

Retrospective Study on Characteristics of 104 Zopiclone Abusers in a Substance Abuse Clinic in Hong Kong

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ABSTRACT

The liability of abuse of zopiclone has been much debated. The aims of this retrospective study were to find out how common zopiclone abuse was among our clinic cases in the past nine years and their characteristics, and to test significant differences between the primary and secondary groups of abusers. Medical records were reviewed and 104 zopiclone abusers were identified. Abuse of zopiclone was on a drastically increasing trend in the past four years. The characteristics of these abusers were described. Compared with the secondary group, the primary group had significant differences in many areas such as social background, psychiatric comorbidity and characteristics of zopiclone abuse. This was the largest case series on zopiclone abuse reported up to 2004.

KEYWORDS: zopiclone, abuse, dependence, retrospective study

INTRODUCTION

Insomnia is a common problem in the general population and medical practitioners, who, no matter in which specialties or clinical settings, have to manage such a problem. The use of barbiturates as a hypnotic has been largely replaced by benzodiazepines since the 1960s. With more experience and evidence, the adverse effects of benzodiazepines, especially the abuse and dependence potential, have been documented (Leung, 1997; Fraser, 1998). The third generation hypnotics or so-called Z-drugs (Zopiclone, Zolpidem and Zaleplon) are marketed as effective drugs for insomnia without dependence and withdrawal. The prescription of Z-drugs has become prevalent and up to 664 million tablets of zopiclone were prescribed in Europe and Japan from June 2001 to June 2002 (source: Sanofi-Synthelabo, Paris).



Zopiclone is a non-benzodiazepine hypnotic reported to have sedative, anxiolytic, muscle relaxant and anticonvulsant properties similar to those of the benzodiazepines. Chemically, it belongs to the cyclopyrrolone class and binds to the benzodiazepine receptor component of the GABA receptor complex but at a different site to the benzodiazepines. It is rapidly absorbed from gastrointestinal tract after oral intake with peak plasma level within 1 to 1.5 hours and the oral bioavailability is approximately 80%. It is widely distributed with 45-80% plasma protein binding. Its concentration in saliva is higher than plasma level and the characteristic bitter taste of zopiclone corresponds to its saliva level (Goa & Heel, 1986). It is also distributed into breast milk (Matheson, 1990). It is extensively metabolised in the liver mainly via decarboxylation into two major metabolites, less active zopiclone-N-oxide (11-15% of a dose) and inactive N-desmethylzopiclone (15-20% of a dose). About 50% of a dose is converted to other inactive metabolites. The metabolites are mainly (80%) excreted by the kidney. Only about 5% appears as unchanged drug in the urine. The elimination half-life is 3.5 to 6.5 hours. The usual dose is 7.5 mg at night but it should be started with 3.75 mg in elderly patients (Wadworth & McTavish, 1993).

Since the introduction of zopiclone into clinical practice in 1985, the liability of abuse and dependence has been debated. Some studies concluded that the risk was low or minimal (Dorian et al., 1983; Lader, 1997; Hajak, 1999; Voderholzer et al., 2001; Jaffe et al., 2004) while more and more cases of abuse, dependence and withdrawal complications were reported in various countries (Aranko et al., 1991 in Finland; Pallavicini & Ximena, 1997 in Spain; Jones & Sullivan, 1998 in UK; Kahlert & Bruhne, 2001 in Germany). A systematic review based on Medline including the years 1966-2002 was conducted (Hajak et al., 2003) and a total of 22 cases of zopiclone abuse or dependence were identified. However, all these case reports contained only a few cases (the largest series was 6, Sikdar & Roben, 1996) and there was insufficient data for detailed analysis of the characteristics of these zopiclone abusers.

Tuen Mun Substance Abuse Clinic (TMSAC), one of the six substance abuse clinics in Hong Kong, was established in September 1995 and provides services to a population of around a million. In recent years, it seemed that there were more and more zopiclone abusers seeking treatment at TMSAC and clinical experience indicated that the characteristics were different between those abused zopiclone as a primary drug and those as a secondary drug. The aims of this retrospective study were to find out how common zopiclone abuse was among our clinic cases in the past 10 years and their characteristics, and to test significant differences between these two groups of abusers.

