

Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data

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ABSTRACT

Aims The non-benzodiazepine hypnotics zolpidem and zopiclone, which are indicated for short-term treatment of insomnia, were considered originally by physicians as almost devoid of abuse and dependence potential. Several recent publications, however, have suggested that both agents carry a significant risk of abuse. To substantiate and re-evaluate this situation, the world literature was reviewed for cases of dependence of both agents; these cases were analysed in order to identify certain underlying patterns, if evident.

Methods A systematic review based on a Medline literature search was conducted including the years 1966–2002 to assemble all available clinical case reports that were analysed for typical features of abuse and dependence according to prespecified criteria. Only case reports were of interest, and clinical studies were excluded. No limitations as to language or publication year were applied. The terms 'zolpidem', 'zopiclone' and 'abuse', 'dependence', 'addiction', 'withdrawal' and 'intoxication' were used to identify relevant publications. Potentially relevant citations were retrieved and assessed for inclusion independently by two authors.

Results A total of 36 cases for zolpidem were identified, most of them reported in recent years, and 22 cases for zopiclone. Both sexes were involved to a similar extent; and cases were reported in all age groups. In extreme cases, dose increases reached a factor of 30–120 above the recommended doses. The majority of patients had a history of former drug or alcohol abuse and/or other psychiatric conditions.

Conclusion On the basis of world-wide prescription numbers, which are approximately twofold higher for zolpidem (1 338 774 000 tablets from June 2001 to June 2002 in Europe, Japan and United States) than for zopiclone (664 897 000 tablets during the same period in Europe and Japan), the relative incidence of reported dependence similar for both drugs and remarkably lower than that of benzodiazepines used for the treatment of disturbed sleep. The findings offer the conclusion that zolpidem and zopiclone are relatively safe drugs. However, as both drugs are psychotropic drugs, patients with a history of abuse or dependence and those with psychiatric diseases seem to be at increased risk of abuse of these agents.

KEYWORDS Dependence, drug abuse, hypnotics, insomnia, review, zolpidem, zopiclone.

INTRODUCTION

Recent large-scale epidemiological studies have confirmed the importance of insomnia as an extremely prevalent condition in the general population (Chevalier *et al.* 1999; Hajak 2001; Ohayon & Zulley 2001) as well as in primary care. Approximately every second patient seeing a general physician in routine care has at least some significant sleep complaints, and every fourth patient fulfils the DSM-IV criteria for insomnia (Wittchen *et al.* 2001).

In the multi-factorial approach, which is required for successful management of insomnia, the basic tenet is that underlying medical or psychological conditions should be treated first. Sleep hygiene and behavioural interventions such as stimulant avoidance, exercise and relaxation are recommended treatments of choice. In more severe cases, however, pharmacological treatment has its place in therapy, with the focus on efficacious, tolerable and safe agents (Roth, Hajak & Üstün 2001). Sleep experts recommend univocally the restriction of the intake of hypnotic drugs to a short-term (Lader & Russel 1993; Clarenbach *et al.* 1995; Lader 1999), leading to the corresponding limitation for use in the labelling of all hypnotic drugs. However, many patients with insomnia, as well as their treating physicians, favour daily intake of these agents even over prolonged periods of many weeks or months (Boixet, Battle & Bolibar 1996; Busto *et al.* 2001).

The use of benzodiazepines (BZ) in the treatment of insomnia has been declining over the past two decades (Walsh & Engelhardt 1992) as a response to studies documenting a number of deleterious effects. Notably, there is a significant risk of a dependence syndrome, psychomotor and coordination problems, danger of falls, especially in the elderly, residual effects on waking, as well as rebound insomnia and withdrawal reactions after prolonged intake (Fraser 1998; Schweizer & Rickels 1998; Longo & Johnson 2000) and also fatal outcome when part of a polydrug use (Gossop *et al.* 2002). At the same time, the prescriptions of the non-BZ hypnotics zolpidem and zopiclone have been increasing substantially. The latter agents are chemically unrelated to the BZ, despite sharing with them—to a varying degree—sedative, hypnotic, anticonvulsant, myorelaxant and amnesic effects. These effects are linked to a specific agonistic activity on a central receptor that belongs to the gamma-aminobutyric acid (GABA) BZ macromolecular receptor complex, comprising the alpha 1 and alpha 2 receptors, which modulate the opening of the chlorine channel.

