Zopiclone

Assessment of the consumption and consequences of zopiclone (Zimovane) among drug-takers in a North-East town

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Executive Summary

This report focuses on zopiclone use, and has two main parts: an overview of the literature on zopiclone; and a presentation of the methods and findings of research into zopiclone use among drug users in a town in North-East England in 2008. Its main application is to provide a knowledge base on which to produce a publication about zopiclone to inform and educate users of the drug.

Zopiclone belongs to a sub-group of hypnosedatives called cyclopyrrolones. It is often grouped together with other benzodiazepine-like drugs (notably zolpidem and zaleplon) under the name of 'Z-drugs'. Though not controlled under the UK's Misuse of Drugs Act, zopiclone is a prescription-only drug, used by doctors to treat insomnia. It is produced in two doses – 3.75 mg and 7.5 mg – and has one proprietary brand (Zimovane), though there are a variety of non-proprietary tablets which come in many forms (colours, shapes, etc.).

Recent prevalence studies suggest that less than 1% of the UK population had used unprescribed zopiclone in the past year, though more than 1% may have been prescribed it – there were almost four and half million prescriptions for zopiclone in England in 2007, making it the second most commonly prescribed hypnosedative after diazepam.

In addition to its primary effect of inducing and sustaining sleep, zopiclone also causes sedation and cognitive deficits (impairments in reasoning and memory). Its main physical effects include a metallic taste in the mouth, and reduced coordination. Experience of both euphoria and dependence (craving, tolerance, and withdrawals) appear to be associated with four inter-linked factors: (a) non-prescribed versus prescribed use; (b) heavy versus lighter (standard-dose) use; (c) escalating rather than stable doses; and (d) taking zopiclone for pleasure (staying awake), rather than using it to sleep. Duration of use **per se** is not a critical factor in zopiclone dependence.

The main health risks of zopiclone, particularly from regular and/or heavy use, include cancer, reduced immunity, accidents/injuries, and overdose/poisoning. The number of deaths from poisoning by zopiclone or zolpidem in England & Wales climbed from zero in 1993 to an average of 40 to 50 per year in the noughties. Most fatal overdoses from zopiclone involved other drugs, notably alcohol.

A focus group with six local service users who had used zopiclone was conducted at a drug agency in a North-East town in July 2008, with additional information provided by two senior staff. The participants confirmed that the main methods of obtaining zopiclone, known as 'zimmies' or 'zimmers' to local users, involved buying diverted tablets (from people prescribed them) or imported tablets. The two main reasons given for taking zopiclone were (1) using it as a substitute for heroin when the latter's availability or quality was poor, and/or (2) using it to cope with the stimulant effects or come-down from crack use.

Participants generally reported swallowing zopiclone tablets, though two had injected them, one regularly. Average doses were 6 to 12 tablets for lighter users, and 20 to 40 tablets for heavier users. The typical pattern of zopiclone use involved bingeing – periods of daily or near-daily use interspersed with periods of abstinence (related to availability and other factors). The main drugs 'mixed' with zopiclone were crack-cocaine and alcohol.

The main physical effects of zopiclone were reported to be an unpleasant metallic taste, and lack of coordination – including an inability to carry out simple actions like sitting down. The main desirable mental effects were reported to be sedation and euphoria. Less desirable mental effects included memory problems (notably post-use amnesia) and emotional problems – notably feeling numb and (conversely) aggressive outbursts.

Heavier users also reported that regular zopiclone use had led them into dependence, including strong craving and severe withdrawal symptoms on discontinuing use - notably fatigue, aching limbs, sweats and insomnia. However, no participants reported overdosing on zopiclone nor requiring medical attention.

It was concluded that publications designed to provide relevant information to zopiclone users should focus on the following consumption risks and harmful consequences: amounts used; methods of use; patterns of use; use with other drugs; behavioural and social problems; and reducing the risks of accidents, overdose, and dependence.

1. Introduction

Over the last decade, drugs workers in the North-East have become increasingly aware of the misuse of zopiclone (Zimovane) among local drug users. Zopiclone is a hypno-sedative drug, prescribed by doctors to people suffering from insomnia, and has been commercially available in Europe since the second half of the 1980s. In order to improve their understanding of the misuse of zopiclone, and to provide a knowledge base on which to design publications (information products) for zopiclone users, Lifeline Publications were commissioned to conduct a small-scale action research project. The project was designed to meet two key objectives:

(1) To conduct focus groups and interviews with clients and staff of a drug agency in a North-East town about local zopiclone use, and produce a report on the research findings, incorporating an overview of the literature on zopiclone use and misuse;
(2) To produce a publication for drug service clients, providing them with information about (a) zopiclone's consumption, effects and consequences, and (b) how to minimise the risks and harms associated with zopiclone use.

2. Methods of investigation

Overview. The design and setting up of the research took place in June 2008. The data-collection stage of the research had three components, each of which was carried out in July 2008:
(1) An overview of the literature on zopiclone (both published work and grey literature);
(2) Focus group work: this was conducted on the premises of a North-East drug agency on the afternoon of Tuesday 8th July, and ran for almost one and a half hours. The focus group took place in a large room with a central table and chairs, and some seating along one wall, with those present seated in a roughly circular fashion. In addition to the six volunteer clients, two Lifeline drugs workers were present, along with the Lifeline researcher (RN). The session began with the researcher explaining the aims and objectives of the research, including making it clear to the clients that participation was voluntary, confidential, and anonymous, and that their assistance would be rewarded with £10 payment. A second focus group was also an option within the research plan, but, following negotiations, the amount and quality of information provided by the first focus group resulted in a decision that a second focus group was not necessary;
(3) Unstructured interviews were also conducted with two members of staff at the agency following the focus group session, who also provided further information over the following two weeks via telephone calls and emails.
The analysis and reporting stages of the research were carried out from July to September 2008.

Focus group participants - profile. At July 2008, the drug agency had 1,061 registered clients, and although only 12 were recorded as using 'other prescription drugs' or 'other sedatives' under the NDTMS classification of primary drug use, the agency managers believed that "a good number" of clients had used zopiclone as 'secondary drugs' in recent years. Six suitable individuals were recruited by the agency to participate in the focus group, based on the primary criterion that they had been or were users of zopiclone - including three men (M1, M2, M3) and three women (F1, F2, F3). Two participants had been attending the Lifeline service for about four years; two had been attending for about six months; and one had been attending for about a year. The sixth participant (F2) was not attending the service, but was the friend of one of the five service-user participants (F1). Three participants were in their early twenties, and three were in their mid-thirties. All six clients were White and British, five of whom were English, and one of whom was Scottish (M1). All were current residents of the North-East town in which the agency was based. Two participants (M1 and F3) were in a sexual relationship. All six participants were alert and attentive throughout the discussion, and none were considered to be too intoxicated by drugs to participate effectively. Indeed, the majority of participants contributed a great deal of useful information, and, with the exception of M2, they approached the task in an enthusiastic and constructive manner.

Focus group procedure. In order to promote a confidential atmosphere and encourage honest responding, all relevant responses were written down by the researcher, rather than tape-recorded. As in any focus group, a degree of meshing (participants speaking at the same time) inevitably occurred, which, combined with a degree of mumbling from some participants, resulted in the loss of a small amount of information. Participants generally stuck to the main topic of discussion (zopiclone and its effects), and discussion of tangential or irrelevant topics took up less than about 5% of the time. Overall, two of the six respondents (F1 and M3) did most of the talking, accounting for about 60% of the information collected; another two respondents

(M1 and F3) did a reasonable amount of talking, accounting for about 30% of the information provided; and the remaining two respondents (F2 and M2) were relatively quiet, contributing about 10% of the information provided. The latter two respondents often attempted to make contributions to the discussion, but were frequently 'talked down' by the more extravert participants in the group. In short, the six participants comprising the focus group were a fairly representative selection of the different types of personality found in any community.

The information provided by participants was generally delivered in an unstructured fashion, though as the end of the session was approached, efforts were made by the researcher to ensure that all relevant issues had been adequately covered (using 'prompts' for core topics which had not been spontaneously covered). The information recorded during the focus group session was 'sifted and sorted', and eventually organised under five key headings: psycho-social context (aetiology, epidemiology, market, etc.), consumption (amounts, methods of use, patterns of use, etc.), short-term effects (physical and mental), harmful consequences (health, social, etc.), and behaviour change (e.g. service attendance).

