to norfludiazepam have been reported in the UK as of March 2020.

3. Flunitrazolam

IUPAC name: 6-(2-fluorophenyl)-1-methyl-8-nitro-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

Flunitrazolam is a triazolo benzodiazepine structurally related to *clonazolam* (*clonitrazolam*), differing by the substitution of 2-chloro with 2-fluoro on the phenyl group. It is also the triazolo version of *flunitrazepam*. It was first discovered in the 1960s but has not yet been marketed as a pharmaceutical in any country [Cornett *et al*, 2018]. As such, there is limited information about doses, effects, safety and tolerability available. However, based on its structural similarity to other triazolo-benzodiazepines, it is likely that the potency of flunitrazolam is greater than of the already highly potent *flunitrazepam* [Orsolini *et al*, 2020]. Peak concentrations (178 pg/ml) were achieved in oral fluid 3 hours after ingestion of a 0.25 mg tablet of flunitrazolam by a single male volunteer [Ameline *et al*, 2019].

A small number of detections of flunitrazolam, branded as 'Rohypnol' (the proprietary name for *flunitrazepam*), were seized at the UK border between 2014 and October 2019 (detailed in Annex C). One case of flunitrazolam detection was reported by the NCA in late 2018. Flunitrazolam has also been notified in Sweden (2016) from a police seizure of tablets. Small-scale seizures of a mixture of tablets and powder have also been notified in Germany (2016) and Denmark (2017).

As of March 2020, no deaths or other harms associated with flunitrazolam have been reported in the UK. However, the specialist benzodiazepine charity, Postscript360, have reported that clients in receipt of treatment for benzodiazepine dependency had anecdotally reported either the use or purchase of flunitrazolam.

4. Methyl clonazepam

IUPAC: 5-(2-chlorophenyl)-1-methyl-7-nitro-3H-1,4-benzodiazepin-2-one

Methyl clonazepam (also known as ID 690, Ro 05-4082) is a 1,4-benzodiazepine originally developed as a pharmaceutical in the 1970s. Although shown to have anxiolytic properties similar to those of *lorazepam* [Ansseau *et al*, 1985], it has never been licensed as a medicine. Methyl clonazepam is structurally related to *flunitrazepam*, differing by the substitution of the fluorine with a chlorine atom. It also shares structural similarities with *diclazepam* and *cloniprazepam*. *In vivo* studies in rats demonstrated that methyl clonazepam is equal in potency to *nitrazepam* and *clonazepam*, and is more potent than *diazepam* for muscle relaxant and anticonvulsant action (all of which are classified under Class C of the MDA) [Fukuda *et al*, 1977].

Methyl clonazepam was first notified in Sweden in December 2017, in a border seizure of powder. As of March 2020, it has not been detected in drug seizures or associated with deaths in the UK. The specialist benzodiazepine charity, Postscript360, have reported that clients in receipt of treatment for benzodiazepine dependency had reported anecdotally either the use or purchase of methyl clonazepam.

5. Cloniprazepam

IUPAC name: 5-(2-chlorophenyl)-1-(cyclopropylmethyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Cloniprazepam (also known as Kloniprazepam and 1-Cyclopropylmethyl clonazepam) is a 1,4-benzodiazepine structurally similar to *clonazolam* (*clonitrazolam*) and *meclonazepam* and described as a pro-drug for *clonazepam* [Mortelé *et al*, 2018]. It is a more potent inhibitor of 3H-flunitrazepam cerebellar or hippocampal membrane binding than diazepam [Sieghart, 1983]. Doses may range from 0.5 to 4 mg but are typically 1–2 mg [Mooseman & Auwärter, 2018]. Symptoms occur 15–45 minutes after ingestion, with clinical effects lasting 6–9 hours [Orsolini *et al*, 2020].

The compound was first notified in January 2016 in Sweden, from a police seizure of capsules. Sales of the substance have been reported online as packs of 20, 60, 120 and 240 capsules of 2.5 mg strength.

Data up to November 2019 shows that cloniprazepam has not been detected in UK Border Force or NCA seizures. There have been no telephone enquiries to the National Poisons Information Service (NPIS) and only 24 accesses to the relevant information on TOXBASE since 2016. No deaths or other harms have been recorded in the UK as of March 2020.

6. Difludiazepam

IUPAC: 7-chloro-5-(2,6-difluorophenyl)-1-methyl-3H-1,4-benzodiazepin-2-one

Also known as Ro 07-4065, difludiazepam is structurally related to *diazepam* and *fludiazepam*, differing by the addition of fluoro substituents in both the 2- and 6-positions (just the 6-position in the case of *fludiazepam*). It is also structurally related to norfludiazepam (considered above, not currently classified under the MDA) differing by the addition of a fluoro substituent in the 6-position on the phenyl ring and the addition of a methyl group attached to the amide. Although a new substance to be identified in illicit drug markets, it was originally described in a 1972 patent, and has been used in research to determine the shape and function of the GABA receptor complex [Orsolini *et al*, 2020].

This compound was first notified in Sweden, May 2017, following a border seizure of a powder originating from China. Seizures made by law enforcement in Sweden have been labelled as 'sample for research'.

As of March 2020, difludiazepam has not been detected in drug seizures and no deaths or other harms have been recorded in the UK.

7. Thionordazepam

IUPAC: 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-thione

Thionordazepam (also known as thionordiazepam), is structurally related to *nordazepam* and *diazepam* and can be used in the synthesis of *alprazolam*. No pharmacological information is currently available.

This compound was first notified in Sweden in June 2017, following a border seizure of powder.

As of March 2020, this compound has not been detected in drug seizures in the UK and no deaths or other harms have been recorded in the UK.

8. Fluclozepam

IUPAC: 2-chloro-4-(2-fluorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine

Originally mentioned in a patent from 1974, fluclozepam is a thienodiazepine, where the diazepine ring is fused to a thiophene instead of a benzene ring. It is structurally related to *brotizolam* and *etizolam*, differing by the substituents at the thiophene and phenyl ring. Based on its similarity to *brotizolam* and *etizolam*, the substance is expected to have sedative hypnotic effects. There are conflicting anecdotal reports on doses used, though claims have been made that it has an approximately 3-fold higher potency and a shorter half-life compared to *etizolam* [Orsolini *et al*, 2020].