The short-acting imidazopyridine hypnotic zolpidem binds preferably to the alpha 1 subtype of the BZ receptor. It is able to produce sedation without interfering with other BZ properties linked to other receptor subtypes and has negligible if any residual effects 9 hours after intake

(Uden & Roth Schechter 1996; Holm & Goa 2000). This lack of residual effects may result from its rapid metabolism via CYP3A4 and CYP1A2 isoenzymes (Pichart *et al.* 1995) and a short elimination half-life. Its bioavailability after oral administration is 70%; C_{max} appears between 0.5 and 3 hours after administration, and the elimination half-life is approximately 2.4 hours (0.7–3.5 hours). It is excreted as inactive metabolites mainly in urine (56%) and faeces (37%). In elderly subjects, clearance is reduced and peak plasma concentrations are increased by 50% without a significant prolongation of the half-life (3 hours) (Holm & Goa 2000). Usually, zolpidem is administered in a total dose of 10 mg, which is reduced to 5 mg in elderly patients (Allain & Monti 1996).

Zopiclone is another non-BZ hypnotic, belonging, however, to the cyclopyrrolone class (Goa & Heel 1986; Wadworth & McTavish 1993; Hajak 1999). Zopiclone is less selective than zolpidem in binding to the recombinant GABA BZ subunits (Allain & Monti 1996). It binds non-selectively to both alpha 1 receptor as well as other subtypes (Langer & Arbilla 1988) that differ from zolpidem *in vitro* (Im *et al.* 1993) and *in vivo* (Lillsunde & Seppälä 1990). The oral bioavailability of zopiclone is approximately 80%. It is rapidly absorbed (C_{max} reached at 1.5–2 hours), and the elimination half-life is 5 hours (3.5–6 hours). The drug is metabolized by the liver and excreted mainly by the kidneys (80%) as active and inactive metabolites. In elderly subjects the half-life increases, with the average half-life being 7 hours. The usual daily dose is 7.5 mg. The recommended dosage in elderly subjects is 3.75 mg, possibly increased to 7.5 mg (Goa & Heel 1986; Wadworth & McTavish 1993).

Zolpidem was introduced into clinical practice in 1988, zopiclone in 1985. Since then, the efficacy and safety profiles of both agents have been studied in a substantial number of clinical studies and several large post-marketing surveillances. On the basis of the available epidemiological and clinical data, reviews conclude generally that the risk of dependence is low or minimal (Lader 1997; Rush 1998; Darcourt *et al.* 1999; Hajak 1999; Soyka, Bottlender & Möller 2000), while at least some warnings have been released about the drugs' misuse (Clee, McBride & Sullivan 1996; Rooney & O'Conner 1999).

To substantiate and re-evaluate this situation, the world literature was reviewed for cases of dependence of both agents; these cases were analysed in order to identify certain underlying patterns, if evident.

METHODS

In August 2002, we conducted a Medline literature search including the years 1966–2002. The terms

'zolpidem', 'zopiclone' and 'abuse', 'dependence', 'addiction', 'withdrawal' and 'intoxication' were used to identify relevant publications. These terms had to be part of the title, keywords or abstract, if available. Potentially relevant citations were retrieved and assessed for inclusion independently by two authors. Only case reports were of interest, and clinical studies were excluded. The reference lists of the retrieved articles were screened for additional relevant sources. No limitations as to language or publication year were applied. Publications in languages other than English or German were translated into German by certified translators. The case reports were analysed according to prespecified criteria (Soyka, Bottlender & Möller 2000). Particular attention was paid to data reporting the use of higher than recommended doses, intake in other than the recommended indication (i.e. intake of the hypnotic during daytime), loss of efficacy due to development of tolerance, dose increase over time and occurrence of withdrawal symptoms after cessation of drug intake.

RESULTS

Our search retrieved 36 cases of dependence on zolpidem and 22 cases of dependence on zopiclone. The number of cases per year is displayed in Fig. 1.

