REVIEW

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Zopiclone misuse on a methadone maintenance programme

This study highlights the prevalence of zopiclone misuse in clients attending a methadone maintenance programme in Dublin through detection of its degradation product, 2-amino-5-chloropyridine (ACP) on urinalysis. Urine samples from all 158 clients were tested for the presence of ACP, opiates, benzodiazepines, cocaine, alcohol and cannabis. Of the 37 (23%) clients who tested positive for ACP, 23 (62%) were interviewed and details regarding their demographics, drug history, viral status, recent urinalysis results and opinions on zopiclone were collected. Of the 14 (38%) clients who were not interviewed, information was obtained from their case notes and urinalysis results.

A description of zopiclone misusers is outlined. The prevalence of zopiclone misuse is 23%. Re-testing at four to five months indicates a persistence of zopiclone misuse of 17%. Benzodiazepines were the most popular drug of misuse with zopiclone followed by heroin/opiates. Zopiclone is being misused by drug users in the context of many other drugs and prescribing it in primary and secondary care should be restricted, especially among drug users.

INTRODUCTION

Zopiclone was initially introduced in 1987 for the treatment of insomnia.[1] It is a cyclopyrolone, chemically unrelated to benzodiazepines and acts on the gamma-aminobutyric acid (GABA)-A receptor complex, potentiating neuronal.[2] It has a half life of five hours (up to eight hours in the elderly).[1] The drug was marketed as a safe and non-addictive hypnosedative and, as such, was less likely to cause dependence, withdrawal symptoms or rebound phenomena.[1-5] It is commonly prescribed in the management of insomnia in primary care and general hospital settings.

Chronic use of either benzodiazepines or alcohol may cause some receptor modification at the GABA receptor which may lead to cross-tolerance with zopiclone.[2,6] These changes may be significant in the pathophysiology of tolerance and withdrawal states and may explain the altered sensitivity to the subsequent administration of either of these drugs.[2,7] There appears to be a cross-tolerance between benzodiazepines and zopiclone and transference of misuse from a benzodiazepine to zopiclone has been previously documented.[1] Studies suggest that patients can be readily weaned off long-term benzodiazepines through an intermediate stage of zopiclone prescribing.[8-10]

There are well-documented case reports of zopiclone misuse, dependency, rebound insomnia and withdrawal symptoms in opiate and polydrug users[2,5,6,11-15] and in those cases without co-morbid opiate misuse.[2,11,13,16,17] These problems have also been described in patients with anxiety and dependent personalities.[12] A withdrawal syndrome has been recognised after high dose zopiclone misuse[1,13,16,18-20] and rebound insomnia occurring in normal volunteers after only two to three weeks on zopiclone.[1,13,21] Withdrawal seizures following abrupt withdrawal of zopiclone have also been described.[22]

Fatalities have been documented following ingestion of zopiclone, one case involved a 72 year old man who was being treated for lung cancer and died following an overdose of zopiclone 90mg.[23] Also two other deaths have been described following ingestion of zopiclone.[24] In 2001, the National Poisons Information Centre in Ireland received 238 calls regarding zopiclone (total 11,401 calls to the centre) which was the fourth most enquired about agent after ethanol, paracetamol and Dalmane.[25] To date, there have been no reports of fatalities in Ireland relating to zopiclone ingestion.[26]

AIM

The aim of this study was to assess the prevalence of zopiclone misuse in all clients attending a methadone maintenance programme through detection of its degradation product, ACP, on urinalysis. A description of clients who misuse zopiclone is outlined. Warnings regarding the potential for zopiclone misuse or dependency in clients receiving methadone from their primary care physician or psychiatrist are highlighted.

METHODS

All clients (158) attending the methadone maintenance programme were tested for the presence of ACP. Thirty-seven (23%) samples tested positive for ACP, and so were also tested for the presence of opiates, benzodiazepines, methadone, cannabis, alcohol, tricyclic antidepressants and

cocaine. Of this sample, 27 (17%) were re-tested for ACP four to five months later. Ten clients were unable to submit samples — three were in prison, five no longer attended the clinic and two were on the harm minimisation programme. All clients were supervised during urine sampling to reduce the likelihood of bogus samples.

Of the 37 clients (17 male) who tested positive for ACP on initial screening, 23 agreed to be interviewed by the specialist registrar in psychiatry. Details regarding their demographics, drug history, viral status, recent urinalysis findings and personal views and experiences on zopiclone were obtained. Fourteen (38%) clients were not interviewed: six refused, three were in prison and five were no longer attending the clinic. Of the 14 clients who were not interviewed, information was obtained from their case notes regarding the prescribing of zopiclone and documented urinalysis results. Information was analysed using SPSS Windows 8.0.