METHODS

From September 1995 to September 2004, there were 872 cases registered at TMSAC and brief computerised medical records were searched to identify all zopiclone abusers. These abusers were categorised, according to our usual practice at the time of intake, into three groups as they might abuse zopiclone as a primary drug (most frequent drug of abuse in the past one year), secondary drug (still actively abused in the past one year but not the primary) and past drug (abused before but stopped at least in the past one year). The manual medical records of all zopiclone abusers were reviewed and the information about basic characteristics was retrieved. These included demographic information (age, sex, marital status, educational level, employment status, criminal records), co-morbid psychiatric disorder (excluding drug-induced conditions) and polysubstance abuse (defined as actively abuse three or more drugs in the past one year). As there was no detailed information on zopiclone abuse available in the medical records of those with just past history, only those active abusers (primary and secondary groups) would be reviewed in depth to get the clinical information on zopiclone abuse at the time of intake (diagnosis of abuse or dependence, duration of abuse, maximal daily dose ever used, frequency and usual dose of abuse in the past one year, reasons of initiation, adverse effects and withdrawal symptoms) or in terms of outcome till September 2004 or by the time of termination of service (duration of treatment at TMSAC, latest condition of zopiclone abuse).

For diagnosis of zopiclone dependence, the criteria of DSM-IV were followed. However, for zopiclone abuse, a broader definition by WHO was used (persistent or sporadic excessive use inconsistent with or unrelated to acceptable medical practice) because some of the abusers might not have any clinically significant impairment or distress to their functioning as defined in DSM-IV.

Chi-square or t-test was applied to test differences between different groups of zopiclone abusers.

RESULTS

Number of zopiclone abusers

Among the 872 registered cases, 104 were found to have a history of zopiclone abuse. There were 41, 46 and 17 cases abusing zopiclone as a primary, secondary and past drug respectively. The number of cases in each group by years (Table 1) showed that the proportion of zopiclone abusers



was increasing drastically in the past four years and up to 30% of new clinic cases.

Table 1: Number of zopiclone abusers by years

Year	95-96	96-97	97-98	98-99	99-00	00-01	01-02	02-03	03-04	4-9/04	Total
Primary	0	1	0	1	1	2	8	15	9	4	41
Secondary	0	0	0	1	1	3	5	11	16	9	46
Past	0	0	0	0	0	1	4	7	2	3	17
Total no. of abusers	0	1	0	2	2	6	17	33	27	16	104
TMSAC new cases	38	108	80	75	71	93	111	124	119	53	872
% of zopiclone abusers	0	0.9	0	2.7	2.8	6.5	15.3	26.6	22.6	30.2	11.9

Basic characteristics of three groups of zopiclone abusers

The detailed figures were shown in Table 2. For the whole group of 104 abusers, the sex distribution was more or less equal (47 males and 57 females), the mean age was 34.6, 75% attained junior secondary school level or below, around 60% were unemployed, 54% had criminal records and 59% had co-morbid psychiatric disorders. The statistical methods (Chi-square or ANOVA) were applied to test differences among the three groups for each basic characteristic. The items found to be significantly different were sex, marital status, criminal records, primary drug of abuse, polysubstance abuse and psychiatric co-morbidity. The abusers in the primary group had more females, more divorcees/separateds and far fewer criminal records. Heroin and cough mixture were the two most common primary drugs of abuse for the secondary and past groups. The percentage of polysubstance abusers in the secondary group was almost double those of the primary and past groups.

Comparison of basic characteristics between primary and secondary groups

Chi-square or t-test was used to detect differences between these two groups. The test values and p values were shown in Table 2. There were significant differences in many areas. In the primary group, there were more females (78% vs 34.8%), more divorcees/separateds (43.9% vs 13.1%), fewer criminal records (26.8% vs 71.7%), fewer polysubstance abusers (24.4% vs 58.7%) and more co-morbid psychiatric disorders (70.7% vs 45.7%) especially depression (53.7% vs 32.6%, $\chi^2=3.93$ and $p=0.047$).