Research instruments.
(1) schedule of topics to be covered in each focus group;
(2) semi-structured format for recording comments and discussion in each focus group.

The schedule of topics was generated systematically from a conceptual model of drug use, covering risks, effects, consequences and interventions (Newcombe 1992, 2008). If a core topic was not covered spontaneously during the focus group discussion, then participants were prompted on it by the researcher toward the end of the session. Expressed in the form of questions, the core topics were:

What are/were your primary drugs of misuse?
Have you or your friends used zopiclone - ever or in the past year?

Have you been prescribed zopiclone for insomnia or other problems?

How common is zopiclone use among local drug users?

What are the main reasons for zopiclone use among drug users?

How is zopiclone used by local drug users – particularly (a) routes of use, (b) amounts used per session, and (c) patterns of use?

What drugs is zopiclone usually taken together with?

What are its positive and negative effects on (a) the mind and (b) the body?

What problems (harmful consequences) does zopiclone use result in?

How habit-forming is zopiclone, and what kind of craving does a zopiclone habit involve?

Does regular use lead to withdrawals, and if so, what are the main symptoms?

Have you ever used other 'Z drugs' – such as zolpidem (Stilnoct) or zaleplon (Sonata)?

Have you ever used other insomnia medications – such as temazepam (Normison), nitrazepam (Mogadon) or other sleeping pills?

Given the aims of the research, and in order to emphasise confidentiality and encourage honest responding, questions were generally focused on drug use in the unspecified 'past', and questions geared toward 'present' drug use (i.e. past week/ month) were avoided.

The drug agency in which the research was based was launched in 2004. It is located in the city centre, and is open 9am to 6pm Monday to Friday, and from 10am to noon on Saturdays. It is an open-access, self-referral drug and alcohol agency, and has various out of hours and community based sites available. The services it offers include advice, information and support; assessment and referrals; needle exchange; and a range of health and social interventions. The original service was expanded in 2008 to incorporate a specialist stimulant service. At the time of the research, full-time staff included a nurse, a community development worker, a pharmacy coordinator (whose time was split between two services), and three drug advice workers. These were complemented by a part-time needle exchange/ administration worker, and a team of volunteers, of which about 15 were active at any given time.

3. Findings

The findings of the research are presented below under two headings: an overview of the relevant scientific literature; and a report on the findings of the research, including the focus group with service users, and interviews with staff.

3.1 Overview of literature on zopiclone

There is an extensive and scattered literature on zopiclone covering several disciplines and professions, and it was not possible to provide a comprehensive and systematic review of this literature within the scope and resources of the present small-scale project. Instead, this section provides a thorough overview of relevant issues based on available reviews of the literature (eg. psychopharmacology, toxicity, dependence, illicit use), as well as salient research work - both classic studies and recent investigations. The main review paper was published by the World Health Organisation in 2006, though other papers reviewing aspects of the zopiclone literature include NICE (2004) and Dundar et al. (2004). These reviews show that apparent conflicts in the evidence are typically due to differences between prescribed and non-prescribed users, and between light and heavy users – as well as between users who take the drug to aid sleep and those who use it because they like it or need it. The information covered by the present overview is summarised below under the following headings: appearance, chemistry, medical issues, psychopharmacology, other Z-drugs, epidemiology, legal status, short-term effects, and harmful consequences.

Appearance. When first synthesised, zopiclone is a white to light-yellow crystalline solid. The appearance of tablets can differ according to five main variables: shape, colour, size, markings (e.g. scored line across diameter, lettering), and coating (e.g. film-coated). As with many other pharmaceutical drugs, there are two types of zopiclone available: proprietary and non-proprietary. Pharmacists stock both types in 28-tablet packs. The proprietary tablet is generally marketed in the UK under the brand name Zimovane (Rhone-Poulenc Rorer), though Opus markets it as Zileze (mainly in Ireland). The non-propietary zopiclone tablet is marketed by about 10 pharmaceutical companies. Consequently, zopiclone tablets are available in numerous shapes, sizes, colours, etc.. Zimovane tablets are film-coated (f-c) and scored, but its not clear if all the non-proprietary forms of zopiclone are film-coated or scored. Tablets of either type also come in two doses: 7.5 mg and 3.75 mg. The 7.5 mg Zimovane tablet is white and marked ZM; while the 3.75 mg tablet (labelled Zimovane LS) is blue and marked Z – but neither MIMS nor BNF indicates the shape of Zimovane tablets. The 7.5 mg non-proprietary tablet is also white, though its shape can be either round or oblong (depending on the pharmaceutical company making it). The 3.5 mg non-proprietary tablet is pale brown and round. Information about the physical size of the various tablets is not routinely available.

It should be noted that zopiclone has many other brand names and formulations in other English-speaking countries - notably Imovane in Canada, Australia, New Zealand and South Africa. Thus, imported zopiclone tablets may differ from the standard appearances described above. Lastly, injectable formulations have also been synthesised recently, but are not yet available from pharmaceutical companies (see below).

Chemistry. The full chemical name of zopiclone is chloropyridinoxotriazabicyclonona-trienylmethylpiperazinecarboxylate ($C_{17}H_{17}ClN_6O_3$). Psychoactive drugs can be usefully organised and understood by categorising them within a hierarchical system similar to that used to classify life-forms, notably: class, order, family, genus (specific drug) and species (specific form of drug). Zopiclone belongs to the CNS depressant class of drugs, within which it comes under the hypnosedative order - the other two orders of depressants are opioids (notably heroin) and inebriants (notably alcohol). Hypnosedatives are also divided into two sub-orders: anxiolytics (which reduce anxiety during waking hours) and hypnotics (which induce and assist sleep). Zopiclone belongs to the latter sub-order. Hypnosedatives include the two main families of barbiturates and benzodiazepines, along with more recent families such as cyclopyrrolones – the family to which zopiclone belongs. Although cyclopyrrolones share a number of characteristics and effects with benzodiazepines, they are a novel chemical family structurally unrelated to existing hypnosedatives. It should also be noted that zopiclone is a racemic mixture of two enantiomers (mirror-image molecules): (R)-zopiclone and (S)-zopiclone. Only the latter form, also known as eszopiclone, is psychoactive. Though not available in the UK, eszopiclone is marketed as Lunesta (3.5 mg) in the USA. Research generally indicates that eszopiclone has fewer side-effects than racemic zopiclone – for instance, on next-day psychomotor performance. Lastly, like all drugs, zopiclone can also be produced in different chemical formulations (e.g. salts) for specific purposes – such as the more water-soluble zopiclone hydrochloride (see below).

Classification of zopiclone

Class	Order	Family	Specific drug	Specific form(s)
Depressant	Hypnosedative (Hypnotic)	Cyclopyrrolone	zopiclone	eszopiclone zopiclone HCl

In its standard form, zopiclone is "practically insoluble", even when routine methods for improving solubility are applied, such as co-solvency, pH control and hydrotrophy (Swamy et al., 2008). It thus needs to be chemically converted into a suitable formulation – notably zopiclone hydrochloride – to become soluble enough to be efficiently and effectively injected: "since zopiclone is a weak base, a hydrochloride salt with the required solubility … was used for the formulation of injection" (Swamy et al., op. cit., p.102).

Medical issues. Zopiclone is recommended for the treatment of insomnia (transient, situational, or chronic), including insomnia secondary to psychiatric disturbances. The effective dose of zopiclone for reducing insomnia in adults is generally regarded to be in the range 5 mg to 7.5 mg – though elderly people need around half as much as younger adults, while people with some types of psychiatric disorder may need up to 15 mg. Like most other hypnosedatives, zopiclone is generally not recommended for children – nor for people with liver or kidney disease, or pregnant or breast-feeding women. Due to its dependence and tolerance potentials, UK medical authorities recommend that prescribing of zopiclone to insomniacs be restricted either to short-term daily use (up to 2 weeks in general, and 4 weeks as a maximum) or long-term infrequent use (BNF and MIMS). NICE guidance (2004) advises that patients who have not responded to one Z-drug should not be prescribed any of the others.