SAMPLE COLLECTION AND STORAGE

The sample preparation and analysis was based on a method described by Galloway.[27] Samples were deemed to be positive for zopiclone on the basis of the detection of ACP in a sample. Further details regarding this method of analysis may be obtained from the author.

RESULTS

Thirty-seven (23%) clients from a total of 158 attending a methadone maintenance day programme were positive for the zopiclone metabolite, ACP. On re-testing four to five months later, 27 (17%) of the total 158 clients remained positive for ACP, and 23 of them were interviewed.

The mean age of the sample interviewed was 32 years. Six (26%) were male, 17 (74%) were female, 16 (70%) were single, 10 (44%) were living in rented accommodation and 4 (17%) were homeless. Although the majority of the sample had had partial secondary school education, only 3 (13%) had obtained the Intermediate/Junior certificate and the Leaving certificate. One hundred per cent of the sample were unemployed (see Table 1).

The mean age of the other 121 clients who tested negative for zopiclone was 30.5 years (range 19-48 years); 95 (78.5%) were male and 26 (21.5%) were female.

Of the sample interviewed, the mean ages of first drug use and intravenous use was 14.5 years and 20.2 years, respectively. The mean duration of intravenous drug use was 11.2 years. Almost all clients (22, 95%) had a history of intravenous drug use and the prevalence of hepatitis C infection was 74% (see Table 1). The overall prevalence rate of hepatitis C among clients was 70%, and 98% of clients had a history of intravenous drug use.

Of the 37 (23%) clients who tested positive for ACP on initial screening, 16 (43%) also tested positive for opiates and 24 (69.9%) tested positive for benzodiazepines at that time. All clients had a past history of opiate misuse.

Table 1. Sociodemographic and clinical characteristics of sample interviewed (n=23)

Age (years)	Mean (SD) Range	32 (5.6) 22-43
Gender	Female	17 (74%)
Marital status	Single Co-habiting Widowed	16 (70%) 6 (26%) 1 (4%)
Living with	Alone Partner/children Family of origin	4 (17%) 4 (17%) 9 (39%)
Accommodation	Family home Rented Homeless	8 (34%) 10 (44%) 4 (17%)
Employment status	Unemployed	23 (100%)
Education	Partial primary Partial Secondary Partial third level	3 (13%) 19 (83%) 1 (4%)
Examinations	Junior/Intermediate certificate Leaving certificate	3 (13%) 3 (13%)
Age (years) **1st drug use**	Mean (SD) Range	14.5 (3.6) 11-27
1st IV drug use	Mean (SD) Range	20.3 (6.1) 14-36
Duration of IV drug use (years)	Mean (SD) Range	11.2 (6.2) 2-23
Viral status	Hepatitis C positive Hepatitis B positive HIV positive	17 (74%) 2 (9%) 2 (9%)
SD=standard deviation First admission: Re-admissions:		 5 (11%) 40 (89%)

Of the 23 clients interviewed, all had a history of opiate, benzodiazepine and cannabis misuse with a mean duration of misuse of 11.8 years, 10.1 years and 13.5 years, respectively. Nineteen clients (82%) had a history of alcohol and ecstasy misuse with a mean duration of misuse of 15.6 years and 4.5 years, respectively. The most popular current drugs of misuse were benzodiazepines, followed by heroin, which is evident from the first urinalysis results, whereby 23 (100%) tested positive for benzodiazepines and 14 (61%) tested positive for heroin. Although alcohol was admitted to be a current drug of use, it was not identified on urinalysis. Cocaine was identified in 14 clients (61%) on first urinalysis testing. The findings of the second urinalysis indicate a reduction in the use of heroin, benzodiazepines and cocaine; however, benzodiazepines remain the most popular drug of misuse.

Although zopiclone was prescribed for eight clients, with three claiming they were taking it as prescribed, urinalysis results did not provide information on the level or pattern of

Table 2. Past and current drug use of the clients interviewed (n=23)

	Past drug use (as per interview)	**Mean duration of abuse** (years)	**Current drug use** (as per interview)	**1st urinalysis**	**2nd urinalysis** (4-5 months later)
Heroin/opiates	23 (100%)	11.8	12 (53%)	14 (61%)	9 (39%)
Benzodiazepines	23 (100%)	10.1	16 (70%)	23 (100%)	15 (65%)
Cocaine	19 (82%)	5.0	4 (17%)	14 (61%)	1 (4%)
Alcohol	19 (82%)	15.6	17 (46%)	0	0
Ecstasy	19 (82%)	4.5	1 (2.7%)	3 (13%)	0
LSD	20 (86%)	5	*	*	*
Amphetamines	20 (86%)	5.3	*	*	*
Cannabis	23 (100%)	13.5	17 (46%)	12 (52%)	13 (56.5%)

*Analysis not routinely performed

Table 3. Zopiclone misuse (n=23)

Dose (mg)	Mean dose range	50.2 15-300
Age of first use (years)	Mean (SD) Range	28 (7.2) 16-40
Duration of misuse (years)	Mean (SD) Range	4.2 (3.1) 1-10
Frequency of misuse	Daily 2-4 occasions/week Once-weekly	12 (52%) 3 (13%) 2 (8.7%)

SD=standard deviation

use. The mean age of first use of zopiclone was 28 years and the mean duration of use was 4.2 years. The mean dose taken was 50.2mg (range 15-300mg) with 12 (52%) of the sample taking zopiclone daily. No client had injected zopiclone (see Table 3).

