ACMD

Advisory Council on the Misuse of Drugs

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Minister for Crime Prevention, Jeremy Browne MP
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5 September 2013

Dear Minister for Crime Prevention,

Re: ACMD advice on the control of Z-drugs (zaleplon, zolpidem and zopiclone)

I am writing to provide you with the Advisory Council on the Misuse of Drugs' (ACMD) consideration of the compounds zaleplon, zolpidem and zopiclone, known as 'Z-drugs'.

Zolpidem is already controlled under the Misuse of Drugs Act as Class C and listed under Schedule 4, Part 1 of the Misuse of Drugs Regulations. The ACMD recommends that the other two Z-drugs, zaleplon and zopiclone, are similar in nature to zolpidem and should be controlled in the same manner.

The Z-drugs are sedatives and induce sleep (known as a 'hypnotic' effect). They were developed as an alternative to benzodiazepines, which have a similar hypnotic effect and are used in the treatment of insomnia. Since 1991, the volume of Z-drug prescriptions has risen while benzodiazepine prescriptions have fallen. Benzodiazepines are controlled under the Misuse of Drugs Act and Regulations as a Class C, Schedule 4 or 3.

Z-drugs and benzodiazepines share the same basic mechanism of pharmacological action. There are no very significant differences in therapeutic efficacy or adverse effect potential between benzodiazepines and Z-drugs, or between the Z-drugs themselves. The suggested differences that

have been reported, include a reduced abuse potential and propensity to tolerance and withdrawal with Z-drugs compared to benzodiazepines.

There are several mechanisms available for estimating the level of misuse of the Z-drugs. Overall, zaleplon tends to be reported as the least misused while zopiclone and zolpidem are both reported as the most misused, depending on the reporting mechanism e.g. MHRA, UK user surveys and international user forums.

The harms associated with Z-drugs were summarised by a Department of Health report in 2011 as a risk of coma, respiratory depression and death associated with use of excess doses of Z-drugs in combination with alcohol or other Central Nervous System (CNS) depressants. There are reported psychosocial effects including depressed mental activity and alertness, memory loss and amnesia and personality and mood changes through drowsiness, lethargy, disinhibition, chronic paranoid behaviour and aggression.

Data from the National Program on Substance Abuse Deaths (npSAD) suggests that Z-drugs play a small role in drug related deaths in the UK, mainly in combination with other CNS depressants, and principally implicated in episodes of intentional poisoning.
The ACMD considers that due to the similarities of structure and effects described above, the potential social harm from the misuse of zopiclone and zolpidem would be similar to the social harms associated with the misuse of zolpidem and the benzodiazepines.

The ACMD has concluded that the similarity between the three Z-drugs in terms of pharmacological mechanism and potential to cause physical and social harm supports a recommendation to control all three as class C and Schedule 4, Part 1 under the Misuse of Drugs Act and Regulations respectively.

Yours sincerely,

Professor Les Iversen FRS

Cc: Parliamentary Under Secretary of State for Health, Anna Soubry MP

ACMD

Advisory Council on the Misuse of Drugs

Z-drugs: a review of the evidence of misuse and harm.

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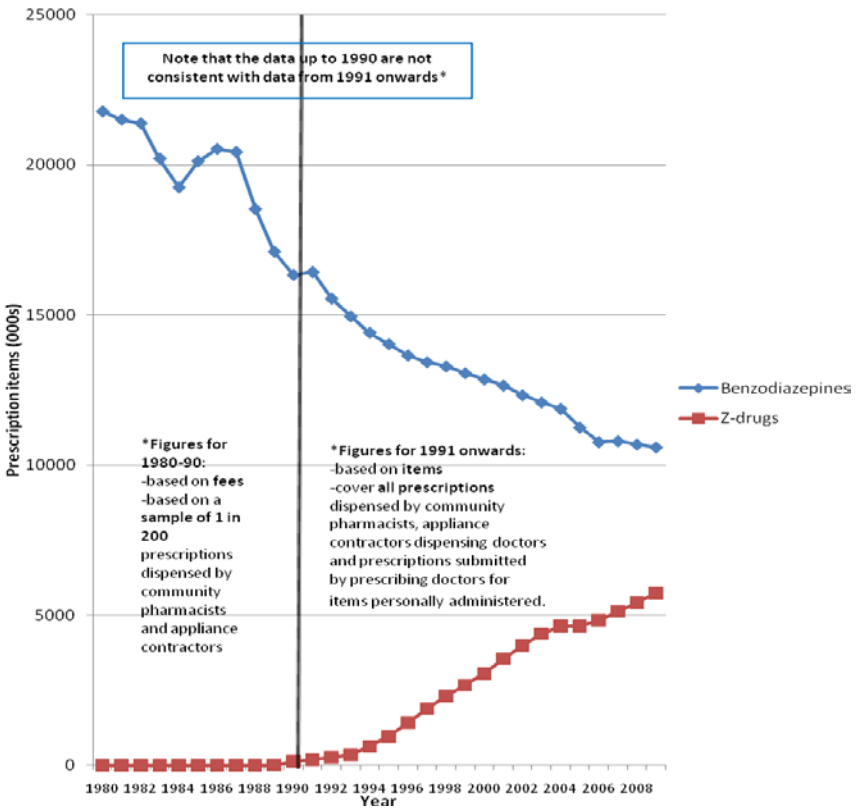
Background

1. The Z-drugs comprise of a group of three non-benzodiazepine hypnotics: zaleplon, zolpidem and zopiclone. Zolpidem is the only Z-drug which is controlled under the Misuse of Drugs Act and its Regulations (Class C, Schedule 4, Part 1).