One recent paper has provided a systematic review of the literature on the clinical efficacy and cost-effectiveness of the three Z-drugs compared with benzodiazepines (Dundar et al. 2004). Unfortunately, the 24 relevant studies (including 13 with evidence about zopiclone) suffered from "a confusing diversity" of comparisons, outcome measures and methods. The authors tentatively concluded that there were no major differences between the two groups of hypnosedatives either in their efficacy or safety.

The latest update of "Drug Misuse and Dependence: Guidelines on Clinical Management" (2007) recommends that zopiclone be prescribed for anxiety and insomnia (rather than diazepam) in the symptomatic treatment of opioid addiction in people who have also been dependent on benzodiazepines.

Psychopharmacology. After oral administration, zopiclone is rapidly absorbed in the gut, with a bio-availability of about 80% - though consumption of high-fat foods prior to zopiclone ingestion may delay the onset of effects. It is rapidly distributed all over the body, including the brain. Zopiclone is very similar to benzodiazepines in its effects on the brain, and has an almost identical pharmacological profile – though it also has some barbiturate-like properties. Its main mechanism of action involves modulating neuron receptors for the neurotransmitter GABA, and it also benzodiazepine-like effects on dopamine and serotonin receptors. Zopiclone is partly metabolised in the liver into two metabolites, one inactive (zopiclone-N-oxide) and one active (N-desmethyl-zopiclone). When ingested, about half of the dose of zopiclone taken is decarboxylated and excreted via the lungs (breathed out), and almost a third is excreted in urine (7% as unchanged zopiclone, 93% as metabolites). Zopiclone and its two metabolites are also excreted in saliva and breast milk (so should not be used by nursing mothers). At mid-2008, commercially available body fluid tests for illicit drug use (including urine, saliva and sweat tests) did not include zopiclone or its metabolites in the various sub-groups of chemicals which they cover (diazepam and temazepam are the only hypnosedatives routinely covered by drug testing devices at present).

Other Z drugs. Z-drugs are hypnosedatives, typically sleeping pills, whose chemical names begin with the letter 'z' (as do some of their many trade names). There are three main Z-drugs - zopiclone, zolpidem, and zaleplon – all of which are prescription-only medicines (POMs). Since illicit users of zopiclone may sometimes use other Z-drugs, by 'accident or design', each of the other two main Z-drugs will be briefly described here. Zolpidem (Stilnoct), as noted above, is the only Z-drug controlled under MODA 1971 (made Class C in 2003). It belongs to a family of benzodiazepine-like hypnosedatives called imidazopyridines. They

are generally marketed as 5 mg or 10 mg white scored oblong film-coated tablets, with the higher-dose variety marked 'SN' - though some may be marked with the letters 'ZIM', which is one reason why they may be mistaken for Zimovane. Zaleplon (Sonata), like zopiclone, is not classified under MODA 1971, and belongs to a family of benzodiazepine-like hypnosedatives called pyrazolopyrimidines. It is dispensed in the UK in the form of capsules, either 5 mg (white or light brown) or 10 mg (white). The powder contained in the capsules can be emptied out and snorted, though, as with zopiclone, the powder is highly insoluble and so not easily injected. Zaleplon is also shorter-acting than either zopiclone or zolpidem. Consequently, unless sold illicitly in powder form (i.e. purported to be crushed tablets rather than capsule contents), zaleplon is unlikely to be mistaken for zopiclone. Indeed, unlike the other Z-drugs, zopiclone has a unique distinguishing feature which enables illicit users to identify it - namely, its strong metallic after-taste.

Epidemiology of use. Little is known about the prevalence and characteristics of prescribed and illicit (non-prescribed) users of zopiclone in the UK, because it is not itemized separately either in annual surveys of the prevalence of drug use (eg. British Crime Survey) or one-off studies of samples of drug users. As with official statistics, research typically incorporates zopiclone under such general headings as 'hypnosedatives' or 'tranquillisers', or under such residual categories as 'other drugs'. One exception is a study by Jaffe and colleagues (2004), which surveyed 297 drug addicts attending treatment agencies at three sites in the UK regarding their use of nine hypnosedatives (five benzodiazepines, two Z-drugs, and two anti-histamines) and three anti-depressants. Slightly more than half of the sample reported zopiclone use, which was ranked fourth by level of use after diazepam, temazepam and nitrazepam. About 80% of zopiclone users had been prescribed it, while 42% reported having purchased it 'on the street' (i.e. through illicit sales). Regarding reasons for use, although nine in ten (89%) reported taking zopiclone to aid sleep, over half (57%) reported taking it 'to feel better' and almost a quarter (23%) reported taking it 'to feel high'. Similarly, about half of zopiclone users stated that they liked its effects, 28% felt that they needed it, and 5% believed that they were addicted to zopiclone – though a further 20% thought that they might become addicted to it. Higher levels of self-reported addiction to the 12 prescribed drugs covered by the study were reported only for the three more popular benzodiazepine drugs (diazepam, temazepam and nitrazepam).

Other studies of zopiclone use among drug treatment clients suggest that there is wide variation in prevalence of use among drug addicts, which is possibly related to the quality of illicit heroin in the areas studied. For instance, a study of 100 poly-drug using heroin addicts consecutively attending Liverpool drug dependency unit found that only six reported zopiclone use (Sikdar & Ruben 1996). By contrast, 38 (69%) of 55 patients attending a methadone program in Ireland reported zopiclone use (Rooney & O'Connor 1998).

As noted, the annual British Crime Survey (BCS) does not itemise zopiclone separately, but does report figures for 'tranquillisers', defined as including benzodiazepines and barbiturates. Given that zopiclone is a classified as a benzodiazepine-like hypnosedative, it is possible that respondents may have indicated zopiclone use by checking the 'tranquillisers' item. Whatever the situation, BCS figures for tranquilliser use arguably provide a 'rough and ready' indicator of the general scale of illicit zopiclone use in England & Wales. Between 1995 and 2007/08, past-year prevalence of tranquilliser use has remained between 0.4% and 0.7% for adults (16-59s), and between 0.6% and 1.5% for young adults (16-24s) (Home Office 2008). Similar annual levels of tranquilliser use (0.4%-0.5%) have been reported among 11-15 year olds in annual surveys of secondary schoolchildren in England up to 2007 (NCSR/NFER 2008).

The latest annual bulletin on prescription costs in England reported that there were 4,415,000 prescriptions for zopiclone dispensed from community pharmacies in 2007, compared with 4,125,000 in 2006 (NHS Information Centre 2008). The statistics for each year also show that almost two-thirds of zopiclone prescriptions were for higher-dose (7.5 mg) tablets, and just over a third were for lower-dose (3.75 mg) tablets; and also that just 2% of zopiclone prescriptions involved the proprietary brand Zimovane. By comparison, there were only 686,000 prescriptions of zolpidem, and just 32,000 prescription of zaleplon in 2007. Indeed, zopiclone was the second most common hypnosedative prescription in England in 2007 - only the number of diazepam prescriptions was (slightly) higher: 4,722,000. There were also 356,000 prescriptions of zopiclone dispensed from pharmacies in Scotland in 2006/07 – for a total of 10.5 million tablets (a mean of about 29 tablets per prescription).

Legal status. Zopiclone is not classified under the Misuse of Drugs Act (MODA 1971), and so is legal to possess and use without a prescription. However, zopliclone is a prescription only medicine (POM) under the 1968 Medicines Act, and so supply is legally restricted to doctors (prescribing) and pharmacists (dispensing).

To complete the picture on the legal status of hypnosedative drugs, all drugs within the two main families have been legally controlled since the mid-1980s. That is, barbiturates (barbs) were brought under Class B of MODA in 1985, and benzodiazepines (benzoes) were brought under Class C in 1986. Regarding medical controls, barbiturates are in Schedule 3, along with three benzodiazepines (temazepam, flunitrazepam and midazolam); and all other benzodiazepines are in Schedule 4i. Only three other hypnosedative drugs are controlled under MODA: methaqualone, zolpidem and GHB. Methaqualone (Mandrax or Quaaludes) was made a Class B, Schedule 2 drug under the original 1971 Misuse of Drugs Act. Zolpidem and GHB were made Class C, Schedule 4i drugs by a MODA Modification Order in 2003. All other hypnosedative drugs remain unclassified – including anti-histamines (e.g. diphenhydramine), aldehydes (e.g. chloral hydrate), and cylopyrrolones (e.g. zopiclone).