This compound was first notified in Sweden, October 2017, in a police seizure of tablets. It was notified in the same month in Denmark, in a border seizure of blotters originating from the Netherlands. As of March 2020 it has not been detected in drug seizures or associated with deaths or other harms in the UK.

9. Tofisopam

IUPAC: 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine

Unlike many of the classical 1,4-benzodiazepines under international control, tofisopam is a 2,3-benzodiazepine. The 1,4- and 2,3-benzodiazepines differ in the position of the nitrogen atoms in the diazepine ring. As a result, the compound contains a stereogenic centre and exists as a pair of enantiomers.

Tofisopam is authorised as a pharmaceutical in some European countries under the name Grandaxin. It is also known as tofizopam, Emandaxin, EGYT 341, Nodeprine, Seriel and TF. It is administered orally at a dose of 300 mg daily for the treatment of neurosis and somatic disorders associated with tension, anxiety, vegetative disorders, lack of energy and motivation, apathy, fatigue, depressed mood and alcohol withdrawal syndrome [Orsolini *et al*, 2020].

Unlike typical 1,4-benzodiazepines the literature suggests that tofisopam does not act on the GABA-A receptor but enhances the binding of other benzodiazepines to their binding sites [Petócz, 1993]. It has anxiolytic activity with reduced sedative and muscle relaxant side-effects in humans. Under some circumstances it has stimulant properties, although sedation may occur after high doses and tofisopam may enhance the effects of barbiturates and ethanol [Petócz, 1993]. The lack of action on the GABA-A receptor raises the

possibility that sedative effects may not be reduced by the benzodiazepine antidote flumazenil. Tofisopam is rapidly absorbed from the intestinal tract but undergoes extensive first-pass hepatic metabolism; peak plasma concentrations are reached within 1–1.5 hours. The major pathway for the metabolic transformation of tofisopam is demethylation and its elimination half-life is 6–8 hours.

Tofisopam was first notified in Europe in November 2017, following a border seizure of tablets in Sweden. It has not been detected in drug seizures or associated with deaths or other harms in the UK as of March 2020.

10. Clobromazolam

IUPAC: 8-bromo-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

Clobromazolam (sometimes called Phenazolam) is the 2-chloro derivative of *bromazolam* and shares structural similarities with *clonazolam* and *flubromazolam*, respectively. Clobromazolam is also structurally related to *phenazepam*, *alprazolam* and *triazolam*. It differs from *triazolam* due to the replacement of chlorine with bromine at the 8-position on the benzodiazepine moiety. Oral administration in mice resulted in central nervous system depression, ataxia and convulsive reactions at doses of 0.2–1 g/kg, with symptoms lasting more than 24 hours [Polívka *et al*, 1983].

Clobromazolam was first notified in Sweden in March 2016, from a police seizure of capsules. From data up to March 2020, there is no evidence of prevalence or health harms associated with clobromazolam in the UK.

11. Cinazepam

IUPAC: 4-[[7-bromo-5-(2-chlorophenyl)-2-oxo-1,3-dihydro-1,4-benzodiazepin-3-yl]oxy]-4-oxo-butanoic acid

Cinazepam (also known as BD-798) is structurally related to benzodiazepines *phenazepam* and *3-hydroxyphenazepam*. It appears to have high-potency binding (in the nanomolar range) to the GABA-A receptor [Makan *et al*, 2007].

Cinazepam has been used in medical manufacturing in the Ukraine and has recently been included in the patent of a novel therapy for treating anxiety disorders, epilepsy, and pain. It is reported to produce hypnotic and anxiolytic effects and relatively weak sedative and muscle relaxant effects and to be more potent than phenazepam. *In vivo* it is substantially converted to the

active metabolite *3-hydroxyphenazepam*. The median elimination half-life of cinazepam was reported as 16–23 hours.

Cinazepam was first notified in Norway in March 2016, in a border force seizure of tablets. There is no direct evidence of prevalence or health harms associated with this compound in the UK, from data up to March 2020. Numbers of accesses to the cinazepam information on TOXBASE have increased from 4 in 2017 to 56 in the first quarter of 2019. It is not known if these accesses relate directly to the management of patients with exposure to cinazepam or have been made for other reasons.

12. Bentazepam

IUPAC: 5-phenyl-1,3,6,7,8,9-hexahydro-2H-[1]benzothieno[2,3-e][1,4]diazepin-2-one

Bentazepam (also known as thiadipone or tiadipone) is a thienodiazepine, i.e. a benzodiazepine derivative where the diazepine ring is fused to a thiophene instead of benzene. This class of compounds also includes *etizolam*, *metizolam*, and *fluclozepam*, but bentazepam differs from these three substances due to the presence of a cyclohexane ring fused to the thiophene instead of a triazole fused to the benzodiazepine.

Bentazepam was previously used as a medicine in Spain. It is known to produce anxiolytic, anticonvulsant, sedative and muscle relaxant effects and is used for the treatment of anxiety, including when associated with social phobia and post-traumatic stress disorder [Honorato *et al*, 1990]. Dosage reports have indicated that a low dose is 15–30 mg and a typical dose is 30–50 mg. Pronounced effects are experienced with doses greater than 50 mg. Clinical effects develop 15–45 minutes after oral intake and may last for up to 8 hours after administration [Orsolini *et al*, 2020]. Unlike other benzodiazepines, hepatitis and severe liver damage have been associated with therapeutic use [De-la-Serna *et al*, 1997; Andrade *et al*, 2000; 2006] as well as cases of colitis [Fernández-Bañares *et al*, 2003].

The compound was first notified in Sweden in March 2014, in a police seizure of tablets. As of March 2020, there is no evidence of prevalence or health harms associated with bentazepam in the UK.