2. They were developed with the aim of overcoming some of the disadvantages of benzodiazepines e.g. slow onset of action, next day sedation, dependence and withdrawal (NICE, 2004). However, the sedative effects may still persist to the next day and the Summary of Product Characteristics (SPC) for each drug also highlights the potential to cause tolerance, dependence and withdrawal symptoms.

3. In 2004, NICE concluded that there was "no compelling evidence of a clinically useful difference between the Z-drugs and short acting benzodiazepine hypnotics from the point of view of their effectiveness, adverse effects, or potential for dependence or abuse" (NICE, 2004) however this has been challenged by some commentators (Lader, 2005 in Reed *et al*., 2011 and Nutt, 2005).

Figure 1: Prescriptions dispensed in the community in England from 1980 to 2009 (from Reed at al, 2011)



4. The volume of prescribing (measured through dispensing data) for Z-drugs has shown an increase across England for the 19 year period 1991 to 2009 with a corresponding decrease in benzodiazepine prescribing (figure one). The vast majority of these prescriptions are also thought to be prescribed as part of a series rather than stand-alone prescriptions with prescribing outside the SPC guidelines in one in three cases (Reed *at al*., 2011).

5. During the twelve month period December 2011 to November 2012 a total of 6,179,814 items for Z-drugs were dispensed in England with the majority for zopiclone (88.18%), followed by zolpidem (11.80%) then zaleplon (0.02%) (Harrison and Waterhouse, 2013).

Pharmacology

6. The Z-drugs produce their sedative/hypnotic effects by binding to brain GABA-A receptors which are ligand gated chloride channels mediating inhibitory neurotransmission. Despite being chemically distinct, Z-drugs share this basic mechanism of action with benzodiazepines.

7. There are many sub-types of this receptor with both benzodiazepines and Z-drugs acting as agonists at α1, α2, α3, and α5 $GABA_A$ receptor sub-types (Skerritt & Johnson, 1983.; De Deyn & Macdonald, 1983) although the relative activity varies from drug to drug. Activity at α1 receptors appears to be associated with sedative effects whereas activity at the α2 and α3 sub-types seems to be associated with anxiolytic effects (Nutt and Stahl, 2010). The exact number of these receptor sub-types is still not clear (Sigel *et al*., 2012), but small differences in binding patterns have been shown between Z-drugs and benzodiazepines and between the three Z-drugs.

8. Perhaps the most reliable way of differentiating between drugs is in functional studies using electrophysiology and here zolpidem preferentially potentiates the action of GABA at receptors containing the α1 subunit (sedative effect) (Wafford *et al*.,1993). Sanna *et al*. (2002) have shown that zaleplon had a similar α1 preferring although it was about half as potent as zolpidem and both of these Z-drugs were similar in receptor profile to triazolam, a benzodiazepine that is also used as a hypnotic.

9. These small differences in sub-type selectivity have been used in attempts to demonstrate relative advantages in terms of clinical efficacy or adverse effect liability. However, a meta-analysis of randomised clinical trials comparing benzodiazepines and Z-drugs showed few consistent differences between them in terms of a number of indices of therapeutic benefit or in occurrence of adverse effects (Dunbar *et al.*, 2004). On the other hand there is some evidence to suggest that Z-drugs have a lower propensity to cause tolerance and withdrawal symptoms due to their lower activity at α2 receptors compared to benzodiazepines (Nutt, 2005). A recent authorative review also concluded that although zolpidem, zaleplon, zopiclone, eszopiclone[1] and indoplon[1] could be shown to have some selectivity for receptors containing the α1 subunit (sedative effect). It is uncertain whether these small differences *in vitro* are enough to differentiate these agents from other similar drugs in clinical use (Wafford and Ebert, 2008).

[1] Not available in the UK

10. Pharmacokinetically the three Z-drugs differ in their elimination half-lives (table one) but all are short acting compared with classical benzodiazepines such as diazepam.

Table 1: Elimination half-lives, indication and maximum treatment episode lengths of the Z-drugs

Drug	Elimination half-life (hrs)	Indication	Maximum treatment episode
Zaleplon	1.0	Initial insomnia that is severe, disabling or subjecting the patient to extreme distress.	Two weeks
Zolpidem	2.5	Short term treatment of insomnia where it is debilitating or is causing severe distress for the patient.	Four weeks
Zopiclone	3.5-6.5	Short-term treatment of insomnia (including difficulties in falling asleep, nocturnal awakening and early awakening, transient, situational or chronic insomnia, and insomnia secondary to psychiatric disturbances) in situations where the insomnia is debilitating or is causing severe distress for the patient.	Four weeks

11. Overall, as might be expected from a commonality of pharmacological action, it may be concluded that there are no very significant differences in therapeutic efficacy or adverse effect potential between benzodiazepines and the Z-drugs or between the individual Z-drugs

Misuse and Harms

12. As stated in the previous section, all three Z-drugs have been suggested to have a reduced propensity to tolerance and withdrawal, compared to benzodiazepines as predicted from their pharmacology (Nutt, 2005 and Soldatos *et al*., 1999 in Reed *et al.*, 2011). However, some case reports are available in the literature which demonstrate that Z-drugs do have some abuse potential.

13. For example, a review of cases between 1966 and 2002 identified 22 reports of abuse concerning zopiclone and 36 reports on zolpidem. The abuse potential and estimated risk of abuse for both zopiclone and zolpidem was found to be approximately one third of that of the benzodiazepines (Hajak *et al*., 2003 in Reed *et al.*, 2011). Zopiclone withdrawal was particularly associated with increased dosage and prolonged use and included the following symptoms:
    - Anxiety
    - Tachycardia
    - Tremor
    - Sweating
    - Rebound insomnia
    - Flushes and palpitations
    - Derealisation and
    - Convulsions

14. An analysis of case reports in France associated with zolpidem from 1993 to 2005 yielded 53 “relevant cases” (Victorri-Vigneau *et al*, 2007 in Reed *et al*, 2011). The majority had been using it to treat insomnia but within a “few weeks to months” the dose had escalated. In one case a daily dose of 1,120mg was consumed with the average dose across the cases studies being 300mg. In one case the person was injecting the drug.