Short-term effects. The physical and mental effects of zopiclone are mediated by how it is consumed – most notably, the intensity and/or duration of effects increases with the amount consumed (other relevant factors include frequency of use, setting of use, other drugs used, etc.). There are no salient gender or race differences, though age is relevant – a key finding is that elderly people require about half the standard dose to experience the same effects (and to reduce negative after-effects like daytime fatigue). Another general point, already mentioned in the previous section, is that zopiclone has very similar effects to benzodiazepines.

The main **physical effect** of zopiclone is listed by standard medical texts as being an unpleasant **metallic after- taste** in the mouth (dysgeusia), which is experienced by most users within an hour or so of swallowing the tablet(s), and often continues the next morning. Less prevalent but fairly common physical side-effects include stomach disturbances (nausea, vomiting, etc.), dry mouth, lack of coordination, dizziness and headaches. Allergic reactions are rare, and typically involve skin rashes.

The main **mental effect** of zopiclone is to induce and sustain sleep - for periods of 6 to 8 hours. Zopiclone has a very fast onset of action compared with many other sleeping pills, and clinical trials in sleep laboratories have shown that "zopiclone leads to an increase in total sleep duration, a decrease of stage 1 sleep and increases of stages 2, 3 and 4 sleep" (WHO 2006: 2). In short, zopiclone prolongs total non-REM sleep and reduces total REM sleep (i.e. dream-sleep). The WHO review also concluded that zopiclone is more "suitable for maintaining a complete night's sleep than sleep induction" (2006: 5), and that it increases total sleep time and improves sleep quality. People awakened from zopiclone-induced sleep are likely to be very groggy (semi-conscious), particularly if woken during the first 3 or 4 hours of sleep. Drowsiness and **sedation** are the main mental effects of zopiclone in people who stay awake after taking the drug. However, unlike many benzodiazepines, research generally suggests that standard doses of zopiclone are not anxiolytic in humans (i.e. do not reduce anxiety).

As a correlate of these primary hypnotic and sedative effects, zopiclone is also reported to produce **cognitive deficits**. These impairments to reasoning and memory affect performance of various skilled tasks, mainly during the first six to eight hours of intoxication (if users remain awake). For instance, memory deficits peak at one to two hours after swallowing a standard dose, with declining residual effects for six to eight hours. However, some studies have also found impairments in reasoning and coordination during the morning after zopiclone-induced sleep (i.e. 8 to 12 hours after ingestion) – though zopiclone has also been found to have less effect on daytime alertness than nitrazepam. Consequently, people on zopiclone are advised to avoid driving, cycling or operating machinery – for up to 24 hours after last use of the drug - otherwise there may be an increased risk of **accidents and injuries.**

The WHO literature review pointed out that no research has explicitly assessed the impact of zopiclone on **euphoria**, though noted that case studies and small-scale surveys reporting euphoric effects typically involve illicit drug users and/or people with psychiatric disorders. Also, although **aggression** is generally reduced with prescribed use of standard doses of zopiclone, there is also case-study evidence that dependent or heavy users may become aggressive when intoxicated, sometimes to the point of criminal violence (see next section).

Harmful consequences. Although zopiclone was initially regarded as a non-addictive hypnotic with low potential for misuse by drug users, experience over the last two decades has resulted in a widely documented change in medical opinion. The medical literature indicates that prolonged use of zopiclone (daily or near-daily use for between a month and six months) can lead to **dependence** – that is, tolerance, craving and withdrawals. Some research has shown that zopiclone has even greater addictive potential than benzodiazepines. However, there is also consistent evidence that dependence and withdrawals are very rare among people prescribed stable doses for insomnia - particularly compared with non-prescribed users whose daily doses had escalated over a prolonged time. A broader interpretation is that zopiclone dependence is most likely among people with a general predisposition towards drug dependence (whether prescribed zopiclone or using it illicitly). As the WHO literature review concluded, "zopiclone dependency has been reported to occur mainly in patients with a history of drug abuse" (2006: 10). There is also evidence that psychiatric disorders such as depression are also associated with increased risk of developing dependence on zopiclone.

When withdrawal symptoms are experienced, they include anxiety, vertigo, tachycardia, tremor, sweats, flushes, palpitations, derealisation, and rebound insomnia – with convulsions reported in some cases. Animal research indicates that the withdrawal syndrome following discontinuation of regular zopiclone use is less severe than with diazepam but similar to nitrazepam (WHO 2006). To reduce the risk of dependence, medical sources generally recommend that zopiclone be prescribed for no longer than about ten to 14 days in succession, though some texts indicate that up to four weeks of daily use may be justified in some cases (notably patients having no history of drug dependence). To minimise unpleasant withdrawal symptoms, people addicted to prescribed zopiclone may be medically advised to switch to an equivalent dose of diazepam (which has a longer half-life), and to detoxify on a reducing dose of diazepam over several months.

Adverse drug interactions have been reported when zopiclone has been taken at the same time as erythromycin (antibiotic for people allergic to penicillin), trimipramine (tricyclic anti-depressant), or carbamazepine (anti-convulsant and mood stabiliser). Most medical texts also give the general advice not to 'mix' zopiclone with other depressant drugs, particularly other hypnosedatives and alcohol.

Due to the cognitive deficits described earlier, there is likely to be an increased risk of **accidents and injuries** among zopiclone users, particularly heavy or dependent users. The WHO literature review reported several studies which found evidence of impairments in driving skills associated with use of standard doses of zopiclone up to 12 hours after ingestion. For instance, "comparative analyses … have consistently shown that in the standard dose, zopiclone impairs driving ability 10-11 hours after intake to a comparable extent to alcohol levels above common legal blood limits for driving" (2006: 6). The risk of overdose on zopiclone is increased when it is mixed with other CNS depressants such as alcohol, benzodiazepines or opioids. Overdose cases present with excessive sedation and depressed respiratory function, which may progress to coma and possibly death. A key indicator of moderate overdose, or an early sign of serious overdose, is ataxia – which includes a severe lack of coordination (shakiness, clumsiness), and an inability to initiate or complete simple actions (such as walking or talking – or even sitting down). Zopiclone overdose can be treated with the benzodiazepine receptor antagonist flumazenil, which rapidly reverses its effects.

Hypnosedatives acting on the brain's benzodiazepine receptors, including Z-drugs, generally have a relatively low lethal dose compared with other types of drug. Several cases of fatal overdoses on zopiclone have been reported in medical journals over the past two decades, though accurate estimates of the LD50 for zopiclone - the lethal dose for the average, non-tolerant human - are not available. Most research on the toxicity of zopiclone involves animals (rats, monkeys, etc.), and there are no reliable methods for extrapolating animal LD50s to humans. Based on available case reports on humans, it can be hypothesised that lethal doses may begin at around 100 mg for susceptible individuals (elderly, small, etc.), rising to around 250 mg for the average non-tolerant person. Tolerance to zopiclone emerges from long-term regular use, and this permits far higher doses to be taken without fatal consequences (eg. 340 mg daily in one case study). More research is urgently needed to produce a more accurate estimate of the LD50 for both 'naïve' and tolerant users. It should also be noted that fatal overdoses on zopiclone typically involve consumption of multiple drugs (see below).

Injecting-related damage and diseases are also high risk outcomes among drug users who 'share needles' when injecting zopiclone, notably HCV, but also HIV, HBV, and bacterial infections. Vein damage

from sores to abscesses is particularly likely because (1) zopiclone per se has very low solubility in water (see above), and (2) zopiclone in tablet form is, therefore, practically insoluble (i.e. people intent on injecting it would have to inject a sludge rather than a solution).

But perhaps most worrying of all is the potential of zopiclone for causing **cancer**. A review of 15 epidemiological studies and research into animals and humans concluded that zopiclone and other Z-drugs are carcinogenic (affecting brain, lung, bowel, breast and bladder), and also that they have an adverse effect on the **immune system**, increasing the rate of colds and viral infections. The review author concluded that "the likelihood of cancer causation is sufficiently strong now that physicians and patients should be warned that hypnotics possibly place patients at higher risk for cancer" (Kripke 2008).