13. Alprazolam triazolobenzophenone derivative

IUPAC: [2-[3-(aminomethyl)-5-methyl-4H-1,2,4-triazol-4-yl]-5-chlorophenyl]phenyl-methanone

This compound was developed by the Upjohn Company in the 1980s as a water-soluble pro-drug of alprazolam intended for administration as an injection or infusion. It rapidly converts to alprazolam at neutral pH. Acyl derivatives of the primary amino group of this compound have also been studied as prodrugs for alprazolam [Cho *et al*, 1986].

The alprazolam triazolobenzophenone derivative was first notified by Spain in March 2014, in a border seizure of powder that had originated from India. There is no evidence of prevalence or health harms associated with this compound in the UK from data up to March 2020.

6. Conclusions

- 6.1. There is evidence from drug seizure data of prevalence for 3 of the 13 compounds in the UK, namely flualprazolam, flunitrazolam and norfludiazepam. Numbers of seizures have been greatest for flualprazolam and this compound has also been associated with 12 deaths in the UK.
- 6.2. For the other 10 novel benzodiazepines considered in this report, there is currently no analytical evidence of prevalence or health harms in the UK. All of these compounds have the potential to cause health harms should they emerge into the UK drug market. They are currently controlled via the PSA and this remains appropriate until further evidence of harm emerges.
- 6.3. Whilst there are examples of some of the novel benzodiazepines being used as licenced medical products abroad, there is no evidence for legitimate medicinal uses of these substances in the UK.
- 6.4. There is an ongoing risk in the UK that further uncontrolled novel benzodiazepines may appear. Continued monitoring for evidence of prevalence or health harms related to compounds that are not currently controlled via the MDA therefore remains important. Benzodiazepines that are not currently classified under the MDA will fall within the provision of the PSA. The ACMD have previously advised [ACMD, 2019] that Temporary Class Drug Orders (TCDO) can be used in conjunction with the PSA as a mechanism to apply stricter controls for emerging compounds causing particular problems. By the action of a TCDO, the ACMD would have 12 months to collect, collate and make a recommendation on the uncontrolled novel benzodiazepine(s) covered by that order, for potential inclusion under the MDA.
- 6.5. The ACMD has considered the possibility of adopting a generic control of benzodiazepines based on chemical structure, similar to the German

legislation. This is not recommended as it is not possible within UK legislation where only descriptive text is used and the PSA is in place to support wider control of benzodiazepines.

7. Recommendation

The ACMD recommends that the following substances are classified under Class C of the Misuse of Drugs Act 1971, like other classified benzodiazepines, and placed under Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) because they have no medicinal use:

- 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (flualprazolam)
- 6-(2-fluorophenyl)-1-methyl-8-nitro-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (flunitrazolam)
- 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-one (norfludiazepam)

Owing to the absence of asymmetric centres or functional groups that can form esters or ethers, there are no structural derivatives that will need to be considered in this legislation for the above three compounds.

Leads: Home Office, Drugs and Alcohol Unit

Measure of outcome: The inclusion of the 3 compounds under Class C of the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 2001.

Annex A: List of benzodiazepines controlled under the Misuse of Drugs Act 1971 and Misuse of Drugs Regulations 2001

Category	Licensed as medicines in the UK		Not licensed as medicines in the UK		
	Class C	Class C	Class C	Class C	Class C
MDR	Schedule 4 Pt 1	Schedule 3	Schedule 4 Pt 1	Schedule 3	Schedule 1
Examples	Alprazolam Chlordiazepoxide Clobazam Clonazepam Diazepam Flurazepam Loprazolam Lorazepam Lormetazepam Nitrazepam Oxazepam	Midazolam Temazepam	Bromazepam Brotizolam Camazepam Clorazepic acid Clotiazepam Clloxazolam Delorazepam Estazolam Fludiazepam Halazepam Haloxazolam Ketazolam Medazepam Nimetazepam Nordazepam Oxazepam Oxazolam Pinazepam Prazepam Tetrazepam Triazolam	Flunitrazepam	*Adinazolam *Bromazolam *4'-Chlorodiazepam *Clonazolam *Deschloroetizolam *Diclazepam *Etizolam *Flubromazepam *Flubromazolam *Fonazepam *3Hydroxyphenazepam *Meclonazepam *Metizolam *Nifoxipam *Nitrazolam *Pyrazolam

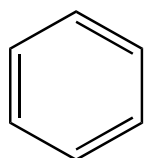
***16 Substances that were brought under control in May 2017, MDA SI 2017/634 and for the MDR SI 2017/631**

Annex B: Benzodiazepine Chemical Structures

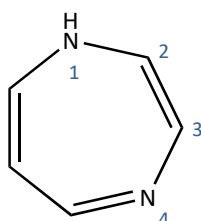
Where the compound is one of the 13 novel benzodiazepines considered, the # number refers to numbered segment within section 5 of the report.

1,4-benzodiazepines

1,4 benzodiazepines have nitrogen atoms in the 1 and 4 position of the diazepine ring, which is fused to a benzene ring. Naming convention is for them to end in 'pam'