15. When opiate users opinions on Z-drugs were investigated, the picture presented was one that supports a reduced abuse potential when compared with benzodiazepines. A study in 2004 looking at a cohort of opiate dependent patients found that Z-drugs (zolpidem and zopiclone) were less liked and less sought after than benzodiazepines (table two) (Jaffe *et al*., 2004 in Reed *et al*, 2011).

Table 2: Patterns of benzodiazepine use by subjects at three UK addiction treatment centres (Jaffe *et al*., 2004, in Reed *et al*, 2011)

	Q4. % subjects use (n = 297)	Q5. % street purchase	Q6. % doctor prescribed	Q7. % not recommended by doctor	Q8. % took to sleep	Q9. % took to get high	Q10. % took to make feel better	Q11. % like the effects	Q12. % think they need	Q13. % addicted	Q14. % might become addicted
Diazepam	86.8	79.3	60.2	56.2	70.7	52.0	80.1	80.1	35.2	13.7	43.8
Nitrazepam	61.7	80.8	41.2	57.7	79.1	48.3	70.3	80.8	22.7	8.2	36.8
Temazepam	80.7	77.3	50.0	58.0	80.2	55.0	71.3	78.6	26.2	10.6	45.3
Amitriptyline	42.4	48.8	42.4	51.2	63.7	29.8	57.3	25.0	11.0	1.6	17.7
Fluoxetine	26.5	34.6	61.5	23.1	12.8	23.1	71.8	16.7	12.8	1.2	12.8
Trazadone	8.2	33.3	62.5	29.2	70.8	16.7	62.5	29.2	25.0	0.0	20.8
Zolpidem	5.8	23.5	76.5	23.5	82.3	23.5	64.7	41.2	11.8	0.0	11.8
Zopiclone	53.7	42.0	79.0	30.6	88.5	22.9	56.7	48.4	28.0	5.1	19.8
Chlorpheniramine	18.2	7.6	28.3	7.6	17.0	3.8	56.6	32.1	18.9	0.0	0.0
Diphenhydramine	29.4	12.8	15.1	19.8	51.2	11.6	46.5	34.9	19.8	1.2	8.1

16. Consistent with other guidelines (BPS, 2007), the risk of dependency to prescribed zopiclone has been linked to a previous history of drug abuse (Wadworth and McTavish, 1993; Ayonrinde and Sampson, 1998, Hajak, 1999 in WHO, 2006) and other mental health problems e.g. depression (Strohle *et al*., 1999 in WHO 2006). However, some exceptions to this rule do exist. For example, Jones and Sullivan describe four cases of daily use of up to 30mg zopiclone where only one person had been dependent on benzodiazepines previously (Jones and Sullivan, 1998 in WHO, 2006).

17. Clinical practice does suggest that there is a tolerance and withdrawal syndrome associated with the Z-drugs although this is less problematic when compared to the benzodiazepines. Dependence has been found to be associated with higher than recommended doses of zopiclone and one study has demonstrated significant levels of dependence on zopiclone among alcoholics compared to the general population (Johansson *et al*., 2003 in Reed *et al*., 2011). Duration of zopiclone treatment has also been reported to be a less important factor in dependence than increasing dose (Krystal *et al*., 2003 in Reed *et al*, 2011).Nevertheless some commentators have reported that withdrawal from zolpidem and zaleplon is not usually problematic (Lader, 1998., in Reed at al., 2011).

18. Reports of substance-related disorders to the Medicines and Healthcare Regulatory Authority (MHRA) are presented in table three below.

Table 3: Reports of "Substance-related disorders" reported to the MHRA for the three z-drugs and diazepam and lorazepam as benzodiazepine comparators (MHRA Drug Analysis Prints).

Drug	Reaction Name	Total unique reports
Zaleplon	Substance –related disorder	0
Zolpidem	Substance-related disorder	20 (3 dependence; 6 drug abuse; 9 drug dependence; 2 withdrawal syndrome)
Zopiclone	Substance-related disorder	132 (28 dependence; 9 drug abuse; 43 drug dependence; 1 intentional drug misuse; 51 withdrawal syndrome)
Diazepam	Substance-related disorder	82 (1 alcohol withdrawal syndrome; 4 dependence; 7 drug abuse; 20 drug dependence; 4 intentional drug misuse; 46 withdrawal syndrome)
Lorazepam	Substance-related disorder	80 (9 dependence; 1 drug abuse; 24 drug dependence; 46 withdrawal syndrome)

19. The MHRA figures suggest a more significant problem for zopiclone while zolpidem has only 20 reports with zaleplon not recording a single report (although prescribing levels are considerably smaller than its two counterparts: Harrison and Waterhouse, 2013). We must, however, be mindful of the fact that this relies upon healthcare professionals reporting adverse effects. It is, perhaps, surprising that diazepam and lorazepam have fewer reports than zopiclone but the literature suggests that these have a greater propensity for misuse and dependence. Perhaps the culture of reporting and individual practitioners views on different classes of drugs have influenced yellow card reporting, for example, the "general consensus" view that benzodiazepines are known to be problematic which decreases the chance of a practitioner reporting dependency or withdrawal to the MHRA.