The degree of precision and detail of reporting of the case reports varied considerably across the reports. Furthermore, the terminology used for reporting differed. For example, a clear differentiation between various insufficiently defined features of abuse or dependence, such as craving or desire, was lacking. None the less, a number of relevant outcomes can be distilled from the reports. Cases were reported in similar frequencies for both men and women, and in all age groups (see Tables 1 and 2). The recommended dose was exceeded for zolpidem, if used

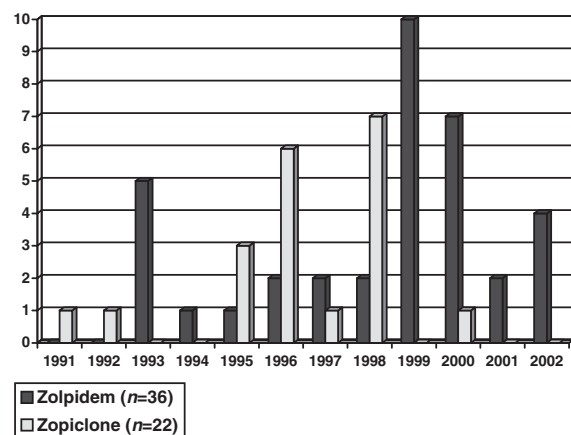


Figure 1 Number of cases reported on dependence/abuse of zolpidem or zopiclone per year. Source: Medline. Note: some references detail more than one case report

alone, by a factor of 8–120 (i.e. up to 1200 mg/day in one extreme case) (Correas *et al.* 2002), with a mean of about 400 mg/day, and for zopiclone, by factor 3–51 (the mean was not calculated due to some missing values). In one zopiclone case (Gilbert & Staats 1997) dependence was reported at usual daily doses in a formerly pethidine-dependent patient. Intravenous use of the agent was reported in only one zopiclone case (Pallavicini & Ximena 1997). For almost all patients the typical features of dependence were reported, namely dose increases over time, tolerance (loss of efficacy) and withdrawal symptoms. Two features appear to be associated closely with abuse of or dependence on both agents: almost all cases were reported in former drug or alcohol abusers, or the patients had recognized psychiatric disorders other than drug abuse or dependence. There were no fatalities.

DISCUSSION

Case reports are usually published for single interesting cases, which are for the most part rarities, or where there was some difficulty in reaching a diagnosis and where there is a teaching point. It was interesting to find that more than a decade after introduction of zolpidem and zopiclone into clinical practice, and after extensive post-marketing experience, there is still high interest on the part of authors and journals to publish cases: between January 1999 and August 2002, 24 cases were reported in nine different publications.

We focused our search deliberately on the Medline database to ensure easy and swift access for the readership to the original articles. We applied no restrictions on publication year, language or manuscript type, and we refined the search by including all case reports mentioned in the references of the papers found. We are aware that we might still have missed a few reports from other sources such as congress abstracts not formally published (Dickersin, Scherer & Lefebvre 1994). At the same time, we might have missed reports from countries such as Greece or Romania that allow over-the-counter distribution of zolpidem and zopiclone, which undoubtedly increases the risk of abuse. None the less, we believe our survey is currently the most comprehensive one on case reports published for both zolpidem and zopiclone. The likelihood of zopiclone and zolpidem to lead to abuse or dependence is not zero, as had been hoped in the early years of use of the substances. The 58 reports that we identified in the literature may be accompanied by hundreds of unreported cases occurring in clinical practice. However, when taking into account the high number of prescriptions (for zolpidem 1 338 774 000 tablets from June 2001 to June 2002 in Europe, Japan and the United States, for

Table 1 Case reports on dependence/abuse of zolpidem.

