

Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey

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Aim

To show that the nonbenzodiazepine hypnotic zolpidem has a higher abuse potential than previously documented.

Method

An official enquiry was carried out by the Nantes Centre for Evaluation and Information on Pharmacodependence (CEIP). The authors made a review of literature and analysed French data corresponding to the drug's postmarketing period collected by the CEIP network from 1993 to 2002.

Results

The literature review yielded mixed results concerning the behavioural effects of zolpidem. Data from the CEIP and the 53 literature case reports highlight significant dependence and abuse potential of zolpidem.

Conclusions

This study adds to the growing evidence that zolpidem has the potential for abuse and dependence. As a consequence, the French drug monograph has been modified by the French Health Authorities.

Introduction

Zolpidem is a nonbenzodiazepine hypnotic which binds to the benzodiazepine binding site on the GABA-A receptors. It was marketed in France in 1987 (Stilnox®). Benzodiazepines are still commonly prescribed for short-term insomnia, but they are gradually being replaced for this indication by imidazopyridine zolpidem, the first short-acting hypnotic selective for the α_1 subtype of the benzodiazepine binding site on the GABA-A receptor. This compound is clinically effec-

tive, safe and well tolerated, and also has a favourable pharmacokinetic profile for use as a hypnotic (rapidly absorbed and eliminated), characteristics that have contributed to its popularity. It is thought to be a safer drug than benzodiazepines because initial clinical trials have reported no evidence of abuse or dependence potential [1].

However, over the last few years, in various European countries and in the USA, numerous cases of zolpidem abuse or dependence have been reported [2–30].

The World Health Organization (WHO) considered that the frequency of zolpidem abuse and dependence was similar to that of benzodiazepine; on 15 July 2002, zolpidem was transferred to Schedule IV of the 1971 Convention (for drugs inducing dependence such as benzodiazepines). The aim of this convention is to control both traffic and abuse of psychotropics [31, 32].

In France, the observation and assessment of drug abuse and dependence associated with psychoactive medication falls under the responsibility of the national Committee for Narcotics and Psychotropic Drugs. In order to assist this Committee, a network of 10 centres for evaluation and information on pharmacodependence (CEIP) was created in France. The three main aims of the CEIP are: (i) to collect data and assess the potential for dependence on psychoactive drugs (under French regulations it is mandatory for health professionals to notify the relevant territorial CEIP in case of drug abuse or pharmacodependence) [33]; (ii) to provide information on the risk of abuse or dependence on psychoactive substances; and (iii) to develop research [34].

The decision was taken by the French health authorities to launch an official enquiry aimed at reassessing the dependence potential of zolpidem; the Nantes CEIP carried out this investigation.

This study set out to show that zolpidem carries a higher potential for abuse than previously documented.

Methods

Definitions

Drug abuse is defined as the lasting or sporadically excessive use of a drug in a way which does not conform or correspond to acceptable medical practice, leading to clinically significant impairment or distress as manifested by one or more items defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) (Table 1). It is therefore an intentional use of excessive or therapeutic doses for different purposes than the indication for which the drug was prescribed. However, the medical use of a drug is not considered as drug abuse, even when it leads to pharmacodependence.

Pharmacodependence for a patient is characterized by the loss of behaviour control. DSM-IV has defined seven criteria to qualify this situation (Table 1). Meeting at least three out of the seven criteria leads to a diagnosis of pharmacodependence syndrome.

With this definition, tolerance and withdrawal are not sufficient to diagnose pharmacodependence, if no other criterion is met. Conversely, a subject can be considered as dependent even if there is neither tolerance nor withdrawal, as long as three of the criteria are met.

Methodology used to assess the abuse and pharmacodependence potential of zolpidem

Results of preclinical and clinical studies conducted with laboratory animals and humans The reinforcing effect of a drug may be the single most important determinant of its abuse potential. Preclinical studies typically assess a drug's reinforcing effect by determining whether it induces self-administration.

The goal of discriminative studies was to compare discriminative-stimulus effects of a drug with those of a drug known to have an addictive potential.

Behavioural studies have demonstrated the presence of tolerance (item 1) and withdrawal (item 2).