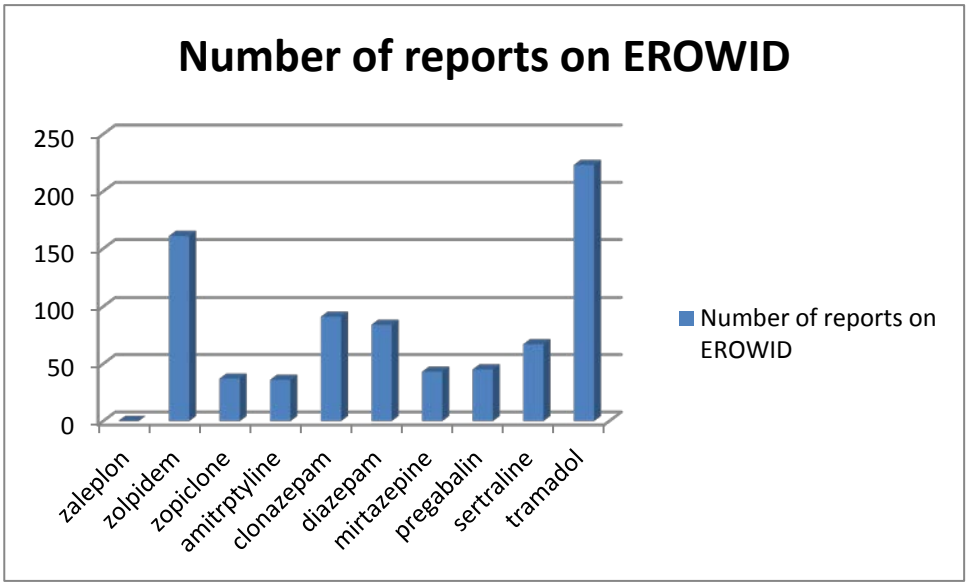
20. A recent internet survey conducted by Wood *et al.,* 2013 using a market research company has investigated misuse of Z-drugs in the UK. For validity of the data set, lifetime prevalence of cannabis, powder cocaine and MDMA ('ecstasy') was also collected and shown to be comparable to population level data from the 2011/12 British Crime Survey [cannabis (31.0%-vs-28.1%), cocaine 9.5%-8.1% and MDMA ('ecstasy') 8.6%-vs-8.2%]. The survey was completed by 1,500 individuals, of whom 737 (49.1%) were male and 763 (50.9%) female. The life-time prevalence of misuse of benzodiazepines and Z-drugs is shown in the table below.

Table 4: Life-time prevalence of misuse of benzodiazepines and Z-drugs (Wood *et al.,* 2013)

	Drug	Reported life-time prevalence of misuse
Benzodiazepines	Diazepam	4.3%
	Lorazepam	1.8%
	Alprazolam	1.3%
	Nitrazepam	0.8%
	Oxazepam	0.9%
Z-drugs	Zopiclone	1.9%
	Zaleplon	0.8%
	Zolpidem	0.4%

21. Reports on the user led website EROWID suggest there is more engagement with zolpidem than zopiclone or zaleplon in terms of misuse. Zolpidem has 161 reports, zopiclone 37 while zaleplon has no reports associated with it. It should be remembered that this is a global user led forum which may be influenced by the different availabilities and prescribing and drug use culture in different countries. Nevertheless, there is service user activity for at least two of the Z-drugs demonstrated through user input onto EROWID. Figure three illustrates the three Z-drugs in comparison to other drug reports on the EROWID website.

Figure 3: Number of reports of a selection of drugs from the user-led website EROWID (accessed 1/2/2013 at http://www.erowid.org/)



22. The health harms associated with non-benzodiazepine hypnotics (Z-drugs) have been summarised in the Department of Health document "A summary of the health harms of drugs" (Department of Health, 2011). The report states that there is a risk of coma, respiratory depression and death associated with use of excess doses of z-drugs in combination with alcohol or other CNS depressants. Risk of injury arising from the sedative properties of Z-drugs is highlighted as are the psychological effects of depressed mental activity and alertness and memory loss/amnesia (organic/neurological). Personality and mood may also be affected through drowsiness, lethargy, dishinibition, chronic paranoid behaviour and aggression (Department of Health, 2011).

23. The toxicology of the Z-drugs has further been reviewed by Gunja in a recent article (Gunja, 2013). The author reports that overdose, chronic abuse, poisoning and death have been reported with all Z-drugs and is linked to the availability and prescription numbers rather than the "inherent toxicity" of the individual Z-drugs. Gunja cites a review of 344 cases of acute zolpidem poisoning by Garnier *et al* which demonstrated that 6% of zolpidem cases died although none were attributed to zolpidem (Garnier *et al*, 1993 in Gunja, 2013). A 10-year audit of coronial deaths in New South Wales, Australia identified 90 cases where zolpidem was detected in the post-mortem blood or liver with the majority of deaths mixed drug overdoses most commonly with alcohol, antidepressants, benzodiazepines and opioids (Darke *et al*, 2012 in Gunja, 2013).

24. The fatal toxicity index (FTI) of Z-drugs compared to benzodiazepines and barbiturates has been calculated in a UK review (Buckley and McManus, 2004 in Gunja, 2012). Looking at deaths between 1983 and 1999 the authors concluded that zolpidem and zopiclone, which the study quoted as having the lowest FTI of the anti-insomnia drugs, caused around 2 deaths per million prescriptions in England and Scotland compared to around 7 for benzodiazepines and 150 for barbiturates. However, a New Zealand study has contradicted this finding for zopiclone showing it to have a similar FTI to commonly prescribed benzodiazepines (Reith *et al*, 2003).