No.	Age (years)	Gender	Highest daily dose (mg/day)	Intake during daytime	Dose increase	Tolerance	Withdrawal symptoms	Former dependence	Psychiatric complications	Reference
1	67	F	100	+	+	+	+	+	+	Madrak & Rosenberg 2001
2	43	F	450-600	-	+	+	+	-	nr	Aragona 2000
3	39	M	120-480 ^b	nr	+	nr	+	-	+	Golden & Vagnoni 2000
4	42	F	300	nr	+	+	+	+	+	Vartzopoulos et al. 2000
5	30	F	400-500	nr	+	+	+	+	+	Vartzopoulos et al. 2000
6	26	F	160-200	nr	+	+	+	+	+	Vartzopoulos et al. 2000
7	33	M	120	nr	+	+	+	+	+	Vartzopoulos et al. 2000
8	45	F	40 (+zopiclone)	+	+	+	+	-	+	Harter 1999 ^a
9	49	M	50-80	+	+	+	+	-	-	Ströhle 1999
10	50	F	=600	+	+	+	+	+	+	Hofmann & Eichmann 1998
11	44	F	30-300	+	+	+	+	nr	+	Sakkas 1999
12	63	F	300	+	+	+	+	nr	?	Courtet 1999
13	28	F	800	-	+	-	+	nr	?	Courtet 1999
14	69	F	200	+	+	+	-	nr	?	Courtet 1999
15	32	M	60	+	+	+	-	nr	?	Courtet 1999
16	45	M	120	+	+	+	+	nr	?	Courtet 1999
17	40	M	200	+	+	nr	nr	+	?	Courtet 1999
18	35	M	100	+	+	nr	nr	nr	?	Courtet 1999
19	55	F	=200	nr	+	+	+	nr	+	Ravishankar 1998
20	28	M	=100	nr	+	nr	+	nr	+	Ravishankar 1998
21	53	M	140	+	+	+	+	+	-	Bottlender 1997
22	37	M	130	+	+	+	+	-	-	Gilbert & Stats 1997
23	35	M	200-300	-	+	+	+	-	+	Chamorro-Garcia 1996
24	33	M	300-400	+	+	+	+	-	nr	Sanchez 1996
25	75	M	70	+	+	+	+	-	nr	Thome 1995
26	33	M	150-280	+	+	+	+	-	+	Gericke 1994
27	42	F	nr	nr	nr	nr	+	+	+	Bruun 1993
28	52	M	60-70	nr	+	+	+	+	+	Bruun 1993
29	55	F	=120	+	+	+	+	+	+	Bruun 1993
30	60	F	100	nr	+	+	+	+	nr	Bruun 1993
31	31	F	70-80	+	+	+	+	nr	+	Cavallaro 1993
32	67	F	100	nr	+	+	+	nr	+	Cavallaro 1993
33	50	F	450	+	+	nr	+	-	+	Göder et al. 2001
34	51	M	1200	+	+	nr	+	-	nr	Barbero-Hernandez et al. 2002
35	46	F	200	nr	+	nr	+	+	nr	Correas Lauffer et al. 2002
36	40	F	200	+	+	nr	+	+	+	Correas Lauffer et al. 2002

M = male, F = female; nr = not reported. ^aConcomitant abuse of zopiclone and zolpidem. ^b10-40 quaque hora somni (qhs; every hour of sleep).

Table 2 Case reports on dependence/abuse of zopiclone.

No.	Age (years)	Gender	Highest daily dose (mg/day)	Intake during daytime	Dose increase	Tolerance	Withdrawal symptoms	Former dependence	Psychiatric complications	Reference
1	59	F	150	+	+	+	+	+	+	Kahlert & Brühne 2001
2	45	F	nr (+ zolpidem)	+	+	+	+	-	+	Harter 2000 ^a
3	29	M	22.5 (poly)	-	+	+	+	-	-	Jones 1998
4	26	M	30	+	+	+	+	-	+	Jones 1998
5	49	F	22.5	nr	+	+	+	-	+	Jones 1998
6	36	F	30	+	+	+	+	+	+	Jones 1998
7	60	F	22.5	nr	+	+	nr	nr	nr	Ayonrinde & Sampson 1998
8	40	M	15	+	+	+	+	+	+	Ayonrinde & Sampson 1998
9	71	F	15	nr	+	+	+	nr	+	Ayonrinde & Sampson 1998
10	55	F	?	?	?	?	?	?	?	Pallavicini & Ximena 1997
11-17	nr	M/F	Mean 105 (90-380 mg) ^b	nr	+	+	nr	+	nr	Sidkar & Ruben 1996
18	17	M	30	+	+	+	-	+	+	Sullivan 1995
19	16	M	37.5	+	+	+	-	-	-	Sullivan 1995
20	18	M	nr (i.v)	+	nr	+	-	+	-	Sullivan 1995
21	36	M	45	+	+	+	+	+	+	Thakore 1992
22	29	M	7.5 (single dose) ^c	-	-	-	+	+	-	Sutherland 1991

nr = not reported. ^aConcomitant abuse of zopiclone and zolpidem. ^bReport on a total of six cases of polytoxicomania, during methadone therapy. ^cFormerly pethidine-dependent patient.

zopiclone 664 897 000 tablets during the same period in Europe and Japan; source: Sanofi-Synthelabo, Paris), the relative incidence of dependence and abuse appears extremely low. Especially striking is the risk gradient to the BZ hypnotics, which have been recognized as major drugs of abuse and addiction as up to a third of all long-term users are estimated to be physically dependent (Lader 1999). When considering that approximately twofold more zolpidem than zopiclone was prescribed in the reference period, the relative risk for zolpidem and zopiclone appears very similar.