French data collected by the CEIP network in the postmarketing period, from 1993 to 2002: these data are used to assess the liability to abuse of drugs (associations, use of new administration patterns, dealing) In order to achieve its goals, the CEIP developed many original tools for collecting data:

- Records of dependence or abuse cases notified by health professionals (NotS for spontaneous notifications, 'Notifications Spontanées' in French) [34].
- Epidemiological survey of falsified or forged prescriptions in a network of volunteer pharmacies: (OSIAP for 'Ordonnances Suspectes Indicateur d'Abus Possible') [35–37]. This system provides information on the potential liability to abuse of drugs marketed in France. This survey gives the number of OSIAP related to zolpidem. To compare zolpidem with other medications, the falsification ratio [37] was taken into account; this ratio was obtained by dividing the number of falsification reports for zolpidem by the sales data in the same period.
- Annual surveys with drug users in drug centres: the aim of OPPIDUM (OPPIDUM for abuse of lawful and unlawful psychotropic drugs, 'Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse' in French) [38–40] is the survey of products used by drug addicts who consult physicians in drug addict care centres.

Literature case reports are used to assess dependence potential We collected all case reports from 1993 to 2005 (to our knowledge); for each case, we determined overdose, time to onset of symptoms, associated psychiatric disorders, abuse, dependence, withdrawal syndrome, search for positive effect and any other addiction.

Table 1

Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for substance abuse and substance dependence

Substance abuse

The DSM-IV defines the diagnostic criteria for substance abuse as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home (e.g. repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household).
2. Recurrent substance use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use).
3. Recurrent substance-related legal problems (e.g. arrests for substance-related disorderly conduct).
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g. arguments with spouse about consequences of intoxication, physical fights).

Substance dependence

The DSM-IV defines the diagnostic criteria for substance dependence as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:

1. Tolerance, as defined by either of the following:
 - The need for markedly increased amounts of the substance to achieve intoxication or desired effect.
 - Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
 - The characteristic withdrawal syndrome for the substance.
 - The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. Taking the substance often in larger amounts or over a longer period than was intended.
4. A persistent desire or unsuccessful efforts to cut down or control substance use.
5. Spending a great deal of time in activities necessary to obtain or use the substance (e.g. driving long distances) or to recover from its effects.
6. Giving up social, occupational or recreational activities because of substance use.
7. Continuing the substance use with the knowledge that it is causing or exacerbating a persistent or recurrent physical or psychological problem (e.g. continuing to drink despite an ulcer made worse by alcohol use).

Results

Behavioural preclinical studies

Rodents Results of early rodent studies have revealed no evidence of tolerance to the sedative effect or physical dependence as assessed by the lack of withdrawal symptoms after long-term administration and drug discontinuation, unlike benzodiazepines [41, 42]. In contrast, there is complete tolerance to the hypothermic and muscle-relaxant effects in rodents after 8 days of treatment (in rodents, zolpidem has three effects: hypothermic, muscle relaxant and sedative) [41]. Drug discrimination studies highlight the fact that rodents discriminate between zolpidem and benzodiazepine [2].

Baboons Griffiths *et al.* have conducted several studies which examined various behavioural effects of zolpidem [43, 44] in baboons. These studies showed that the rates of zolpidem self-injection were higher than those produced by benzodiazepines under similar conditions. In drug discrimination studies, baboons were not able to

discriminate between zolpidem and lorazepam. Zolpidem produced ataxia and sedation, which progressively decreased over seven consecutive days of administration. Moreover, substitution with saline after chronic zolpidem administration produced a time-limited spontaneous withdrawal syndrome.

In conclusion, withdrawal, discriminative stimulus effects, and tolerance shown with zolpidem were similar to those shown with benzodiazepines under similar conditions [43, 44].

These results are inconsistent with those observed in rodents.

Humans

- **Discrimination studies:** drug-discrimination studies conducted with humans led to mixed results regarding differences between zolpidem and benzodiazepines. However, it is likely that these mixed results could be attributed to the use of different methods, notably the drug-discrimination procedures.
- **Reinforcing effects and abuse potential:** two reports assess zolpidem's reinforcing effects and abuse poten-

tial in individuals with histories of ethanol or drug abuse. Zolpidem and triazolam produced comparable increases in rates of 'drug liking'. Thus, the reinforcing effects and potential for abuse of zolpidem are probably not significantly different from those of most available benzodiazepine hypnotics [45, 46].