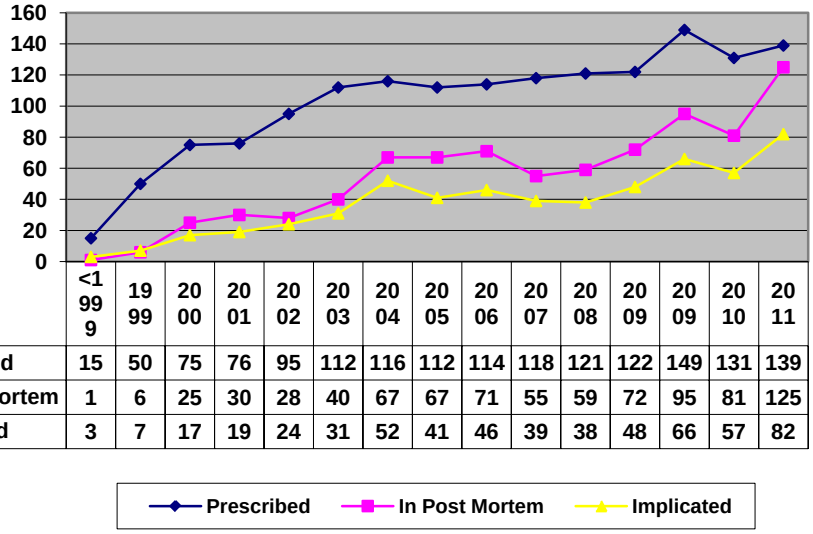
25. In the UK, there were no reported Drug Related Deaths (DRDs) attributable to or where Z-drugs were mentioned in the 2011 figures produced by the Office of National Statistics (ONS) or the National Programme on Substance Abuse Deaths (np-SAD)[2] (ONS, 2012; Ghodse *et al*., 2012). However, a more detailed review of the data has been undertaken by the National Programme on Substance Abuse Deaths (np-SAD), International Centre for Drug Policy and St George's University of London in response to a request from the ACMD (Corkery *et al*, 2013: Appendix One).

26. Cases were extracted where Z-drugs had been prescribed, found in the Post Mortem (PM) toxicology or implicated in the death[3]. A dataset of 1934 or 7.1% of cases were identified from the 27,194 cases received since the np-SAD database was established in July 1997. The relative contributions of each Z-drug is similar to the levels of prescribing in England between December 2011 and November 2012 i.e. Zopiclone 88.18%, Zolpidem 11.80%, Zaleplon 0.02% (Harrison and Waterhouse, 2013).

27. Figure four illustrates the trends in Z-drug cases reported to the np-SAD. Corkery *et al* have noted that there does appear to be a gradual increase in the number of cases where a Z-drug was prescribed, found in the PM toxicology and implicated in death. This should, nevertheless, be seen in the context of an increasing trend in the prescribing of Z-drugs (figure one) and may reflect the greater availability of the Z-drugs.

[2] Z-drugs may be classified under "hypnotics/sedatives" in the np-SAD report although this is not specifically stated and the group is reported chiefly as diazepam and temazepam.
[3] Mentioned in the cause of death as either causing or contributing to that event, or in the coroner's verdict.

Figure 4: Trends in Z-drug cases reported to np-SAD (Corkery *et al*, 2013)



	<1999	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2009	2010	2011
Prescribed	15	50	75	76	95	112	116	112	114	118	121	122	149	131	139
In Post Mortem	1	6	25	30	28	40	67	67	71	55	59	72	95	81	125
Implicated	3	7	17	19	24	31	52	41	46	39	38	48	66	57	82

28. The majority of deaths where Z-drugs were implicated involved a combination of Central Nervous System (CNS) depressants, for example, alcohol, opiates/opioids and benzodiazepines. This is similar to the findings by Gunja in his 2013 report (Gunja, 2013). Finally, the main underlying cause of deaths involving Z-drugs, whether as a contributory factor (usually as a component in a poly-drug overdose) or as a sole agent, was suicide (40.7% and 53.2% respectively) (Corkery *et al*, 2013).

29. Interpretation of the role of Z-drugs in DRDs is complicated by a number of factors. These include their short half-lives, considerable inter-patient variability, small sample sizes and the presence of co-ingestants. Gunja concludes that polydrug overdose was a major cofounder in deciding whether fatalities are attributable to detected Z-drugs (Gunja, 2013). The np-SAD report suggests Z-drugs do play a role in DRDs in the UK, mainly in combination with other CNS depressant agents, and principally implicated in episodes of intentional poisoning.

30. In conclusion published case reports, manufacturers warnings, user-led reports, ADR reporting and the Jaffe study (demonstrated around 1 in 4 opiate dependent patients took a Z-drug to “get high” and up to approximately 1 in 2 of the same cohort “liked the effects” (48.4% for zopiclone), suggest there is an abuse potential for the Z-drugs and this evidence seems to be more robust for zopiclone and zolpidem. However there is insufficient data to estimate the prevalence of Z-drug misuse in the UK population (Reed *et al*, 2011) and polydrug use can make it difficult to disentangle the exact role of Z-drugs in DRDs.

Recommendation

1. As it appears the harm associated with all three Z-drugs are commensurate with Class C and Schedule 4, Part 1 control, the current situation, where only one of the Z-drugs is controlled, represents an anomaly.

2. The ACMD recommends that zaleplon and zopiclone be controlled and brought in line with the current classification of zolpidem, i.e. class C of the Misuse of Drugs Act and Schedule 4 Part 1 of its Regulations.

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Appendix One - UK deaths associated with 'Z' drugs (Zopiclone, Zolpidem & Zaleplon).

The National Programme of Substance Abuse Deaths (np-SAD, The International Centre for Drug Policy.

Prepared by the np-SAD team (Salvatore Casula, Hugh Claridge, John Corkery, Carla Gimeno Clemente, Christine Goodair, Barbara Loi, Fabrizio Schifano)

March 2013

Introduction

This report has been provided to the Advisory Council on the Misuse of Drugs (ACMD) exclusively for its consideration of the 'Z' drugs (Zopiclone, Zolpidem and Zaleplon). Its use is therefore limited to the purposes of the ACMD.