Table 2: Basic characteristics of 3 groups of zopiclone abusers & comparison between primary & secondary groups

Characteristics		Primary group(n=46)	Secondary group(n=41)	Past group (n=17)	Test @ (value)	p
Sex	Male	9 (22)	30 (65.2)	8 (47.1)	X2 (16.41)	<0.001*
	Female	32 (78)	16 (34.8)	9 (52.9)		
Age (mean/SD)		36.98/7.71	33.39/10.69	32.06/8.25	T(1.77)	0.08
Marital status	Single	4 (9.8)	22 (47.8)	7 (41.2)	X2 (18.26)	<0.001*
	Married/cohabiting	19 (46.3)	18 (39.1)	5 (29.4)		
	Divorced/separated	18 (43.9)	6 (13.1)	5 (29.4)		
Educational level	Primary	11 (26.8)	11 (23.9)	2 (11.8)	X2 (0.13)	0.939
	Form 1-3	22 (53.7)	25 (54.3)	7 (41.2)		
	Form 4-7	8 (19.5)	10 (21.7)	8 (47.1)		
Occupation	Employed	9 (21.9)	10 (21.7)	6 (35.3)	X2 (6.41)	0.093
	Unemployed	22 (53.7)	32 (69.6)	8 (47.1)		
	Housewife	10 (24.4)	3 (6.5)	3 (17.6)		
	Student	0	1 (2.2)	0		
Criminal records	Yes	11 (26.8)	33 (71.7)	12 (70.6)	X2(17.49)	<0.001*
	Drug-related CR (mean/SD)	0.32/0.96	0.65/1.52	0.47/0.51	T(2.50)	0.014*
	Other CR (mean/SD)	0.44/1.63	0.84/1.89	0.82/1.02	T(3.72)	<0.001*
Primary drug of abuse	Imovane	41 (100%)	0	0	X2 (87.00)	<0.001*
	Heroin/methadone	0	21 (45.7)	7 (41.2)		
	Cough mixture	0	17 (37)	4 (23.5)		
	Others	0	8 (17.4)	6 (35.3)		
Polysubstance abuse(≥3 drugs)		10 (24.4)	27 (58.7)	5 (29.4)	X2(10.48)	0.001*
Co-morbid psychiatric disorder#	Yes	29 (70.7)	21 (45.7)	11 (64.7)	X2(5.58)	0.018*
	Depression	22 (53.7)	15(32.6)	6(35.3)	X2 (12.92)	
	Psychosis	1 (2.4)	3 (6.5)	2(11.8)		
	Neurosis	5 (12.2)	2 (4.3)	0		
	Personality disorder	7 (17.1)	2 (4.3)	3(5.9)		
	Others	0	2 (4.1)	1		

() percentage of its own group

some clients have more than one psychiatric disorder

@ test between primary & secondary groups

* significant at p value of 0.05



Comparison of zopiclone abuse characteristics between primary and secondary groups

Again, there were significant differences in many areas between these two groups (Table 3). In the primary group, there were more cases with diagnosis of zopiclone dependence (97.6% vs 30.4%), longer duration of abuse (64.5 vs 46.9 months), higher maximal dosage ever used (34.4 vs 6.5 tablets a day), more daily abuse (97.6% vs 43.5%), higher frequency of use in the past one year (356 vs 206 days) and more tablets used in the past one year (4,175 vs 943 tablets). Among all the reasons of initiation of zopiclone abuse, only depressed mood (34.1% vs 6.5%) was found to have a significant difference. More cases in the primary group experienced adverse effects (85.4% vs 47.8%) and withdrawal symptoms (90.2% vs 39.1%). In terms of outcome till September 2004 or by the time of termination of service, more cases in the secondary group were successful in keeping abstinence (45.7% vs 29.3%) although the difference was not statistically significant.