- Tolerance studies: several clinical trials and studies have failed to find tolerance to zolpidem's sleep-promoting effects following long-term administration [45]. These results were confirmed by a meta-analysis in 1999, which summarized 137 studies. This meta-analysis did not report evidence of tolerance with zolpidem as there is with triazolam [47]. One study that directly compared zolpidem and triazolam has suggested that tolerance to the hypnotic effects developed for both zolpidem and triazolam [48].
- Withdrawal effects: it is necessary to make a distinction between symptoms of withdrawal, rebound insomnia (significant worsening of sleep difficulties relative to predrug levels) and recurrence of insomnia following repeated administration [49]. Most authors take into account the chronology of the onset of symptoms. The delays described depend on the drug half-life. Rebound insomnia appears early; symptoms are transitory and similar to those of insomnia before treatment. In the withdrawal syndrome, there is an association of physical withdrawal symptoms with psychological anxiety symptoms. Less frequently, very suggestive symptoms, such as seizures, can appear. Finally, recurrence of insomnia appears slowly and progressively within 2–3 weeks.

There is no evidence of insomnia rebound after chronic treatment with 10 mg zolpidem in most studies [48, 50, 51]. There is evidence from the meta-analysis [47] that the night following drug discontinuation, one observes a more important insomnia rebound with zolpidem than with a placebo. Many studies failed to find withdrawal symptoms. However, an increasing number of authors have published reports highlighting evidence of physical dependence: Lemoine [52] has described withdrawal symptoms after discontinuing zolpidem chronic treatment (3 months on a therapeutic dose) in a randomized, double-blind study.

In conclusion, it seems that despite the chemical difference between zolpidem and benzodiazepines, the behavioural effects of zolpidem are generally similar to those of benzodiazepines. Studies in humans show mixed results, but the variability seems to be linked to dosage and to the population studied [53]. Individuals with a history of alcohol or drug abuse should be monitored closely while receiving zolpidem.

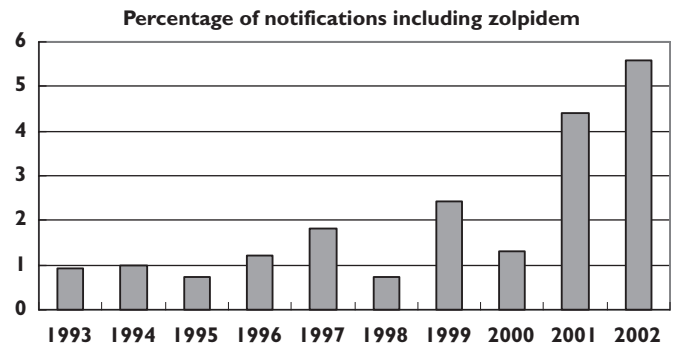


Figure 1

Percentage of notifications concerning zolpidem reported to the French network of Centres for Evaluation and Information on Pharmacodependence (CEIP) over a period of 10 years. The percentage of notifications including zolpidem reported to the CEIP network has increased significantly since 1993

Postmarketing monitoring CEIP data

NotS Between 1993 and 2002, 235 NotS concerning zolpidem were reported to the CEIP network. Figure 1 shows the evolution of the percentage of notifications including zolpidem vs. time. In numerous notifications there was a very high incidence of overdose (20–80 tablets per day). Association with benzodiazepine and maintenance treatments was frequently reported as an association with illicit drugs. Four cases of intravenous abuse were reported.

OSIAP Between 1995 and 2002, 159 forged prescriptions or OSIAPs involving zolpidem were reported. The percentage of zolpidem-related OSIAPs has increased over the last few years, as shown in Figure 2. With these data, it is possible to determine the position of zolpidem each year compared with other individual drugs found in OSIAPs. Since 1998, zolpidem has been listed as one of the 10 drugs most frequently found in OSIAPs. It ranked number 6 in 1999 and number 1 in 2004.