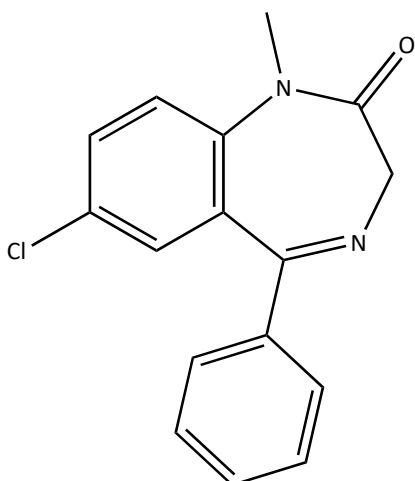


Benzene

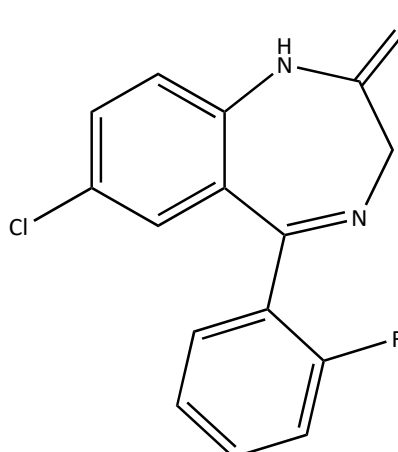


1,4 diazepine

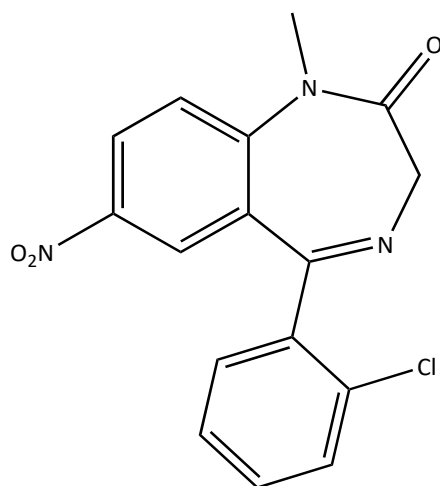
Diazepam (Class C under the MDA)



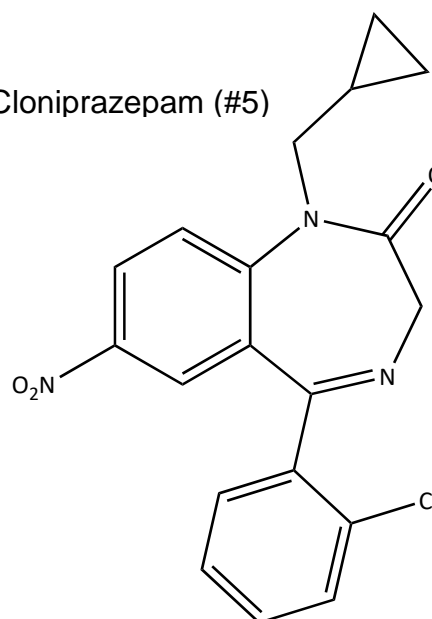
Norfludiazepam (#2)



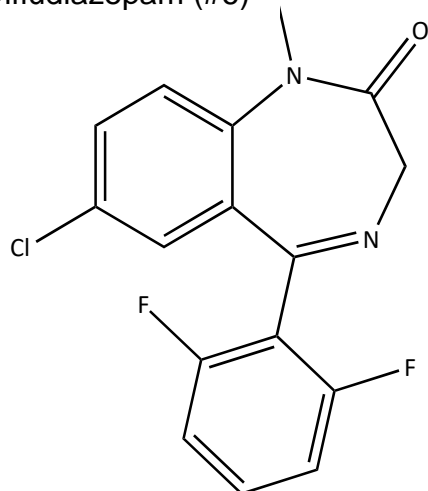
Methyl clonazepam (#4)



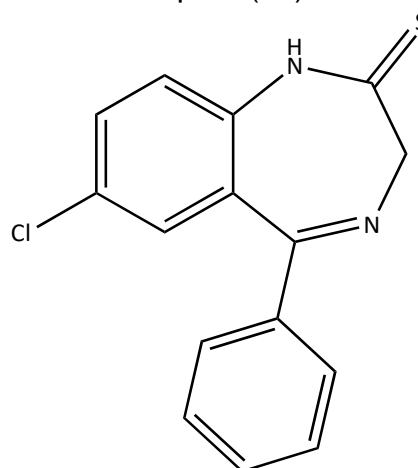
Cloniprazepam (#5)



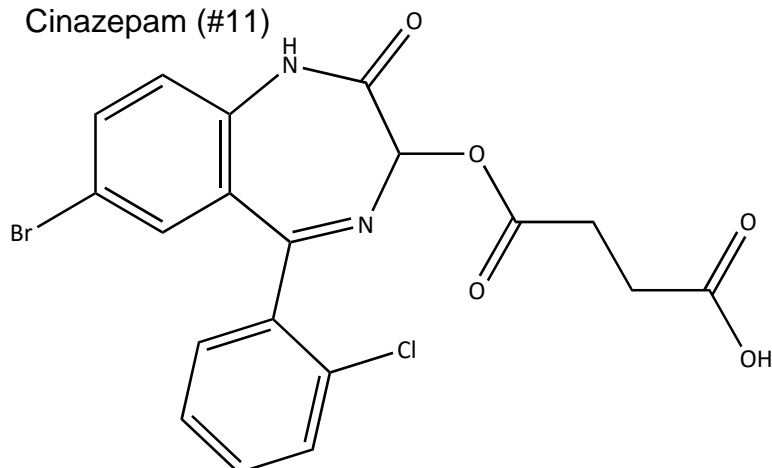
Difludiazepam (#6)



Thionordazepam (#7)

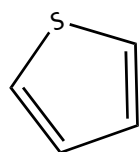


Cinazepam (#11)

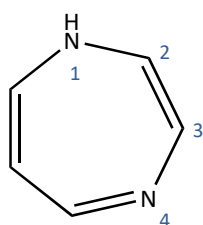


Thienodiazepine analogues of 1,4-benzodiazepines

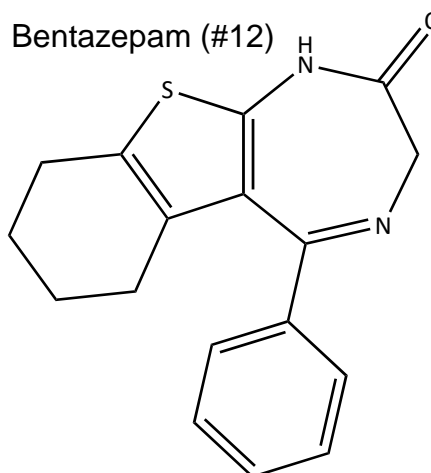
This is a sub-group of 1,4-benzodiazepines in which the fused benzene ring is replaced with a fused thiophene ring. As the thiophene ring is bound to a 1,4-diazepine the naming convention is to end in 'pam' as above.