Table 3: Comparison of zopiclone abuse characteristics between primary & secondary groups

Characteristics		Primary group (n=41)	Secondary group (n=46)	Test (value)	p
Diagnosis	Abuse	1(2.4)	32(69.6)	X2 (41.49)	<0.001*
	Dependence	40(97.6)	14(30.4)		
Duration of abuse (months) range/mean/SD		4-204 64.56/21.27	0.33-108 46.93/24.30	T (5.49)	<0.001*
Max. dosage ever used (tab/d) Range/mean/SD		1.5-200 34.38/50.30	1-30 6.53/7.66	T (3.71)	<0.001*
Daily abuser		40	20	X2(29.63)	<0.001*
Freq of use in past 1 yr(d) Range/mean/SD		8-365 356.30/55.75	3-365 206.35/150.71	T (6.01)	<0.001*
No. of tablets used in past 1 yr Range/mean/SD		23-36500 4175.81/6326.24	3-7300 943.44/1322.24	T (3.39)	0.001*
Reasons of initiation	Insomnia	36(87.8)	36(78.3)	X2(1.38)	0.239
	Boredom	3 (7.3)	0	X2(3.49)	0.062
	Depression	14(34.1)	3(6.5)	X2(10.52)	0.001*
	Stress	8(19.5)	3 (6.5)	X2(3.31)	0.069
	Others	9(22)	10(21.7)	X2(0.001)	0.981
Adverse effects	Present	35(85.4)	22(47.8)	X2(13.52)	<0.001*
Withdrawal Sx	Present	37(90.2)	18(39.1)	X2(24.36)	<0.001*
Duration of FU till Sept 2004 mean/SD (months)		21.93/14.45	15.74/13.82	T(2.04)	0.044*
Outcome	Abstinence	12(29.3)	21(45.7)	X2(2.47)	0.116
	Abstinence duration mean/SD (mth)	15.67/15.84	15.52/13.16	T(0.03)	0.978
	BDZ substitution	4(9.8)	0	X2(4.70)	0.030*
	Dependent	15(36.6)	6(13)	X2(6.56)	0.010*
	Tablets/yr mean/SD	1993.5/ 1879.8	1703.3/ 1912.9	T(0.32)	0.754
	Intermittent use	5(12.2)	7(15.2)	X2(0.17)	0.683
	Deceased	3(7.3)	1(2.2)	X2(1.31)	0.253
	Unknown	2(4.9)	9(19.6)	X2(4.23)	0.040
Others	0	2(4.3)	X2(1.83)	0.177	

() percentage of its own group

* significant at p value of 0.05



DISCUSSION

Limitations

As this study is a retrospective study of substance abuse clients, it carries some basic and intrinsic limitations. First of all, since there is only one specialised substance abuse in our catchment area with a one-million population, cases from our clinic is unavoidably subjected to 'referral filter bias' and it is likely that the samples represent the most severe cases. Moreover, the differences between the primary and secondary groups may be due to recall bias of clients (primary abusers are more likely to remember the details of zopiclone abuse as it is their major drug of abuse) and information bias (medical records are more likely to record the details of zopiclone abuse for those primary abusers).

Is zopiclone abuse really rare?

Based on the Fifty-three Report of the Central Registry of Drug Abuse of Hong Kong (collect and analyse all voluntary reports of drug abuse cases), there was no reported case of zopiclone abuser between 1994 and 2003. However, our data showed that there were at least 87 cases actively abusing this drug in the past nine years (1995-2004). Although the exact number of zopiclone abusers is small but it is up to 30% of new cases of TMSAC in 2004 having history of abusing this drug.

In Hajak et al.'s paper (2003), he commented that although only 22 case reports of zopiclone abuse were identified, it might be accompanied by hundreds of unreported cases in clinical practice. He quoted a report from the National Institute of Forensic Toxicology in Norway (Bramness et al., 1999). It reported that from the suspected drugged drivers between 1994 and 1999, 101 cases were found to have zopiclone in their blood and 60% had blood concentration of zopiclone above the normal concentration observed after intake of therapeutic doses.

According to the TMSAC data and the above report from Norway, the incidents of zopiclone abuse are definitely more than the case reports in the literature. Although this study of 104 cases is the largest series so far, it only represents the tip of an iceberg of this problem. Therefore, workers in this drug abuse field as well as medical practitioners should be more alert to the abuse potential of this drug.

Is there any association between polysubstance abuse and psychiatric co-morbidity?