The zolpidem falsification ratio is moderate. This ratio is obtained by relating the number of falsification reports for zolpidem to its sales data during a given period. It was assessed in order to compare zolpidem with other marketed drugs found in OSIAPs. The fact that the falsification ratio for zolpidem is moderate, although it is now the most frequently found drug in forged prescriptions, is linked to the fact that zolpidem is the most prescribed hypnotic. However, this ratio is increasing and the zolpidem ratio is higher than that of the leading benzodiazepine, a good basis for comparison.

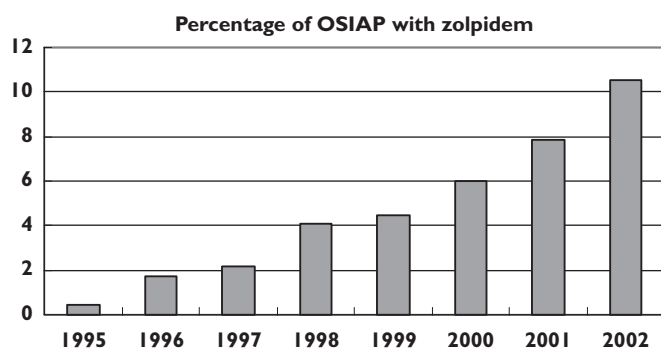


Figure 2

Percentage of falsified or forged prescriptions (OSIAP) concerning zolpidem reported to the French network of Centres for Evaluation and Information on Pharmacodependence (CEIP) over time. The percentage of notifications concerning zolpidem reported to the CEIP network has increased significantly since 1995

In conclusion, zolpidem is flagged when using the system providing information on potential liability to abuse of drugs marketed in France.

OPPIDUM OPPIDUM is a national French programme: in 2002, 3422 patients were included in the OPPIDUM survey, the aim of which was to investigate substance used by drug addicts. Among these drug addict patients, the number of patients using zolpidem increased from <1% (10 patients/1462 in the 1998 survey) to nearly 2% (36 patients/2030) in 1999 and 4% since 2001 (112 patients/2858). Nearly all patients using zolpidem practise polyconsumption; three out of four receive maintenance treatment, one out of two receives benzodiazepines and four out of 10 consume cannabis. The OPPIDUM database provides information linked to misuse such as the ways in which drugs are obtained. Zolpidem has been misused. Until 1998, 100% of the patients obtained it through medical prescriptions, but since 2001 nearly 15–20% have bought it through street deals (479 patients among the 3422 in the 2002 study). Finally, the OPPIDUM database which includes various items in relation to pharmacodependence shows that >50% (1563 patients/2858 in 2001) of patients answered positively to the aspect of ‘search of positive effects’. Suffering from discontinuation appears for more than 1/3 of them. Two cases of intravenous abuse are reported.

In conclusion, the OPPIDUM database allows us to conclude that zolpidem is a drug used within the population of drug addict patients who call physicians in drug addict care centres, and that various aspects of misuse and pharmacodependence are evident.

Literature case reports

We found 53 case reports of chronic abuse, tolerance, misuse and withdrawal symptoms (Table 2) [2–30]. Twenty-six (52%) were female and 24 (48%) male patients. For three cases, information was not available. The average age was 42 years (range 17–80 years).

Most of the time, patients began treatment for insomnia with a 10-mg daily dose, then rapidly (1–2 weeks to 2–3 months) increased the dose and took zolpidem in the daytime. The maximal dose average was 298.3 mg per day (range 10–1120 mg). For all patients, the mode of administration was oral except for one patient using inhalation (no. 19 in Table 2) and one using parenteral administration (no. 51 in Table 2).

Thirty-three patients (63%) had a history of somatic or psychiatric disorder (borderline personality disorder, depression, etc.), 43% of patients had a previous history of substance abuse (alcohol, benzodiazepine) and 43 patients (81%) developed withdrawal symptoms after they stopped taking zolpidem.

Tolerance-related events were observed for 27 patients (51%). Thirty-three patients (62%) fulfilled the criteria for dependence on zolpidem.