Thiophene



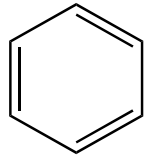
1,4 diazepine



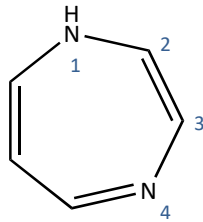
Bentazepam (#12)

Triazolo 1,4-benzodiazepines

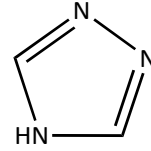
These compounds have a triazolo ring fused to the 1,4 diazepine ring, as well as a benzene ring. Naming convention is for them to end in 'lam'



Benzene

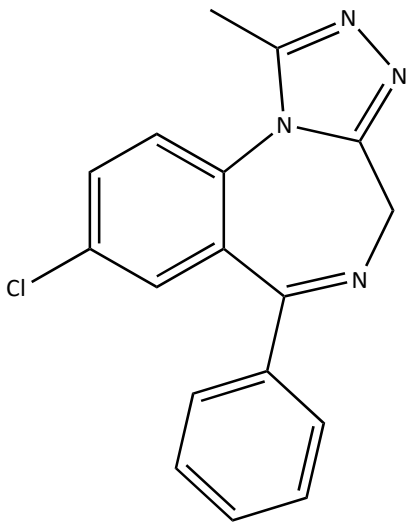


1,4 diazepine

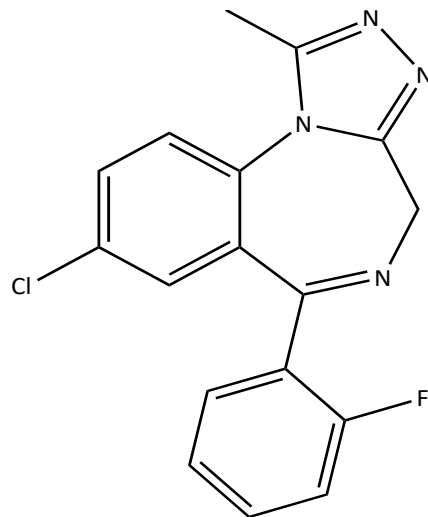


Triazolo ring
(1,2,4-triazole)

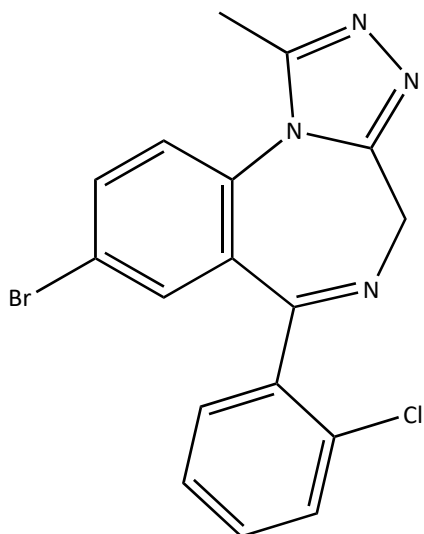
Alprazolam (Class C under the MDA)



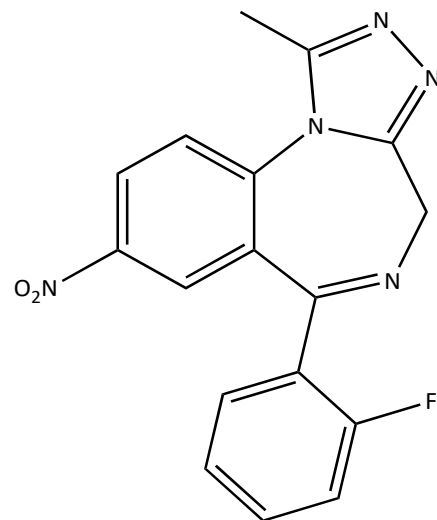
Flualprazolam (#1)



Clobromazolam (#10)



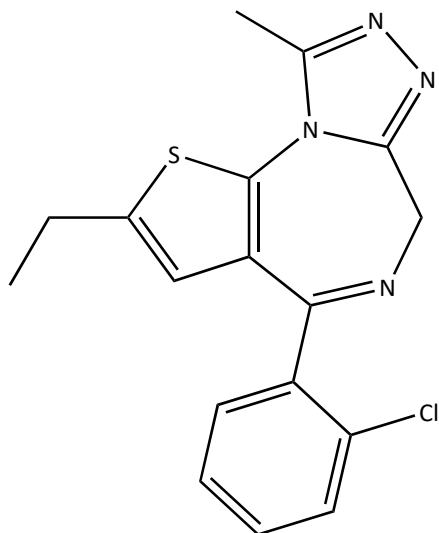
Flunitrazolam (#3)



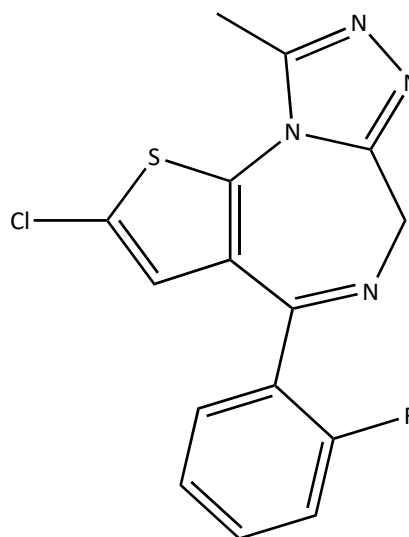
Thienodiazepine analogues of triazolo 1,4-benzodiazepines

This is a sub-group of triazolo 1,4-benzodiazepines in which the fused benzene ring is replaced with a fused thiophene ring. As the thiophene ring is bound to a triazolo 1,4 diazepine the naming convention is to end in 'lam' as above.