Official statistics on drug-related poisoning **deaths** in England & Wales combine figures for zopiclone and zolpidem into a single 'Z-drug' figure (ONS 2008). Mortality statistics do not distinguish deaths from illicit (non-prescribed) use and deaths from prescribed use. Annual figures for all such deaths are shown below for the period 1993 to 2007. They show a clear increase from around the turn of the century, since when deaths from these two Z-drugs have jointly averaged about 40 to 50 deaths per annum, with peaks of 57 in 2004 and 51 in 2007. Unfortunately, it is not known how many of these 'Z-drug' deaths were attributable to zopiclone rather than zolpidem, nor how many were accidental rather than intentional (suicide). But research in other countries (eg. Sweden) has found that zopiclone has joined other benzodiazepines (notably flunitrazepam and nitrazepam) as a drug commonly involved in suicides among the elderly.

93	94	95	96	97	98	99	00	01	02	03	04	05	06	07
0	9	6	10	12	14	20	41	37	47	40	57	48	39	51

Recent figures are also available for the past five years about the number of Z-drug poisoning deaths in England & Wales which (a) involved no other drugs (i.e. single-drug deaths), and (b) involved alcohol. First, deaths involving zopiclone/zolpidem only numbered 8 in 2003 (20%), 12 in 2004 (21%), 15 in 2005 (31%), 10 in 2006 (26%), and 15 (30%) in 2007. In short, since 2003 about two or three of every 10 Z-drug deaths have involved no other drugs – which means that a clear majority (at least two-thirds) of recent zopiclone or zolpidem have involved other drugs. Second, deaths from zopiclone/zolpidem which also involved alcohol numbered 11 in 2003 (28%), 24 in 2004 (42%), 18 in 2005 (38%), 13 in 2006 (33%), and 15 in 2007 (29%). In short, since 2003 about three or four in every 10 Z-drug deaths have also involved alcohol.

There were four deaths involving zopiclone in Scotland in 2007 – one involving zopiclone only, and three involving zopiclone and other drugs (two with Co-codamol, and one with tramadol).

Figures for poisoning deaths from zopiclone and zolpidem are also available for Wales only for the eight-year period ending 2006 (Hansard, 3rd March 2008). These averaged about one per year from 1999 to 2004, rising to two per year in 2005 and 2006, making eight Z-drug deaths in total – all of which involved other drugs in addition to Z-drugs.

A small number of studies have also been conducted into the nature and prevalence of zopiclone-related fatal poisonings. A study in Finland between 1995 and 2000 reported 1,006 cases of fatal poisoning from drugs and/or alcohol, of which just over half involved benzodiazepines. Zopiclone was involved in 38 cases, and was considered by the pathologist to be the primary cause of death in 21 cases (Koski et al., 2003). A study in New Zealand found that one in five of the 200 drug poisoning deaths in 2001 involved hypnosedatives, and that 12 (31%) of these 39 hypnosedative-related deaths involved zopiclone - with most cases being in the age-range 30 to 59 years. When death rates were carefully compared, the risk of death from zopiclone was similar to that of benzodiazepines in general (Reith et al., 2003). A study in Britain assessed fatal poisonings involving hypnosedatives in the 17-year period from 1983 to 1999, and found 23 cases attributable to zopiclone – just over one per annum (Buckley & McManus 2004). The fatal toxicity index (FTI), expressed as the number of deaths per one million prescriptions, was estimated to be 2.1 for zopiclone (including the rider that we can be 95% confident that the actual figure lies somewhere in the interval between 1.4 and 3.2). This is lower than the FTI indicator for zolpidem (2.3), and lower than the figures for most benzodiazepines - from 3.6 for nitrazepam to 20.5 for flurazepam. Reflecting the official statistics on zopiclone-related deaths in England & Wales (see above), the recent WHO review of the research literature on zopiclone concluded that "benzodiazepine receptor agonists are rarely the only drug present in poisoning deaths, and act rather as contributory factors rather than primary substances" (WHO 2006: 7).

It should be noted that, with the exception of the mortality statistics reported above, zopiclone is rarely itemised separately in official statistics about drug problems in Britain (such as overdoses, treatment cases, etc.). Instead, it is generally subsumed under such general categories as hypnosedatives, CNS depressants, or 'other drugs'.

3.2 Research with service users and staff concerning zopiclone

As noted, the research component of the project was based on a focus group with six zopiclone users and interviews with two senior staff at a North-East drug agency. Rather than presenting the information in the same order in which participants provided it in the focus group and interviews, it is much more useful to organise and present it within a set of hierarchical categories adapted from a conceptual model of drug-related risks and harms (Newcombe 1992, 2008). The five broad classes of information are: psycho-social issues (sources, reasons for using, etc.); consumption (risk behaviours); short term effects (physical and mental); harmful consequences (health and social outcomes); and behaviour change (abstinence and safer drug use – including experiences of interventions by official agencies.

3.2.1 Psycho-social context

This category of information covered a broad range of relevant 'background' issues - including aetiology (reasons for use, causal factors), epidemiology (prevalence of use, other drug use, demographics of users), and the illicit market for zopiclone (sources, availability, price, etc.).

Participants drug use. Before starting the semi-structured group discussion, the researcher first asked each participant for basic information about their primary illicit drug use, their injecting status, and their experience of zopiclone (Zimovane). Four participants reported that, since attending the service, their primary drug had become methadone, though before attending the service they had primarily been using heroin and crack – though one of these (M1) stated that he had been using 'just about anything'. All four of these participants also reported that they had been regular injecting drug users. The other two participants were not drug injectors, and both stated that their primary drug had been zopiclone – one had been using zopiclone only (F2), while the other had started off with crack smoking before moving onto zopiclone (F1). Five of the six participants had been regular users of zopiclone, and one had been an occasional user (F2). Only one participant (M3) reported injecting zopiclone – on a fairly regular basis (he also described himself as having a general "needle fixation"). Three participants (F1, M1 and M3) reported relatively heavy use of zopiclone (see below).

Slang names. Among local drug users, zopiclone tablets are typically referred to as 'zimmers' or 'zimmies', a contraction of the trade name Zimovane – though they have various slang names around the UK (e.g. 'zim-zims' in South Wales).

Sources. The main form that Zimovane is available in the UK is 3.75 mg and 7.5 mg tablets, though some participants also stated that they had also purchased higher-dose tablets, which they believed contained 15 mg of zopiclone. These higher-dose tablets were generally believed to be imported, and though participants were unsure of the countries of origin, the main suggestions were Spain and Turkey. Another possible source is France, where zopiclone is among the top ten medications obtained using false prescriptions. Zopiclone can also be mail-ordered from Internet websites, though no-one mentioned this source. Participants were in general agreement that once local doctors had 'wised up' to the abuse potential of zopiclone, and became more cautious about prescribing them to known or suspected drug misusers, two main **sources** of the drug remained: (1) purchasing them off 'straight' people prescribed them for insomnia (e.g. senior citizens, relatives, neighbours), or (2) buying them off drug users/ dealers who had obtained them abroad. Participants agreed that local zopiclone users often believed that the imported tablets were cut with rat poison (warfarin). Conversely, another common belief was that the local 'gear' (illicit heroin) was sometimes cut with powdered zopiclone tablets. Indeed, about two years ago, one batch of heroin on sale locally became known as 'date-rape heroin' because of its highly sedative effects – this too was rumoured to be 'cut' with zopiclone.

Drug dealers, usually the same people who sold heroin and crack, often acted as 'middle-men' in this process, buying up zopiclone tablets in bulk from one or both of the above sources, and then selling them on to users. However, because of the nature of the two main sources, the supply of zopiclone tended to be unstable and erratic, with 'periods of plenty' being followed by periods of scarcity ('droughts'). When

the researcher asked participants about the present availability of zopiclone, the general response was that it was currently fairly easy to obtain.

Participants agreed that the **price** of zopiclone tablets varied with several general factors which influenced the price of most illicit drugs - particularly the number of tablets purchased, their general availability at the time of purchase, and whether the user picked up the tablets or had them delivered. Focusing on 7.5 mg tablets, when small numbers were purchased, the unit price was generally around £1 a tablet, though the unit price dropped to around 50p when around 10 to 40 were purchased, and to as low as 30p each when 50 or more were purchased (e.g. 100 for £30). Higher-strength imported tablets could cost up to twice as much as the home-produced variety. During periods of widespread 'drought', prices usually climbed, often doubling.