The data presented here are based on notifications received by np-SAD up to the end of November 2012. Therefore, there may be further deaths which have either not yet been reported and/or for which inquests remain to be concluded. In particular, it is expected that there will be further cases for 2011 to be received.

This surveillance programme is based on voluntarily submission of information on cases by coroners; good geographical coverage of England & Wales started in 1999. Scottish data provided by the Scottish Crime & Drug Enforcement Agency commenced in 2004. In addition, although information is sought on any psychoactive drugs prescribed to cases, such information is not always available or submitted.

Background

There are no published data on the presence and/or role of 'Z' drugs in deaths in the UK. The information presented here aims to remedy that situation.

To be recorded in the np-SAD database as a drug-related death, at least one of the following criteria must be met: (a) presence of one or more psychoactive substances directly implicated in death; (b) history of dependence or abuse of drugs; and (c) presence of controlled drugs at post-mortem (Ghodse *et al*., 2013).

At the end of November 2012 the np-SAD database contained 27,194 cases received since being set up in July 1997. Of these, 13,399 (49.3%) had been prescribed a psychoactive drug including 5815 cases of hypnotics/sedatives

(21.4% of the total). Hypnotics/sedatives were reported as present in 4665 cases (17.2%) and implicated in death in 6133 cases (22.6%).[4]

Characteristics of cases analysed

For this investigation, cases were extracted by the np-SAD team where any 'Z' drug had been prescribed, found in the Post Mortem toxicology or implicated in the death.[5] The dataset thus created consisted of 1934 cases (Table 1). The breakdown and role of individual Z drugs are given in Table 2. The relative contributions of each Z drug given in Table 3 is very similar to the breakdowns of individual prescription items prescribed in England between December 2011 and November 2012: Zopiclone 88.18%, Zolpidem 11.80%, Zaleplon 0.02% (see draft ACMD report on Z drugs). This suggests that the np-SAD dataset is representative of the situation generally with regard to these drugs.

Table 1: Composition of np-SAD Z drugs dataset (n = 1934)

Dimension	Number	% of dataset	% of all np-SAD cases
Z drug prescribed	1545	79.89	5.68
Z drug in PM	822	42.50	3.02
Z drug implicated	570	29.47	2.10

Table 2: Composition of np-SAD Z drugs dataset by type of 'Z' drug

Dimension	Drug	Sole mention	% of all mentions	All mentions
Prescribed	Zopiclone	103	7.5	1377
	Zolpidem	6	3.7	161
	Zaleplon	2	16.7	12
	Any Z drug	111	7.2	1545
In PM	Zopiclone	26	3.6	720
	Zolpidem	4	3.8	104
	Zaleplon	0	0.0	3
	Any Z drug	30	3.6	822

[4] The reasons for this apparent inconsistency are (a) that toxicology is not always undertaken at death, (b) the relevant toxicological information was not included on the form submitted to np-SAD, and (c) about 10% of cause of deaths in drug-related cases are described as 'multiple'/'poly' substances ones without the substances being specified.

[5] Mentioned in the cause of death as either causing or contributing to that event, or in the coroner's verdict.

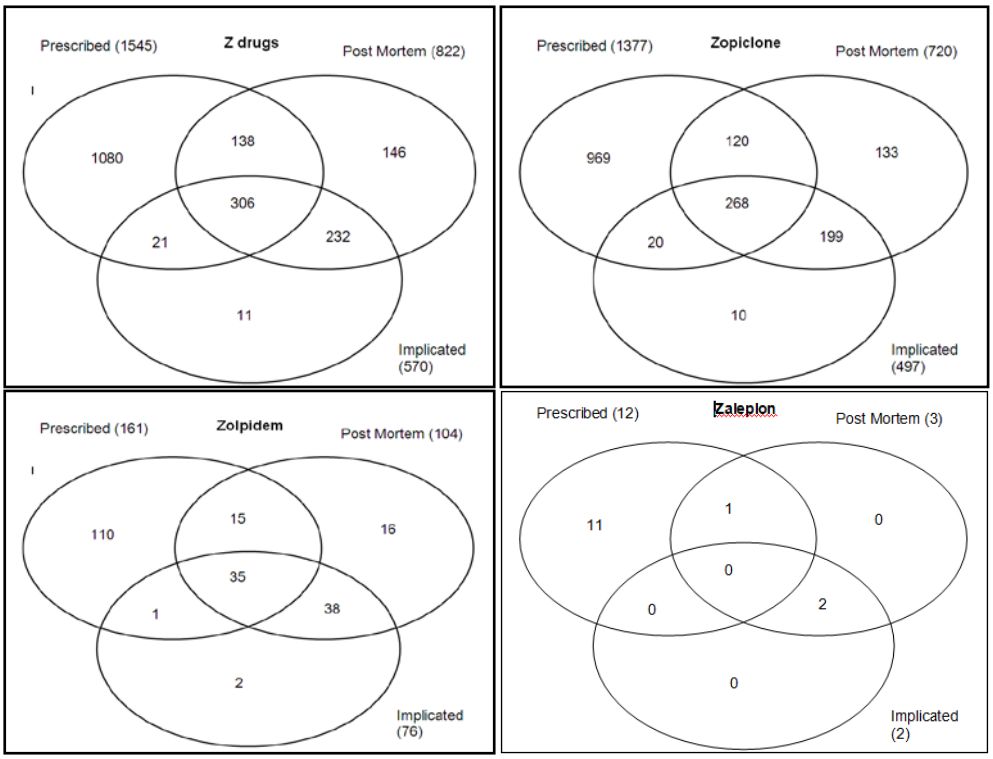
Implicated	Zopiclone	55	11.1	497
	Zolpidem	7	9.2	76
	Zaleplon	0	0.0	2
	Any Z drug	62	10.9	570

Table 3: Relative contribution of individual Z drugs to np-SAD Z drugs dataset

Z drug	Prescribed		In PM		Implicated	
	No	%	No	%	No	%
Zopiclone	1377	88.83	720	87.06	497	86.43
Zolpidem	161	10.39	104	12.58	76	13.22
Zaleplon	12	7.74	3	0.36	2	0.35
All Z drugs	1550	100.0	827	100.0	575	100.0

Figure 1 describes the overlap between prescription history, Post mortem toxicology and role of Z drugs in deaths.