Etizolam (Class C under the MDA)

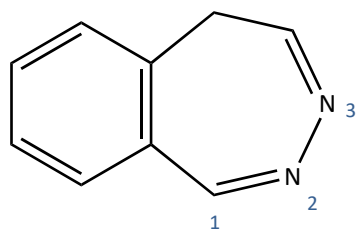


Fluclozepam (#8)



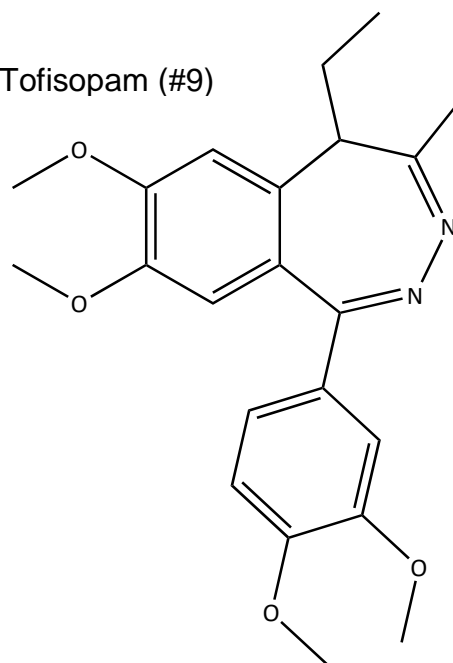
2,3-benzodiazepines

2,3 benzodiazepines have nitrogen atoms in the 2 and 3 position of the diazepine ring, which is fused to a benzene ring. Naming convention is for them to end in 'pam'



2,3 benzodiazepine

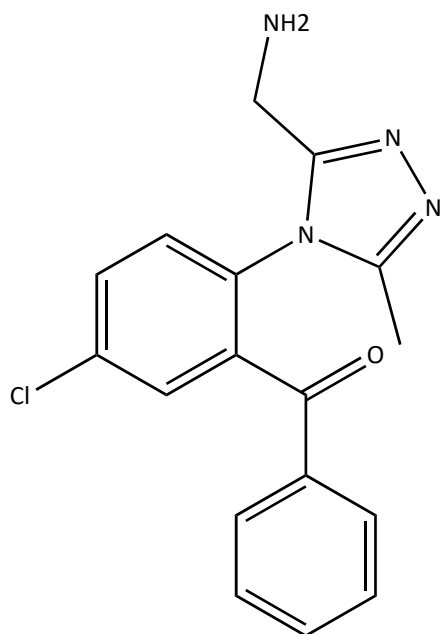
Tofisopam (#9)



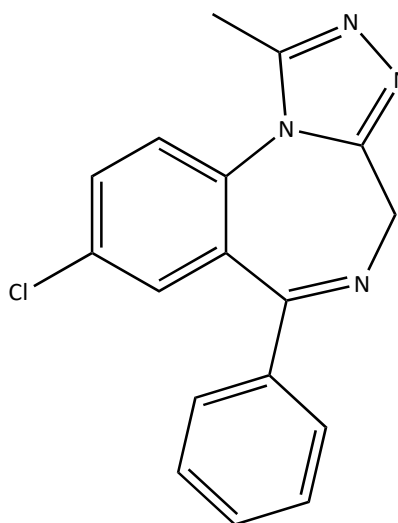
Alternative structures

Some benzodiazepine-type materials are pro-drugs (something that after administration, is metabolized into a pharmacologically active drug). This means that they have alternative structures to the above examples, but then convert to the benzodiazepine moiety in the body.

Alprazolam triazolo
benzophenone derivative (#13)



Alprazolam (Class C under the MDA)



Annex C: Summary of novel benzodiazepine identifications in UK seizure and sampling data

The use of the term 'novel benzodiazepines' in this section refers to the list of 13 compounds that the ACMD has considered in this report for control under the MDA.

UK Border Forces Seizures

A small number of detections of flunitrazolam, branded as 'Rohypnol', have been made at the UK border between 2014 and October 2019. Note that genuine 'Rohypnol' contains flunitrazepam, which is controlled in Class C of the MDA and Schedule 3 of the MDR.

[Official sensitive paragraph has been redacted from the published version of this report]

Forensic Early Warning System (FEWS) Novel Psychoactive Substances (NPS) Collection Plans

As part of the FEWS project, the Defence Science and Technology Laboratory (DSTL) facilitated the collection and analysis of suspected NPS samples seized by UK Border Force officials at five fast parcel and postal hubs in the UK. Participating centres submitted samples seized between April 2018 and February 2019, however, there were no detections of novel benzodiazepines. Of the 149 samples received, 50 (34%) of the samples contained an NPS, but there was only one benzodiazepine detected (4 detections of etizolam, already Class C under the MDA).

In addition to the collection and analysis of suspected NPS samples seized at Border Force, DSTL conducted two further collection plans as part of the FEWS project.

Vulnerable Group Collection Plan

DSTL facilitated the collection and analysis of suspected NPS samples seized between March 2018 and February 2019 by police from the homeless community and non-attributable samples found on the premises at three Immigration Removal Centres. Of the 109 samples received, (98% of which were provided by the participating Immigration Removal Centres) there was only one benzodiazepine detected, diclazepam, which is already controlled by the MDA. No detections of novel benzodiazepines were found in this sample set.

Prison Collection Plan

DSTL facilitated the collection and analysis of suspected NPS in non-attributable samples recovered from 14 participating prison grounds between March 2018 and February 2019. In the 432 samples received there were no benzodiazepines detected.

National Crime Agency (NCA) Seizures

The NCA is a government sponsored agency employed to combat serious and organised crime, working with partners to develop, deploy and maintain specialist capabilities and services that are delivered nationally. They collate information from forensic providers on seizures submitted for forensic examination in England and Wales. In the period from January 2017 to June 2019, the NCA reported the appearance of 2 novel benzodiazepines, flualprazolam and flunitrazolam. No further novel benzodiazepines have been forensically identified in seizures for the time period January 2017 to June 2019.

Drug	2017				2018				2019		Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	
Flualprazolam									3	14	17
Flunitrazolam							1				1
Total no. of benzodiazepine samples	461	509	682	499	407	357	452	507	570	488	4932

TICTAC Communications Ltd.