The **prevalence** of zopiclone use among local drug users is difficult to estimate from the information available to and provided by focus group participants. Estimates varied widely from one participant to another, largely because they were based on the extent of zopiclone use in each participants' network of acquaintances (i.e. in particular neighbourhoods or social networks). But the general impression gleaned from participants' comments was that zopiclone was not as popular among local drug users as heroin and crack, but, over time, had a similar level of use to other misused prescribed drugs – notably methadone, buprenorphine (Subutex), diazepam (Valium) and temazepam. Along with alcohol, tobacco, and cannabis, these six drugs appear to dominate the consumption behaviour of local 'hard-core' poly-drug users – with availability, quality, price and other market factors determining which drugs were most popular at any given time.

For instance, when asked about why local drug users took zopiclone, participants concurred on two main **reasons**: (1) because the purity of local heroin was often poor, and many drug users who missed the pleasures of 'monging out on smack' found that sedatives like zopiclone provided an approximation of some aspects of this opiated state; and (2) the regular use of crack almost invariably led to the need for a depressant drug to 'take the edge off' the main stimulation effect and the subsequent come-down. In addition, zopiclone was believed to be used by many drug users as part of the local culture of poly-drug use (see below) – as M2 put it, "I used just about anything I could get my hands on, I just wanted to be out of it as much as I could". Other reasons for zopiclone use were also mentioned by one or two participants each. For instance, two participants agreed that some of their associates used Z-drugs to self-medicate the symptoms of mental disorders like depression and anxiety: "you can't really worry about your problems when your brain has been zimmied into neutral" (M3). Regarding the motivation for longer-term regular use of zopiclone, participants generally indicated agreement with the core reason suggested by one of them: "zimmers are really addictive, and the rattle is terrible" (F1) [see Section 3.2.4 for more details on zopiclone dependence].

A more general reason underlying the high levels of local drug misuse - whether zopiclone, heroin, crack or other drugs – was reported by a number of participants to be the lack of work and leisure opportunities for young (and not so young) people. This may also explain why this North-East town is rated in the top five towns for binge drinking in England. Several participants also commented that local drug users were "full of petty jealousy", and that 'grassing up' other drug users in your neighbourhood or social network was extremely common – not just for financial rewards, but more often because of such base motives as envy and revenge.

3.2.2 Consumption

The information provided about the consumption of zopiclone tablets has been organised below under five key categories of 'risk' (Newcombe 1992, 2008): methods of use, amounts used, patterns of use, multi-drug use, and settings of use.

Methods of use. There was general agreement that zopiclone tablets could not be sniffed or smoked – it was believed that the majority of local users swallowed them, while a minority injected them. Because of strong craving, one participant (F1) reported sucking and chewing the tablets at the peak of her habit, in order to maximise the metallic taste of the tablets (which she mentally associated with their desired euphoric effects), but also because this seemed to accelerate the onset of the effects of the drug (this could be accounted for by (a) absorption of the drug through the linings of the mouth, and (b) more rapid digestion in the stomach/intestines).

Two participants admitted to having prepared and/or administered zopiclone injections (M1 and M3). They agreed that to prepare zopiclone tablets for injection,

users first had to scrape off and discard the film coating, and then chop up the remaining tablet very finely. Following this step, water was then added to the powdered tablet in the spoon/cooker, the mixture was heated from underneath with a flame, and the heated solution was also given a good stir with the needle cap. Some injectors also added dissolving agents like citric acid or Vitamin-C powder to help break down the tablets, though one participant commented that although this was needed to dissolve heroin powder, it was fairly ineffective and thus pointless with zopiclone tablets. To make sure that the resulting 'sludge' could be drawn up from the cooker, this procedure was carried out with the barrel only, and the needle would be fitted on afterwards. For the same reason, M3 stated that he usually used a fairly wide needle to stop the thick chalky solution (sludge) from blocking it when trying to inject into a vein.

Amounts used. When swallowing zopiclone, participants indicated that the number of tablets generally consumed in a single session by local drug users ranged from about half a dozen to a dozen – with the exact number taken being affected by several factors (availability, tablet dose, other drugs used, tolerance, planned activities, etc.). However, the three heaviest using participants commented that, at the peak of their habits, they had taken between 20 and 40 tablets during the same session, with the highest single dose reported being about 60 tablets (F1). The participant who had regularly injected zopiclone (M3) reported that at the peak of his habit, he was injecting about five tablets per shot.

Patterns of use. Five of the six participants reported that they had used zopiclone tablets regularly (meaning weekly to daily) - sometimes as part of a pattern of poly-drug use ('using just about anything'), and sometimes as a temporary substitute when the quality of the local 'brown' was poor. As far as could be ascertained from their comments, at least two of these five participants could be classified as 'bingers' – that is, having periods lasting a few weeks to a few months when they used zopiclone daily or near-daily, interspersed with periods when they used it infrequently or not at all. By contrast with the five regular users, one participant (F2) had used zopiclone on a small number of occasions only. The participant who had regularly injected zopiclone (M3) reported that during periods of daily injecting, his frequency of zopiclone injecting ranged between one and six times per day.

Multi-use patterns. Poly-drug use patterns (users' repertoire of drug use over time) have already been discussed above (Section 3.2.1). Multi-drug use refers to the combinations of drugs consumed by users in the same 'session' or day. There are two main types of multi-drug use: (1) using two or more drugs together to experience their combined effects (e.g. injecting speedballs); and (2) using one drug after another drug, in order to reduce the unpleasant side-effects or after-effects of the first drug (e.g. using depressant drugs to reduce the unpleasant come-down effects which follow stimulant drug use).

Over the course of the focus group session, most of the participants gave information indicating that they were multi-drug users, with the commonest combination being use of heroin and crack at the same time. As regards zopiclone, of the three heaviest users of this drug, one (F1) indicated that she initially used the drug to help with the side-effects and come-down from smoking crack (including getting to sleep), but eventually ended up using zopiclone exclusively. The second heavy user (M3) also mentioned how zopiclone use helped him cope with crack use and come-downs, but further indicated that he had often consumed one or two litres of wine before or after 'whacking up zimmers', because this substantially magnified the effects of both the alcohol and the zopiclone. Another participant commented that many zopiclone users preferred "Newcy Brown [a strong beer] to boom up the effect". Lastly, the third heavy user (M2) commented that "when I've had zimmers, they make me feel open to taking just about anything, even stuff I wouldn't usually touch". This state of mind appears similar to the disinhibition brought about by heavy alcohol use.

Settings of use. Participants comments and 'stories' gave the consistent impression that their use of zopiclone typically took place in their own home or their friends' homes – indeed, there was agreement that the entire period of zopiclone intoxication could be spent slumped in a chair or across a bed. However, as one participant (M1) pointed out, since the tablets were usually swallowed, they could be ingested in most situations without being conspicuous (i.e. smoking, sniffing or injecting drugs are far more 'visible' methods of drug use). But it was the highly sedative effects which appeared to have led most participants to the conclusion that their homes were the most suitable situation for getting 'off it' on zopiclone. As one participant explained it, experience had taught her that being on 'zimmies' in public places increased your vulnerability to street predators (muggers, rapists, etc) – far more than the effects of heroin or crack did (F1). Even so, most

participants agreed that when taking higher doses of zimovane they often carried out spontaneous, unplanned actions, which were usually much too risky given their sedated state of mind – such as going shoplifting in a store from which they had been banned.

3.2.3 Short-term effects (intoxication)

Physical effects. Participants were in full agreement that the most notable physical effect of zopiclone was the strong and unpleasant bitter **metallic taste** which persisted in the mouth. Although people using the drug to aid sleep generally do not experience this taste until after they wake up, the focus group participants made it clear that zopiclone misusers, who stay awake for several hours after swallowing the drug, experience the metallic taste during this semi-conscious state. Also, some participants commented that the intensity of the metallic taste gradually gave way with regular use, though others disagreed. Furthermore, the two heaviest users of zopiclone both reported that when they were struck by cravings for the drug, these urges incorporated a correlated memory of the unpleasant metallic taste (see 'Dependence', below).