To quantify the abuse and dependence risk for both agents, various additional sources provide valuable information. Among the epidemiological databases, the German 'Early Warning System' for recording abuse patterns of chemical substances in Germany collects data on an annual basis on the incidence of abuse and dependence in representative samples (Keup 1999). Between 1992 and 1997, 21 cases of abuse and/or dependence were reported for zolpidem and 10 cases for zopiclone. Based on 10 000 defined daily doses, the number of abuse reports for both agents taken together is 4.5, which is substantially lower than the 106.7 reports per 10 000 BZ daily doses. On the basis of these figures, the abuse potential of zolpidem and zopiclone was considered to be very low (Keup 1999).

The Drug Commission of the German Physicians in 1999 reported a total of 19 case reports referring to zolpidem drug dependence, 12 to withdrawal symptoms and six to drug abuse, all of them exclusively cases of secondary dependence. These numbers are to be seen against a background of about 150 million defined daily doses in Germany between 1991 and 1998 (Arzneimittelkommission 1999). The Commission highlighted the fact that the possibility of transferring the abuse from BZ to zolpidem has to be taken into consideration, and warned against prescriptions of zolpidem for patients with known BZ dependence. It is important to note that the term 'dependence' used in various reports on BZ dependence does not necessarily match the criteria in current diagnostic systems. Thus the recommendation could have applied, more appropriately, the terms 'known BZ misuse' or 'known BZ abuse'.

The MEDIPLUS database run by the Institute of Medical Statistics (IMS, Frankfurt, Germany) contains anonymous information from 550 general practitioners on more than 3 million patients in Germany and allows relative comparisons of long-term prescriptions. According to an analysis of a subset of 24 571 patients, the risk for long-term use of drugs was high in patients who received BZ that had long half-lives (10%) compared to shorter-acting BZ (5.9%). The risk was considerably lower for zolpidem (2.6%) (Institut für Medizinische Statistik 1997).

Postmarketing surveillances are also an important source of information about drug use under real-life conditions. Large studies have been conducted with zopiclone in 1993 in the United Kingdom (Imman *et al.* 1993) ($n = 13\,177$ patients) and 1994 in Spain (Alvarez 1994) ($n = 3605$), and for zolpidem in 1995 in Switzerland ($n = 1972$) (Ganzoni *et al.* 1995) and 1997 in Germany ($n = 16\,944$) (Hajak & Bandelow 1998). No problems after stopping medication in normal doses have been reported by the authors. A meta-analysis (Soldatos, Dikeos & Whitehead 1999) and a review (Bianchi & Musch 1990) of sleep laboratory studies also have also found that tolerance, rebound and withdrawal phenomena are marginal and mild, at least in the proven population of primary insomniacs. However, long-term, controlled, prospective studies addressing this issue are still lacking.

The National Institute of Forensic Toxicology in Norway reported recently that in blood samples drawn between 1994 and 1999 from 101 suspected drugged drivers with zopiclone detected in their blood (Bramness, Skurtveit & Morland 1999), 60% had blood concentrations of zopiclone above the normal concentration observed after intake of therapeutic doses. Eighty per cent had higher blood concentrations than those expected 8 hours after intake of therapeutic doses. The majority of drivers also tested positive for illegal drugs, prescription drugs with abuse potential or alcohol. The authors concluded that zopiclone is misused or abused and therefore should be used with caution. It is obvious from this and other papers that comorbidities such as alcoholism (Ross 1993), polydrug use (Busto, Romach & Seller 1996; Sikdar & Ruben 1996; Sikdar 1998), dependent personality (Ayonrinde & Sampson 1998; Martinez-Cano *et al.* 1999) or the presence of other psychiatric disorders (Ross 1993; Busto *et al.* 1996; Martinez-Cano *et al.* 1999) may increase critically the patient's individual risk for abuse of or dependence on GABAergic-acting drugs.

Our overview, in the context of supportive evidence from epidemiological studies and phase IV observational trials, offers the conclusion that zolpidem and zopiclone are relatively safe drugs. Dependence accompanying long-term use, as shown by either characteristic withdrawal syndromes or psychological 'craving', is rarely reported, considering the world-wide extent of usage. Abuse, defined as addictive non-medical use, is documented in some cases but is overall quite rare, in comparison with the widely abused benzodiazepines. None the less, patients with a history of abuse or dependence and those with psychiatric diseases are at risk of abuse of these non-BZ agents. Therefore, extreme caution as with BZ should be taken when considering the prescription of zolpidem and zopiclone to these special patient groups.

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