As a provider of drug identification and drug information to the criminal justice and healthcare sectors, TICTAC has reported 2 notifications of novel benzodiazepines (as of August 2019):

- 1 sample received from a forensic lab containing norfludiazepam (December 2017).
- 1 batch of 32 flualprazolam tablets received from seizures at summer music festivals (August 2019). The receipt of batch aligns with a number of counterfeit 'Xanax' tablets received by TICTAC for testing in the summer of 2019.

Welsh Emerging Drug & Identification of Novel Substances (WEDINOS)

Funded by Public Health Wales, WEDINOS provides laboratory testing of samples volunteered by the community. Samples are received anonymously by post from either individuals or participating organisations such as substance misuse services, housing and hostels, youth clubs and young people's services, education, night clubs and bars, mental health community teams, Local Authorities, the Ambulance Service and the Police. Test results are then made publicly available online.

In the period July to September 2019, benzodiazepines were the most commonly identified substances by WEDINOS, with flualprazolam featuring as the 8th most common substance identified [WEDINOS, 2019a]. Between October and December 2019, flualprazolam was the 5th most commonly identified substance [WEDINOS,

2019b]. Over the course of 2019, the presence of flualprazolam in WEDINOS samples increased significantly, with identifications almost doubling from 17 in the second quarter, to 30 in the third quarter of 2019. As seen with TICTAC sampling, most (97%) of these identifications in the third quarter were from samples purchased as something else. In many cases, these samples were counterfeit diazepam tablets or white 'Xanax' bars. This is of concern because of the confirmed potency of this compound and its links to deaths across Europe (see flualprazolam section above).

Including data up to March 2020, no other novel benzodiazepines have been identified in community samples received.

Postscript360

Postscript360 (previously known as Battle Against Tranquilisers) is a charity based in Bristol that provides treatment solutions and referral pathways for people with benzodiazepine dependence. They do not keep data concerning substances used by their client base, however, in January 2020 they confirmed that clients have anecdotally reported either purchasing or using the following substances:

- Flunitrazolam
- Norfludiazepam
- Methyl clonazepam
- Flualprazolam

Data on numbers are not available but Postscript360 estimates that 60-70% of their clients buy benzodiazepines illicitly via the internet.

Annex D: Summary of novel benzodiazepine-related deaths in the UK

The use of the term 'novel benzodiazepines' in this section refers to the list of 13 compounds that the ACMD has considered in this report for control under the MDA.

National Programme on Substance Abuse Deaths (NPSAD)

The NPSAD collates information from coroners about deaths related to drugs in addicts and non-addicts in England and Wales. To be recorded on the NPSAD database, there must be the presence of one or more psychoactive substance(s) directly implicated in the death, a history of dependence or abuse of drugs or the presence of controlled drugs at post-mortem. NPSAD receives drug related death reports from over 80% of its coroners. Cases are recorded by year of death, so figures are subject to change as more reports are confirmed.

NPSAD reported 3 drug-related deaths where flualprazolam was specifically stated in the cause of death or implied cause of death due to multiple drug toxicities. A further 2 cases were reported where flualprazolam was detected at post mortem, but not implicated in the cause of death. No cases associated with the other 12 novel benzodiazepines were reported (data up to March 2020). It should be noted that further novel benzodiazepine-associated deaths may have occurred, but not recorded by NPSAD because of under-reporting and delays to reporting described above. Additionally, specific testing needs to be requested by coroners for these compounds from toxicology labs and not all toxicology labs are equipped to detect these substances. The role of these novel compounds in drug-related deaths may therefore be underestimated.

Northern Ireland Statistics and Research Agency (NISRA)

In Northern Ireland, there have been 2 flualprazolam-related deaths reported to NISRA. In both cases flualprazolam was the cause of death, but toxicity from other substances were also identified. There have been no other confirmed cases involving the other 12 novel benzodiazepines (data up to March 2020).

National Records of Scotland (NRS)

In Scotland, 7 flualprazolam-related deaths had been reported to NRS (data up to March 2020). In all 7 cases, the death was not caused by flualprazolam alone: it was just one of (usually) several substances implicated in the cause of death, in combination. In one additional case, flualprazolam was identified post mortem, but was not implicated in the cause of death. NRS has not been informed of any deaths involving any of the other 12 novel benzodiazepines. As above it should be noted that, due to the time required for toxicology testing and subsequent reporting, further novel benzodiazepine-associated deaths may have occurred but have not been reported to NRS by March 2020.

Annex E: National Poisons Information Service (NPIS) telephone enquiries and TOXBASE accesses concerning novel benzodiazepines

The NPIS provides the healthcare profession in the UK with information and advice on the diagnosis, treatment and management of suspected poisonings in humans. Support is provided via the online poisons information database TOXBASE®, or via a 24-hour national telephone service. The NPIS can provide information on the number of accesses to TOXBASE® and the numbers and details of telephone enquiries made to the service by health professionals. These numbers reflect (but do not measure directly) the frequency of contacts between health professionals and patients presenting following specific suspected exposures.

In the period April 2014 to March 2019 the NPIS did not receive any telephone enquiries in relation to any of the 13 novel benzodiazepines considered in this report.

As these compounds are novel, many do not have a TOXBASE® page available (e.g. flunitrazolam, methyl clonazepam, fluclozepam, tofisopam, flualprazolam, clobromazolam, bentazepam, difludiazepam). Where TOXBASE® pages do exist, they have only recently been made available. There have been very few TOXBASE® accesses to information about these novel benzodiazepines, except for cinazepam and alprazolam triazolobenzophenone derivative.

Summary of NPIS pages available for novel benzodiazepines, and corresponding page accesses from April 2014 to March 2019.