DISCUSSION

The literature is quite limited regarding the misuse of zopiclone. Although abuse and dependence following long-term use can occur, it is rare considering the world-wide extent of usage.[1,4-5,28-30] Large studies have been conducted with zopiclone in the UK19 (n=13,177) and in Spain31 (n=3,605); however, the authors did not report any problems after stopping medication in normal doses.[19,31] A meta-analysis[32] and a review[3] of sleep laboratory studies reported that tolerance, rebound and withdrawal phenomena were marginal and mild, nevertheless, long-term, controlled, prospective studies are awaited to address this issue. A recent review of 22 case studies, revealed that reporting of zopiclone abuse or dependence is rare, and concluded that zopiclone is a relatively safe drug.[5]

Nevertheless, there have been warnings about the drug's misuse.[14,33] The risk of dependency and abuse is greater in alcohol misuers,[34] polysubstance misusers,[1,2,5-6,18,35] clients who have dependent personalities[12,36] or other psychiatric disorders.[5,34-36] All clients in primary and secondary care, with or without a positive psychiatric history, are at risk of zopiclone misuse or dependency. A recent post-marketing study suggests that the risk of misuse of zopiclone is less than that of benzodiazepines, and similar to that of sedating antidepressants.[37] Worryingly, similar problems have also been reported in non-drug users.[2,12,13,16,17]

Results from this study indicate a high level of zopiclone misuse (23% of 158 clients on a methadone maintenance programme). Re-testing at four to five months indicates a persistence of zopiclone misuse as 17% continue to test positive for the zopiclone metabolite, ACP. Zopiclone misusers tend to be marginally older, female, single and unemployed with a long duration of polydrug use. The majority have injected other drugs, and the prevalence of hepatitis C is 74%. All the sample interviewed have a past history of heroin, benzodiazepine and cannabis use, with 82-86% also having a history of alcohol, ecstasy, LSD, amphetamines and cocaine use. Benzodiazepines appear to be the most popular drug of misuse with zopiclone, followed by heroin/opiates, cocaine and cannabis as documented on first urinalysis. On the second urinalysis, zopiclone and benzodiazepines continue to remain the most popular drugs of misuse.

The mean daily dose of zopiclone (50.2mg) was lower than a daily average dose of 105mg (range 90-380mg) reported in the literature, but the duration of misuse in this study (4.2 years) is longer than the previous report of 10 months.[9] Interestingly, a maximum daily dose of 300mg was recorded in this clinic compared to a maximum daily dose of 150mg reported in the literature.[15] Although there were no fatalities, there is a potential risk of fatalities in the future in view of the high doses currently being ingested. Following the death of a 72 year old man from an overdose of 75mg of zopiclone, Meatherall outlined that 75mg may represent a minimum lethal dose of zopiclone.[24]

All clients are misusers of benzodiazepines and prefer zopiclone because it does not cause amnesia to the same extent as the benzodiazepines. They like it, and report that it potentiates their experience on heroin and promotes a feeling of sedation and tranquilisation that is desired. Although zopiclone is only available with a prescription, clients claim that it is easily bought on the streets in Ireland, is cheap and readily prescribed by doctors in primary and secondary care. Our findings are similar to trends in other clinics and concur with real concerns that have been expressed regarding the abuse potential of zopiclone.[1,2,4-6,12,14,22,38-40]

However, while follow up urinalysis and interviews were carried out on 27 (73%) and 23 (62%) clients, respectively, it is important to note that this may not be totally representative of the overall population who were using zopiclone.

CONCLUSION

Zopiclone, which has been known as a 'safe and non-addictive' substitute for benzodiazepines, is clearly being misused by drug users in the context of other drugs (primarily benzodiazepines and heroin/opiates). All clients, even those without a psychiatric history, are at risk of developing zopiclone misuse or dependency. As prescriptions for zopiclone are easily obtained from doctors in most specialties, there is a need for greater restrictions in prescribing this drug to known drug users because of its potential for misuse and dependency. Care should be taken when prescribing zopiclone in primary and secondary care, even if there is no history of substance misuse.

Similar advice should be given to patients when commencing Zopiclone as would be given when prescribing benzodiazepines. As with all drugs in this class, short-term prescribing with careful monitoring is essential. Further evaluation research is necessary to determine the potential for misuse and dependence of zopiclone.

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