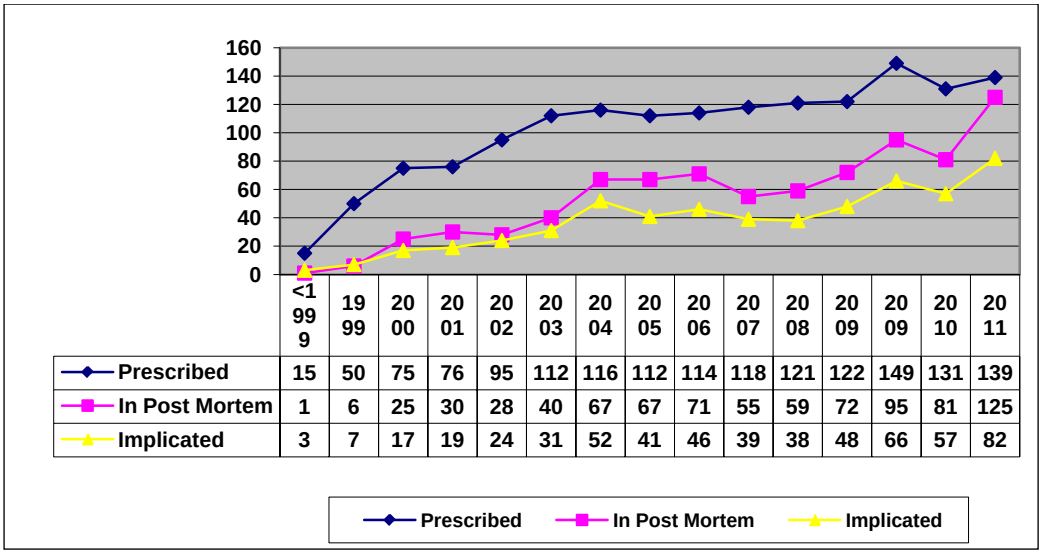
Figure 1: Overlap of Z drugs in Prescribing, Post Mortem toxicology and Implication in death, np-SAD Z drugs dataset



Note: The sum of the individual Z drugs will not necessarily equal the total number of Z drugs as more than one Z drug can be included in Prescribed, Post Mortem and Implicated occurrences.

Over the period 1998-2001, there appears to have been a gradual increase in the number of np-SAD cases where a Z drug was prescribed, found in the PM toxicology and implicated in death (Figure 2).

Figure 2: Trends in Z drug cases reported to np-SAD



	<1999	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2009	2010	2011
Prescribed	15	50	75	76	95	112	116	112	114	118	121	122	149	131	139
In Post Mortem	1	6	25	30	28	40	67	67	71	55	59	72	95	81	125
Implicated	3	7	17	19	24	31	52	41	46	39	38	48	66	57	82

The main demographics of the np-SAD Z drug cases are given in Table 4. This indicates that the male-female ratio is lower than seen in np-SAD cases generally – where there are typically 3 male to 1 female death. The majority of deaths appear to occur in those aged older than 24 years, although the mean age is not that different to typical np-SAD cases (Ghodse *et al*., 2013). Where known, three out of ten had a past history of drug use. Half died in a private residential address. Two-fifths of deaths were regarded as suicide with a quarter being also possible suicides (undetermined intent) compared to one-third being regarded as accidental in nature.

Table 4: Main demographics of deaths where a Z drug was implicated in death

Characteristic	Category	Any mention		Sole mention	
		No	%	No	%
Gender	Male	335	58.8	38	61.3
	Female	235	41.2	24	38.7
Age-group (years)	<15	1	0.2	0	0.0
	15-24	21	3.7	1	1.6
	25-34	97	17.0	3	4.8
	35-44	171	30.0	8	12.9
	45-54	126	22.1	10	16.1
	55-64	85	14.9	16	25.8
	>64	69	12.1	24	38.7
Age at death (years)	Mean	46.77		60.22	
	Min	7.03		24.10	
	Max	94.80		94.41	
	SD	14.79		17.22	
Addiction/drug	Yes	130	30.3	3	5.5

use history, (where known)					
Place of death	Defined residential address	459	80.5	48	77.4
	Hospital	70	12.3	10	16.1
	Other	41	6.2	4	6.5
Manner of death	Natural	3	0.5	0	0.0
	Accidental	194	34.0	9	14.5
	Suicidal	239	41.9	37	59.7
	Homicide	1	0.2	0	0.0
	Undetermined	132	23.2	16	25.8
	Unascertained/unknown	1	0.2	0	0.0
N		*570*		*62*	

The main underlying cause of deaths involving Z drugs was intentional poisoning (40.7%), followed by accidental poisoning (33.5%) and poisoning of undetermined intent (22.6%). Where a Z drug was implicated on its own, the dominant pattern appears to be one of suicide: intentional poisoning (53.2%), poisoning of undetermined intent (25.8%), and accidental poisoning (11.3%) – Table 5.