Novel benzodiazepine with TOXBASE page available	Date page went live	Number of accesses to page			
		2016	2017	2018	2019
Alprazolam triazolobenzophenone derivative	November 2015	5	7	19	37
Cinazepam	May 2016	0	4	73	56
Cloniprazepam	May 2016	0	13	9	2
Norfludiazepam	March 2017	N/A	0	7	7
Thionordazepam	January 2018	N/A	N/A	0	4

Annex F: List of abbreviations used in this report

ACMD	Advisory Council on the Misuse of Drugs
CDC	Centers for Disease Control and Prevention
CND	The United Nations Commission on Narcotic Drugs
DHSC	Department of Health and Social Care
DSTL	Defence Science and Technology Laboratory
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EDND	European Database on New Drugs
FEWS	Forensic Early Warning System
GABA	gamma-aminobutyric acid
IONA	Identification of Novel Psychoactive Substances
IUPAC	International Union of Pure and Applied Chemistry
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MHRA	Medicines and Healthcare products Regulatory Agency
NCA	National Crime Agency
NDTMS	National Drug Treatment Monitoring System
NHSBA	National Health Service Business Authority
NIHR	National Institute for Health Research
NISRA	Northern Ireland Statistics and Research Agency
NPSAD	National Programme on Substance Abuse Deaths
NPIS	National Poisons Information Service
NPS	Novel Psychoactive Substances
NRS	National Records of Scotland
MoJ	Ministry of Justice
ONS	Office for National Statistics
PHE	Public Health England
PSA	Psychoactive Substances Act 2016
TCDO	Temporary Class Drug Orders
UK	United Kingdom
UNODC	United Nations Office on Drugs and Crime
US	United States
WEDINOS	Welsh Emerging Drug & Identification of Novel Substances
WHO	World Health Organization
WHO ECDD	World Health Organization's Expert Committee on Drug Dependence

Annex G: ACMD membership, at time of publication

Dr Kostas Agath	Consultant Psychiatrist (addictions), CGL Southwark
Professor Owen Bowden-Jones	Chair of ACMD, Consultant psychiatrist, Central North West London NHS Foundation Trust
Dr Anne Campbell	Senior lecturer in social work and Co-Director of the drug and alcohol research network at Queens University Belfast
Mr Mohammed Fessal	Chief Pharmacist, CGL
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Mr Lawrence Gibbons	Head of Drug Threat – NCA Intelligence Directorate – Commodities
Dr Hilary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services at NHS Greater Glasgow and Clyde
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham
Professor Tim Millar	Professor of Substance Use and Addiction Research Strategy Lead at the University of Manchester
Mr Rob Phipps	Former Head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Mr Harry Shapiro	Director – DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Paul Stokes	Senior Clinical Lecturer in mood disorders, King's College, London
Dr Ann Sullivan	Consultant physician in HIV and Sexual health
Professor Matthew Sutton	Chair in Health Economics at the University of Manchester and Professorial Research
Professor David Taylor	Professor of Psychopharmacology, King's College, London
Professor Simon Thomas	Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Dr Derek Tracy	Consultant Psychiatrist and Clinical Director, Oxleas NHS Foundation Trust
Ms Rosalie Weetman	Senior Commissioning Manager of Substance Misuse

Annex H: ACMD NPS Committee membership, at time of publication

Dr Kostas Agath	Consultant Psychiatrist (addictions), CGL Southwark
Mr Paul Bunt	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Dr Anne Campbell	Senior lecturer in social work and Co-Director of the drug and alcohol research network at Queens University Belfast
Mr John Corkery	Senior Lecturer in Pharmacy Practice at University of Hertfordshire
Mr Lawrence Gibbons	Head of Drug Threat – NCA Intelligence Directorate – Commodities
Dr Hilary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham
Professor Fiona Measham	Professor and chair in criminology, University of Liverpool; co-founder and co-director, the Loop
Mr Harry Shapiro	Director - DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Ann Sullivan	Consultant physician in HIV and Sexual health
Professor Simon Thomas	NPS Committee Chair, Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble	Retired Laboratory of the Government Chemist (LGC) expert
Dr Mike White	Former Forensic Intelligence Adviser
Dr David Wood	Consultant physician and clinical toxicologist at Guy's and St Thomas' and reader in clinical toxicology at King's College London

In addition to members of the NPS committee listed, significant contributions were made by NPSAD and the NPIS and a special mention would like to be extended to both organisations.

Annex I: Quality of evidence

Range of Evidence

Evidence gathered was considered in line with the ACMD's 'Standard Operating Procedure (SOP) for using evidence in ACMD reports' [ACMD, 2020].

Evidence relating to the identification and prevalence of the 13 novel benzodiazepines in Europe was taken from the EMCDDA's EDND. Each time a new drug is identified by a participating country in Europe, the EMCDDA produces a formal notification document, which details structural, chemical and pharmacological information of the substance if available and then set up a page on the EDND. The database then records any further substance notifications in Europe or reports of adverse effects.

To evidence the identification and prevalence of novel benzodiazepines in the UK, the ACMD's NPS Committee wrote to stakeholders requesting available data on the 13 substances. Responses were received from the following (which include submissions of 'no data held' and anecdotal evidence:

External agencies:

- NCA
- NISRA
- NPSAD
- NPIS
- NRS
- National Drug Treatment Monitoring System (NDTMS)
- Postscript360
- TICTAC Communications Ltd
- WEDINOS

Government Departments:

- Border Force Intelligence Analysis (Home Office)
- FEWS (DSTL)
- MHRA
- Ministry of Justice (MoJ)
- UK Focal Point (PHE)

This report also draws on evidence from peer-reviewed literature (UK and international publications) and government reports. The ACMD also considered international approaches when drafting its recommendations.

Quality of evidence (design, limitations, bias)

For 3 of the 13 novel benzodiazepines considered in this report, there was strong evidence of their availability and harm - allowing the ACMD to make an informed recommendation on their classification and schedule.

Many agencies and departments returned 'no data held' for most of the novel benzodiazepines in this report. It is important to note that owing to the 'novelty' of all of these substances, forensic testing is limited and inconsistent across the UK and as a result, information being fed into reporting agencies that were approached will not be representative. This is proven by anecdotal data provided by benzodiazepine dependence treatment provider, Postscript360, which reported clients either purchasing or using methyl clonazepam, despite there being no forensic evidence available of methyl clonazepam in the UK. As reports have identified these substances elsewhere in Europe, there is potential availability of these substances in the UK, however, this connection is too weak to deduce a classification under the MDA.

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