Two population profiles have appeared. In the first, including half of the patients [25 cases (47%)], zolpidem was not used for sedation but to achieve stimulation, euphoria and anxiolysis. These patients began taking zolpidem to treat their insomnia and experienced a paradoxical effect. The development of addiction was based on the paradoxical effects: the substance abuse brought them ‘euphoria, a feeling of well being, hyperactivity’; they are able to cope with everyday problems. They took 3–5 tablets of zolpidem and the paradoxical effect regularly appeared 15 min after ingestion of the drug and initially lasted 15 min to 1 h. Some patients never felt the sedative effects of the drug. In all these cases, patients rapidly developed dependence and increased doses during the first 2 months. Some of these patients had a history of substance abuse ($n = 12$, 48%): for these patients, zolpidem had been prescribed as a non-addictive option to treat their insomnia, given their history. A patient [24] who systematically used cocaine was prescribed zolpidem for the treatment of insomnia resulting from the cocaine abuse. This patient swallowed 3 or 4 tablets of zolpidem after cocaine inhalation and took between 20 and 30 tablets per day. He claimed that he never used zolpidem as a sedative drug but as a means of progressively reducing his cocaine craving. After using zolpidem, he became more excited, hyperactive, and euphoric. Another patient [28], who had used heroin injection, began taking zolpidem orally initially for

Table 2
Case reports

No.	Reference	Year	Sex	Age, years	Initial dose	Maximum dose	Time of onset	Psychiatric disorders	Abuse	Dependence	Withdrawal	Tolerance	Paradoxical effects	Other drug abuse
1	Bruun [2]	1993	F	42				1		1	1			1 alcohol
2	Bruun	1993	M	52		70		1	1	1	1			
3	Bruun	1993	F	55		120		1	1	1	1			
4	Cavallaro [3]	1993	F	60	10	100	2 months	1	1	1	1			Previous history
5	Cavallaro	1993	F	31	20	80	2 months	d	1	1	1			
6	Gericke [4]	1993	M	33	20	280	<1 month	d	1	1	1		1	
7	Thome [5]	1995	M	75		70		d	1	1	1		1	
8	Chamorro [6]	1996	M	35		300		1	1	1	1			
9	Sanchez [7]	1996	M	33	10	400	2 months	d	1	1	1			
10	Watsky [8]	1996	M	50	10				0	1	1			
11	Bottlender [9]	1997	M	53		140		1	1	1	1		1	Previous history
12	Gilbert [10]	1997	M	37	10	130	2 months		1	1	1			
13	Ravishankar [11]	1998	F	55		200			1	1	1			
14	Ravishankar	1998	M	28		100		d	1	1	1			
15	Hofmann [12]	1998	F	50		600		1	1	1	1			
16	Courtet [13]	1999	F	63	10	300	<1 month	d	1	1	1		1	Alcohol
17	Courtet	1999	F	28		800		1	1	1	1		1	
18	Courtet	1999	F	69		200		1 d	1	1	1		1	
19	Courtet	1999	M	35		100		1	1	1	1			Poly toxicomania
20	Courtet	1999	M	32		60		1	1	1	0		1	
21	Courtet	1999	M	45		120		1	1	1	1		1	
22	Courtet	1999	M	40		200		1	1	1	1			Poly toxicomania
23	Strohle [14]	1999	M	49		80		d	1	1	1			
24	Sakkas [15]	1999	F	44		300	1 month	1 d	1	1	1		1	1
25	Vartzopoulos [16]	2000	F	42	10	300	<1 month	1	1	1	1			1 benzodiazepine
26	Vartzopoulos	2000	F	30		500		1	1	1	1			1 benzodiazepine
27	Vartzopoulos	2000	F	26	10	200		1	1	1	1			1
28	Vartzopoulos	2000	M	33	10	120		1	1	1	1			1