Table 5: Underlying cause of death in cases where Z drugs were implicated

ICD10 code	Any mention		Sole mention	
	No	%	No	%
R99 unascertained	1	.2		
X42 acc poisoning by narcotics & psychodysleptics	113	19.8		
T07 multiple injuries, unspecified	1	.2		
X70 hanging, intentional	1	.2	1	1.6
X47 acc poisoning by gases	1	.2		
X41 acc poisoning by antieps sed/hyps, antipark & psychotrop	66	11.6	7	11.3
X40 acc poisoning by non-opioid analgesics	4	.7		
X44 acc poisoning by other unspecified drugs	7	1.2		
X71 ish by drowning	2	.4	1	1.6
X62 int self poisoning by narcotics & psychodysleptics	85	14.9		
X61 isp by antieps, seda/hyps, antipark & psychotropi	133	23.3	33	53.2
X60 isp by non-opioid analgesics	4	.7		
X64 isp by unspecified drug	7	1.2		
X65 isp by alcohol	1	.2		
J96.9 respiratory failure or depression	2	.4		
X63 int poisoning by & exposure to other drugs acting on the	2	.4		
R09.0 asphyxia general	2	.4	1	1.6
T17.9 aspiration of gastric contents	2	.4		
R09.2 cardiorespiratory failure/arrest	1	.2		
Y11 open verdict poisoning by antieps sed\par	78	13.7	16	25.8
Y10 open verdict poisoning by non-opioid	2	.4		
Y12 open verdict poisoning by narcotic/psychodyl	43	7.5		
R04.8 pulmonary haemorrhage	1	.2		
T42.4 benzodiazepine overdose	1	.2	1	1.6
G96.9 other (inc. depression) of the central nervous system.	1	.2		
X85.0 Assaulted by drugs etc, at home	1	.2		
I25.1 atherosclerotic heart disease	1	.2	1	1.6
W17 Other fall from one level to another	1	.2	1	1.6
Y14.0 Poisoning by other & unspec drugs - undetermined inten	6	1.1		
Total	570	100.0	62	100.0

Causes of death

A closer look at the causes of death reveals several deaths where there was trauma but also the ingestion/involvement of a Z drug (Table 6). This not

surprising given the substantial proportion of cases that were suicidal in nature.

Table 6: Examples of traumatic deaths where Z drugs were mentioned, np-SAD Z drugs dataset

1a Drowning in bath; 2 Ingestion of excessive amount of Zolpidem
1a Drowning; 2 Zopiclone and clozapine Toxicity
1a Drowning in seawater; 2 Presence of Venlafaxine and Zopiclone in over dose
1a Hanging; 2 Excessive ingestion of Zopiclone
1a Multiples injuries [fall from 10th floor]; 2 Excessive ingestion of Zopiclone medication
1a Plastic bag suffocation & toxic effects of Zolpidem
1a Skull fracture & brain contusions [?fall at home]; 2 Drowsiness, impaired co-ordination & dizziness due to the use of Zopiclone and Citalopram

Drug interactions and combinations

Whilst there are many cases of deaths where there are combinations of Z drugs with CNS depressants, there were three cases where the term “drug interaction” was specified in the cause of death (Table 7).

Table 7: Examples of drug interactions where Z drugs were mentioned, np-SAD Z drugs dataset

1a Cardio-respiratory failure; 1b Depression of Central Nervous System; 2 Interaction of Codeine and Zolpidem with over-ingestion of Alcohol
1a Epileptiform fits; 1b Hypoxia & adverse interaction between Alcohol and therapeutic overdose
1a CNS depression; 1b Interaction of drugs – benzodiazepines, Codeine & Zopiclone

Tables 8 and 9 present the combinations of Post Mortem drugs for (a) any Z drug implicated and (b) a sole Z drug implicated in death. The majority of both types of death involve combinations of substances which depress the Central Nervous System, e.g. alcohol, opiates/opioids, and benzodiazepines. Antidepressants also appear frequently in these combinations.

Table 8: PM drug combinations in cases where Z drugs were implicated, np-SAD Z drugs dataset

	No
No drug	22
No Z drug but other drug	6
Z drug alone	30
Z drug + Alcohol only	30
Z drug + Benzo (no Alcohol)	7
Z drug + Alcohol + Benzo	14
Z drug + Alcohol + other	26
Z drug + Antidepressants	51
Z drug + Antidepressant + Alcohol	53
Z drug + Benzo + Antidepressant (+/- Alcohol)	26
Z drug + Opiate/opioid	46
Z drug + Opiate/opioid + Antidepressant	89
Z drug + Opiate/opioid + Benzo	21
Z drug + Opiate/opioid + Antidepressant + Alcohol	20
Z drug + Opiate/opioid + Alcohol	47
Z drug + Opiate/opioid + Benzo + Alcohol	22
Z drug + Opiate/opioid + Benzo + Antidepressant	29

Z drug in any other combination	31
N	*570*

Table 9: PM drug combinations in cases where a Z drug was implicated on its own, np-SAD Z drugs dataset

	No
No drug	2
Z drug alone	29
Z drug + Alcohol only	1
Z drug + Alcohol + Benzo	1
Z drug + Alcohol + other	2
Z drug + Antidepressants	6
Z drug + Antidepressant + Alcohol	3
Z drug + Benzo (no Alcohol)	2
Z drug + Benzo + Antidepressant	2
Z drug + Hypnotic/sedative	2
Z drug + Opiate/opioid	1
Z drug + Opiate/opioid + Benzo	1
Z drug + Opiate/opioid + Antidepressant + Alcohol	2
Z drug in any other combination	8
N	*62*

Reference

Ghodse, H., Corkery, J. Claridge, H., Goodair, C., & Schifano, F. (2013). *Drug-related deaths in the UK: Annual Report 2012*. Drug-related deaths reported by Coroners in England, Wales, Northern Ireland, Guernsey, Jersey and the Isle of Man; Police forces in Scotland; & the Northern Ireland Statistics and Research Agency – Annual Report January-December 2011. 28 February. London: International Centre for Drug Policy, St George's University of London.
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