From the case reports in the literature, most of the zopiclone abusers were associated with polysubstance abuse (Sikdar & Roben, 1996) and co-morbid psychiatric disorders (Jones & Sullivan, 1998; Ayonrinde & Sampson, 1998). This study confirmed the above associations. Among the 104 abusers in this study, 42 (40.4%) actively abused three or more drugs in the past one year at time of intake to our service and the proportion was particularly high in the secondary group (58.7%), and 61 (58.7%) had co-morbid psychiatric disorders with depression (41.3%) being the most common one. Similar association was also found in benzodiazepine abuse (Busto et al., 1996). Kahlert & Bruhne (2001) reported a case of zopiclone abuse in Germany without history of polysubstance abuse and psychiatric co-morbidity. In our series of 104 cases, there were 5 such cases.

Are there any differences between the primary and secondary groups?

Our clinical impression indicated that the profiles of those abusing zopiclone as a primary drug of abuse were different from those taking it as a secondary drug of abuse. A typical case of the primary group was a middle-aged divorced lady with depression and she self-medicated with zopiclone to relieve her depressive symptoms and gradually became dependent with escalating dose. On the other hand, a typical case of the secondary group was a middle-aged single man who abused multiple drugs actively and took zopiclone occasionally to relieve his insomnia that might be part of withdrawal symptoms of his other abused drugs. Although these typical profiles cannot apply to each case, the present study did show statistically significant differences between these two groups of abusers in many areas as tabulated in Tables 2 and 3. It was particularly important to identify the underlying depression of the primary group because it was the most common (53.7%) co-morbid psychiatric condition and it was likely that depressive symptoms were the main reason of initiation of zopiclone abuse (34.1% of the primary group reported that depressed mood was the reason of initiation). Further studies are needed to confirm whether there are different groups of zopiclone abusers.

Is chronic use of zopiclone harmful?

The duration, frequency and dosage of abuse were alarming especially in the primary group. Given such chronicity and severity of abuse, it was expected that these abusers experienced more adverse effects especially long-term ones. 70.7% of the primary group and 23.9% of the secondary group complained of some degree of memory impairment. Several zopiclone abusers with serious amnesia



were reported in the UK (Anonymous, 1990) and a case of amnesiac syndrome was reported after taking zopiclone (15 mg a day) for two years (Fava, 1996). It is, therefore, important to assess the cognitive function of these chronic and heavy abusers.

As 40 cases of the primary group and 14 cases of the secondary group had the diagnosis of zopiclone dependence, it was not surprising that 90.2 % and 39.1% of the corresponding groups experienced withdrawal symptoms on stop of zopiclone. For the whole group of 87 active abusers, insomnia (46%), irritability (25.3%) and anxiety (23%) were the three most common withdrawal symptoms. It was worth noting that there were two cases having convulsion during withdrawal. A previous case of withdrawal fit had been reported (Aranko et al., 1991).

Is liability of abuse of zopiclone really low compared with benzodiazepines?

It was estimated that up to one third of benzodiazepine long-term users would become physically dependent (Lader, 1999). Judging from previous available information (only 22 case reports till 2002), the liability of zopiclone abuse or dependence is indeed very low in comparison with benzodiazepines. The present study, despite the limitations, showed the prevalence of zopiclone abuse or dependence was not as low as previously expected. A recent guideline on 'Zaleplon, zolpidem and zopiclone for the short-term management of insomnia' (NICE 2004) emphasised that these Z-drugs should be prescribed for short periods of time only and should not exceed four weeks for a single period of treatment. Moreover, after review of available studies, the guideline concluded that comparing Z-drugs and benzodiazepines, there were no consistent differences in the incidence of next-day residual effects and no data were identified on the frequencies of symptoms associated with withdrawal or dependence. Again, the present study revealed that there was a significant proportion of cases experiencing adverse effects and withdrawal symptoms after prolonged use.

The degree of liability of abuse or dependence of zopiclone is still not fully established, therefore, it is prudent to use this drug with caution to avoid repeating the history of prevalent abuse and iatrogenic dependence of benzodiazepines which were once regarded as very safe drugs with low liability of abuse or dependence. This warning had been released in an editorial in *Lancet* with heading 'Zopiclone: another carriage on the tranquilliser train', which remarked that 'even now far too many people board the tranquilliser train and too few alight when it makes its infrequent stops' (Anonymous, 1990b).

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