Table 2
Continued

No.	Reference	Year	Sex	Age, years	Initial dose	Maximum dose	Time of onset	Psychiatric disorders	Abuse	Dependence	Withdrawal	Tolerance	Paradoxical effects	Other drug abuse
29	Aragona [17]	2000	F	43	10	600	2 months		1	1	1		1	1 benzodiazepine
30	Golden [18]	2000	M	39		40			1	1	1			1 benzodiazepine
31	Madrak [19]	2001	F	67	10	100		d	1		1			Alcohol Poly toxicomania
32	Fenéon [20]	2001	F	17		1120		1	1	1	1		1	1
33	Correas [21]	2002							1	1	1			1
34	Correas	2002							1	1	1			1
35	Correas	2002							1	1	1			1
36	Barrero [22]	2002	F	50		450			1	1	1			1
37	Liappas [23]	2003	F	28	10	300	2 months	d	1	1	0	1	1	
38	Liappas	2003	F	35		150	1 month		1	1	0	1	1	
39	Liappas	2003	M	29	10	300	1 year		1	1	0	1	1	
40	Liappas	2003	F	80	10	100	2 months	d	1	1	1	1	1	Previous history alcohol
41	Liappas	2003	M	35		450	3 months		1	1	1	1	1	
42	Liappas	2003	F	33		600	a few months		1	1	1	1	1	1 benzodiazepine
43	Liappas	2003	F	46		200			1	1				1 cocaine
44	Liappas [24]	2003	F	30		300			1	1	1	1	1	
45	Liappas	2003	M	30		300			1	1	1	1	1	
46	Liappas	2003	M	42	10	600	a few months		1	1	1	1	1	
47	Tripodanakis [25]	2003	F	43	10	600		d	1	1	1	1	1	
48	Rappa [26]	2004	M	46	5	400	a few months		1	1	1	1	1	Previous history
49	Boulanger [27]	2004	F	35		240	2 months	1	1	1	1	1	1	Polytoxicomania
50	Boulanger	2004	M	30		400		1	1	1	1	1	1	Polytoxicomania
51	Kao [28]	2004	M	35	10	400IV	1 week		1	1	1	1	1	Polytoxicomania
52	Krueger [29]	2005	F	39	10	600			1	1	1	1	1	
53	Sethi [30]	2005	M	42	10	200			1	1	1	1	1	

Column 9 and above: 1, the patient presents with the characteristics; 0, he does not present with any; d, depression; void, no information.

insomnia. He tried injecting zolpidem intravenously and experienced a stronger stimulating effect and euphoria. He increased the dosage of intravenous zolpidem from 20 mg to 300–400 mg day⁻¹ because he experienced tolerance to lower doses. Thirteen patients had no history of abuse: they began taking zolpidem for insomnia and experienced paradoxical effects which led them to increase the doses and develop dependence. For a patient (no. 42 in Table 2) the feeling of exaltation experienced with zolpidem was the first step in drug abuse; she experienced a craving for other psychotropic substances and started smoking marijuana for the first time in her life in order to increase the effect of zolpidem.

For one patient, the use of zolpidem during daytime reduced the tremor caused by his Parkinsonism. Reports of lessening of symptoms for deficiency or mental disorders were published in the literature [54, 55]. Zolpidem reduces these symptoms, thus prompting patients to abuse it in order to cope with their activities, rather than use it as a sedative drug.

The second population included patients who were treated for insomnia and given the drug for sedation. These patients showed significant differences in their responses, yet developed a similar pattern of abuse. They developed tolerance to hypnotic effects after a few weeks, then gradually increased the doses. Watsky (no. 10 in Table 2) and Rappa (no. 48 in Table 2) described withdrawal symptoms at therapeutic doses. In the first case, zolpidem was substituted by diazepam and the second patient, who had stopped when his prescription expired, returned to his physician for a new prescription and began his drug misuse. Finally, Bruun and Courtet [2, 13] have described psychotic reactions with auditory and visual hallucinations after zolpidem intake during withdrawal.

In the first group, patients were younger (the minimum age was 17 compared with 26 years in the second group, the median was 35 compared with 42 years in the second group; the average could not be used for the comparisons because of the high SD). They used a higher dose (the minimum in the first group was 60 mg compared with 40 mg in the second, the median was 300 mg in the first group compared with 200 mg in the second), they took zolpidem during the daytime (in the second group the patients took their drug in the evening and at night in order to sleep). Dependence was more often reported by practitioners in the first group (20 case reports).