According to the participant who had regularly injected zopiclone, the first physical effects experienced after a shot of zopiclone were a feeling "like you are getting your head hammered" – that is, a painful pounding sensation inside the skull for one or two minutes. This effect was not reported by the five non-injecting participants, though some mentioned that they had experienced hangover-like symptoms (e.g. headaches) when 'coming down' from zopiclone use.

The only other physical effects mentioned by participants were **dry mouth and throat; and loss of coordination** – including staggering, swaying, stumbling, dropping things, and knocking things over. Though gastrointestinal effects such as vomiting and constipation/ diarrhoea have been reported in the medical literature, none of the focus group participants reported any such effects from zopiclone use - though constipation was reported to be a symptom of the withdrawal syndrome (see below).

Participants also agreed that, as with users of heroin and crack, regular users of zopiclone developed a distinctive appearance that was recognisable to other drug users. The typical appearance of the habitual zopiclone user was described by one participant as "looking really evil". The details of this 'look' included untidy clothes, messy hair, bloodshot eyes, drooping eyelids, sweaty skin, rasping voice, slurred speech, drooling mouth, and 'the drunken sailor' gait. Other signs of heavy zopiclone use were very slowed-down behaviour, which at worst progressed to an inability to carry out or complete simple actions like lighting a cigarette or taking things out of a bag. For instance: "trying to sit down can take them half an hour – it has to be seen to be believed, if it wasn't so sad it'd be funny" (M1).

Mental effects. After a sufficient number of zopiclone tablets were swallowed, participants agreed that the most notable initial effect was the growing feeling of wanting to **fall asleep**. These mental fatigue effects (inability to concentrate, drowsiness) were usually accompanied by physical fatigue effects (heavy feeling in arms and legs, closed eyes, nodding). But participants agreed that 'the trick' was to resist the urge to 'fall over and snooze', because once this had passed (after an hour or so) they would be rewarded with the desired effects of **sedation** and **euphoria** ('monged out and buzzing'). One participant claimed that some long-term heavy users of zopiclone eventually find that they experience stimulant-type effects from the drug too – including constantly talking, fidgeting, lack of appetite, and sleep disturbances.

But the next most common psychological effects reported after sedation and euphoria were negative ones, namely **memory and cognitive problems.** These centred around the inability to think rationally or clearly; short-term memory problems (e.g. 'constantly forgetting what you were saying'); and partial or total **amnesia**. The latter effect was enthusiastically discussed by the majority of participants, with several anecdotal stories being voiced (some simultaneously). For example, one participant (M2) explained how he had once "necked a handful of zimmies", then several hours later 'came round' in his flat to find himself surrounded by several leather jackets – but he had no memory of how they had come to be there. His partner (F3) explained that she had had to tell him that he had gone shoplifting, stolen the leather jackets (somehow avoiding detection in his heavily sedated state), then brought them back to their flat, dumping them on the floor before collapsing into a deep sleep lasting several hours. Beyond illustrating the amnesia effect, participants agreed that this story also showed one of the stranger effects of zopiclone misuse, namely the delusion that "you become almost invisible to other people" – leading to the belief that they could engage in audacious shoplifting, without being seen

by store detectives as they normally would. This 'delusion of invisibility' may be a distorted reflection of their shrunken sense of self-awareness, and has also been reported by temazepam misusers in previous research.

Another participant (F1) related similar stories of zopiclone-induced amnesia – including (1) how she often forgot about episodes of violent behaviour until friends with wounds and bruises later reminded her of what she had done to them (see below); and (2) how she regularly used to hide drugs and/or money while 'wrecked on zimmers', but had no recollections at all of where the items were hidden when the drugs wore off.

Participants also generally agreed that zopiclone use reduced **emotional responses** of all kinds – "eventually, it makes you lose all your feelings" (F1). One participant stated that she initially took to zopiclone because its effects helped her 'escape' from the emotional trauma of having been raped. Another participant (M3) stated that during a period of heavy zopiclone use, he attended his grandmother's funeral, and was unable to cry even though 'deep inside' he felt that was what he really wanted to do: "it makes you feel totally numb". However, suppression of negative feelings and memories was generally regarded as a desirable aspect of zopiclone's effects - though regular zopiclone use also seemed to block out or diminish positive feelings as well. This included sexual feelings, which participants agreed were almost totally eradicated when under the influence of zopiclone: "a girl could strip naked in front of you, and you would not want sex with her" (M2); and "you have no strength or energy for sex, and no interest in it - or anything at all really" (F1).

The main **after-effects** of zopiclone use (the 'come-down') were largely restricted to the morning (or 3-4 hours after waking), notably cognitive deficits such as lack of concentration and memory failures. Medical sources generally advise people to avoid driving not only while under the influence of zopiclone, but also the following morning – or, more precisely, during the 'come-down' period.

3.2.4 Long-term effects (health and social consequences)

Dependence and withdrawals. Participants were asked about their own and their friends' experiences of zopiclone dependence and withdrawals, and the two heaviest users (F1 and M3) contributed the most information to this part of the discussion. First, these two participants agreed that the period of time needed to get 'hooked on zimmies' was daily use for one or two weeks. F1 suggested that a typical pattern would be starting on a dose of about three tablets, then doubling the dose every day or two until a dose of about 10 to 20 tablets was reached. This is a much shorter period than the 'month or longer' typically suggested in the medical literature, though this may be accounted for by such estimates being largely based on evidence about use of prescribed doses (one or two tablets per day) among insomniacs, as compared with daily doses of over a dozen tablets for users of illicit zopiclone.

Second, participants agreed that the most salient withdrawal symptom was severe craving (i.e. an overwhelming compulsive desire to use and experience the effects of zopiclone). The heavier-using participants agreed that even though the metallic taste of zopiclone was regarded as quite unpleasant, the memory of the taste featured heavily in the cravings for the drug once habituated (this can be attributed to Pavlovian conditioning/association effects). They also agreed that the cravings for zopiclone were stronger than any cravings they had experienced for other drugs, even crack or heroin: "zimmers are the first thing that you think of when you wake up" (M2); and "I made sure that I always had credit on my phone, so that I did not miss any calls from dealers about new batches of zimmers …but waiting for the dealer to turn up with the tabs was agonising – you end up pacing the floor, smashing things, and cursing them" (F1). These participants agreed that, once their zopiclone habits were well established, they much preferred to travel several miles on buses or trains to the source of the drugs rather than wait for them to be delivered, because the anxiety experienced while waiting for dealers to turn up at their homes was too unbearable – "much worse than when waiting for rocks or gear" (M3).

However, these two participants disagreed about the impact of discussing zopiclone in the focus group on their current cravings for the drug. That is, M3 commented that "all this talk about zimmers is making me feel like doing them again", but F1 replied "not me, I think they're disgusting now, I'm never going back to them". The other four participants made no clear comments about this issue. Nevertheless, this raises an ethical issue about doing research of this kind with ex-users of drugs. That is, if discussing their prior drug use arouses cravings for the drugs among at least some participants, then researchers and drugs workers need to devise

debriefing schedules and other procedures which respond to any latent cravings which their data-collection methods may trigger (cf. Williams et al. 2006).

After craving, the other withdrawal symptoms most commonly mentioned included fatigue and muscular weakness ("body like jelly"); aching limbs ("dead legs"), sweats, appetite problems (reduced or increased hunger), and insomnia. Some participants also mentioned constipation and one reported fits. The three heavy-using participants agreed that the zopiclone withdrawal syndrome, including physical and mental symptoms, was far more unbearable than a heroin-related 'cold turkey': "the rattle from zimmies is about five times worse than the rattle from gear". The duration of the zopiclone withdrawal syndrome was comparable to the duration of the heroin withdrawal syndrome: "you rattle for about three to five days" (F1), but "after the worst is over, the craving and other stuff - like thinking about the metal taste - go on for weeks and weeks" (M3).

Health damage and disease. The participant who had been injecting zopiclone reported that he had developed sores and abscesses as a result of this practice. However, injecting problems were not examined further because this participant was the only injector in the group, and it would not have been ethical to make him the focus of attention on this issue in this context.

Perhaps surprisingly, there were no reports of overdoses on zopiclone, and no participants stated that they or friends had ever visited a casualty department because of their zopiclone use. Also, just one participant (F2) reported having experienced fits or fainting after zopiclone use – and this participant was the lightest user in the group. She described one incident where she took four tablets, then "blacked out, and woke up unable to see properly, and ended up crawling round the room, trying to work things out".

Similarly, no-one mentioned cancer or other serious diseases – but if any participant had experienced such serious illnesses, they may not have linked the conditions to zopiclone use; and/or they may not have wanted to discuss such important problems in such a public context, or with a stranger (the researcher).

Lastly, no respondents reported any deaths related to zopiclone use among drug using friends. Even so, it is worth noting that a recent ONS report on drug-related deaths in 171 localities (DAT/LSMAT areas) of England & Wales reported that the North-East town participating in the research ranked lower than 140th from 1993 to 1999, but ranked in the top ten from 2000 to 2006. The recent high ranking represented a drug-related death rate of 68 per 100,000 population, which was based on 67 deaths – almost one per month over the 7-year period (Griffiths et al. 2008).

Aggressive and violent behaviour. Most participants reported episodes of increased aggression when they or associates were under the influence of zopiclone. Zopiclone-induced aggression was found as much among women as men – indeed, some participants believed that women became more aggressive than men on zopiclone. One participant related the story of a female friend who was normally non-aggressive, but who, after taking 20 zopiclone tablets, tried to 'mug' someone for their mobile phone on the street. Another participant reported an incident in which a local drug user under the influence of zopiclone attempted to 'mug' a seven-year old boy. A third incident involved a local zopiclone user who held a used needle to his throat of man he was attempting to 'mug' at a cashpoint. Participants generally agreed that such aggressive confrontational 'robbing' was very rare among heroin addicts, who generally funded their habits through non-violent acquisitive crimes like shoplifting and credit card fraud.

Only one participant reported personal incidents of extremely violent behaviour (F1). During the one-year period in which she had been a heavy dependent zopiclone user, she reported that she had often attacked her friends and associates, particularly her boyfriend - stabbing him with a knife on four separate occasions. She confirmed (1) that these violent incidents were typically due to her intoxicated state, and not to any provocation by her boyfriend; and (2) that she generally had no recollection of her violent behaviour on awaking from the inevitable deep slumber which ended her episodes of zopiclone use. This participant also claimed that zopiclone use made her insensitive or unresponsive to pain, which made her an even more formidable enemy in the numerous fights she got into while under the influence of the drug. The 'emotion numbing' effects of zopiclone are also likely to reduce feelings of guilt and shame that might normally follow violent behaviour.

Social problems. The social problems associated with misuse of zopiclone were similar to those associated with misuse of heroin and crack – notably acquisitive crime; criminalisation (arrest,

prosecution, imprisonment); and upsetting relatives and neighbours, and losing friends. One of the heaviest using participants (F1) had experienced a host of problems above and beyond these – including having her children removed by social services, and getting evicted from her house – all of which she attributed to the effects of zopiclone use on her personality and behaviour.

3.2.5 Experience of interventions and services

Throughout the focus group discussion, all five participants who were attending the agency made direct or indirect comments indicating that the services which they had received had helped them tackle the problems caused by their use of drugs, including zopiclone. These services included advice and information; support and referrals; needle exchange and harm minimisation services; and medical interventions. Some of the five service users reported that they were now abstinent from drugs, while others indicated that they had reduced their drug use and/or its harmful consequences. All five service users made positive comments only about the help they had been given at the drug agency, though it could be argued that this was due to the presence of two senior members of staff from the agency. Even so, most of the participants either emphasised or reiterated their positive views about the services they had received, suggesting that these comments were based on genuine beliefs and attitudes.

As with withdrawals from heroin, one of the worst symptoms of zopiclone withdrawals was considered to be insomnia, because the lack of sleep magnified the unpleasantness of the other withdrawal symptoms, and reduced the individual's mental capacity to deal with them. However, according to the two members of staff present, the policy of the local drug treatment service ruled out prescribing benzodiazepine-based sleeping pills to people recovering from zopiclone dependence, and so the main medication prescribed to such cases was reported to be Nytol - an OTC pharmacy medicine containing diphenhydramine (an anti-histamine with hypnosedative effects, but little euphoria or dependence potential). One participant commented that he needed more than the recommended dose of Nytol to reduce his insomnia, which was met by nods of agreement from other participants.

One of the heaviest users of zopiclone in the focus group (F1) was adamant that using methadone over several months had helped her to reduce the withdrawal symptoms she had experienced when trying to cut down on and eventually abstain from zopiclone. Similarly, another participant (M3) stated that he had once used Subutex tablets to deal with the residual withdrawal symptoms at the end of a zopiclone 'rattle'. However, pharmacologically, a withdrawal-blocking effect would be unlikely because zopiclone is a benzodiazepine-like sedative, while methadone and buprenorphine are opioids. It seems more likely that it is the general analgesic and mood-enhancing effects of these opioid drugs which contributes to reducing the pain and discomfort of withdrawals from zopiclone.

4. Conclusions

A summary of the key points made in the previous section is provided at the front of the report. This final section presents conclusions about the consumption risks and harmful consequences of zopiclone use, focusing on recommendations for interventions and advice which may reduce these risks and harms. These points are organised below according to the seven risk dimensions of drug consumption: context, amount, method, pattern, mixture, access and product (Newcombe 2002, 2008).

Context of use. The safest setting for being under the influence of zopiclone is bed, because it is designed to induce and sustain sleep. Staying awake on zopiclone increases the risk of dependence and accidents/injuries. For those users who do stay awake on it (zopiclone misusers) the safest setting is at home (own home or friend's place). Public places are best avoided, especially workplaces and busy streets. Clearly, zopiclone misusers should totally avoid driving or operating machinery, and should take extra care when involved in everyday activities involving potentially dangerous equipment, like cooking or gardening. People under the influence of zopiclone are also unlikely to be in the required state of alertness for supervising children.

Amounts used. Using escalating doses of zopiclone over time increases the risk of dependence and overdose, as does regular use of high doses. Although the LD50 (lethal dose for the average person) is not known, zopiclone and zolpidem are now linked to 40-50 fatal poisonings each year. Zopiclone overdose can be treated with the benzodiazepine receptor antagonist flumazenil, which rapidly reverses its effects.

Methods of use. Zopiclone tablets are not sniffable or smokable, so most users swallow them. A minority of zopiclone misusers inject the tablets, by scraping off the film coating and preparing the tablets by similar procedures to those used to dissolve heroin for injection. However, zopiclone tablets are 'practically insoluble' and so there is a very high risk of vein and tissue damage – along with the usual risk of picking up and passing on infectious diseases, notably hepatitis C. Harm reduction services are advised to extend their client information systems to record cases of zopiclone use/injecting, so that trends can be monitored (at present, zopiclone is typically 'hidden' under 'other drugs').

Patterns of use. Though some users progress to regular daily use, variations in availability and other factors result in bingeing being a common pattern of zopiclone use – that is, periods of regular use being interspersed with periods of abstinence (or rather switching back to heroin or other drugs). In particular, users who return to taking high doses of zopiclone after a period of abstinence - when their tolerance has dropped – face a high risk of overdosing. Also, daily use for more than four weeks can lead to dependence, and regular use for long periods can reduce immunity (more colds and infections), and even increase the risk of various kinds of cancer.

Mixing with other drugs. Most deaths from zopiclone involve multiple drug use. In particular, using zopiclone in combination with other hypnosedatives - notably alcohol, benzodiazepines and opiates – increases the risk of overdose. Adverse reactions can occur if zopiclone is mixed with any of three prescription drugs, namely erythromycin, trimipramine, or carbamazepine.

Access. Clearly, the safest source of zopiclone is to obtain it on prescription from a pharmacy. Illicit users should avoid imported tablets or tablets sold on the internet, because these are most likely to be counterfeit, adulterated, and/or of unknown dosage.

Products. Even among zopiclone tablets obtained from British pharmacies, there are a variety of different kinds of tablet, which differ in shape, colour and markings. Consequently, illicit users risk confusing zopiclone with other drugs, or confusing the low-dose and high-dose tablets.

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