Discussion

The dependence criterion is difficult to interpret as the various case reports used a heterogeneous terminology for pharmacodependence, abuse and addiction.

The WHO pharmacodependence expert committee [56] played an active role in the elaboration of the terminology related to pharmacodependence. The DSM-IV and its definition criteria seem compatible with WHO definitions.

Current definitions of abuse and dependence phenomena certainly reduced the conceptual confusion for researchers working on drug abuse and for treatment experts, but they raised serious difficulties for surveillance after the drug was put on the market. Practitioners often become more vigilant when they are faced with over-therapeutic doses, behaviour involving fraud (falsification of prescriptions), signs of want, which they logically call abuse, dependence, or withdrawal.

The NotS and case reports mentioned in the literature are based on terms used by practitioners. However, regardless of the definition, the patients described present with symptoms related to dependence: tolerance, signs of withdrawal, use of the drug out of its therapeutic field (high doses, daytime consumption), with a goal other than treatment of insomnia, and they are unable to control the use of zolpidem.

We identified two distinct types of populations among the case reports and NotS. The first one seeks an anxiolytic effect, euphoria, exaltation instead of a hypnotic effect, in full contradiction to the active mechanism of zolpidem. This abuse, to feel pleasure, is similar in its pattern to that observed with triazolam and flunitrazepam [13, 20, 46]. Zolpidem should therefore be prescribed with the same caution as benzodiazepine hypnotics, especially in patients with a history of drug abuse. For these patients, the OPPIDUM survey disclosed the search for positive effects and the existence of street deals. However these patients practice polyconsumption, zolpidem is only one drug of abuse among others. For patients without a history of drug abuse who experienced paradoxical effects, zolpidem could be the first experience of abuse.

Today, zolpidem is the only drug exhibiting high selectivity for GABAA receptors containing α_1 subunits currently in medical use in France. Specific subtypes of the GABAA receptor mediate the various pharmacological effects of benzodiazepines which bind nonspecifically to α_1 , α_2 , α_3 or α_5 subunit receptors. The α_1 subunit receptors are highly expressed throughout most brain regions. The sedative effect is mediated by α_1 -containing receptors, whereas the anxiolytic action of benzodiazepines appears to be mediated by receptors that contain the α_2 subunit [57]. Recently, authors have pointed out the role of the α_3 -containing GABAA receptors in mediating the anxiolytic effects of benzodiaz-

epines in both rodent and nonhuman primate behavioural models of anxiety [58, 59]. Whatever the subunit involved, α_2 and/or α_3 , zolpidem anxiolytic effects should not have been detected, although they were frequently reported in paradoxical effects. Zolpidem may bind less specifically to brain receptors at higher levels. High drug levels may have been high enough to saturate GABAA receptors containing α_1 subunits and bind to lower-affinity receptors that contain the α_2 and/or α_3 subunits as well.

In our study, these paradoxical effects, felt after the ingestion of 3 or 4 tablets, reinforced the need for the patient to take the drug: zolpidem was used to achieve euphoria and stimulation and not for sedation. Patients were then able to deal with everyday problems [13, 15, 20]. Since this effect lasted no more than 1 h, they repeated the intake in the daytime.

There are not enough studies on the use of high doses of zolpidem in the literature, except for those on voluntary intoxication. Supratherapeutic doses have not been tested, although they are the ones involved in abuse [23].

Pharmacokinetic factors (rate of onset, half-life) are thought to be critical determinants of a drug's reinforcing effects and abuse potential. In many studies, zolpidem was compared with alprazolam, triazolam or diazepam because their peak plasma concentrations appear rapidly. Based on these pharmacokinetic data, the reinforcing effects and abuse potential of zolpidem would not be expected to differ significantly from those of benzodiazepines [45].

Physiochemical characteristics are also a factor in abuse. When drugs can be administered intravenously, the onset of their effects is much faster and the risk of abuse probably higher. In the case reports, we described the case of a patient injecting zolpidem intravenously who experienced a stronger stimulating effect and euphoria. We also found four cases of i.v. administration in the NotS and two in the OPPIDUM survey.

Molecular biology, via possible mutations of GABA receptors, may provide some answers as to why some patients increase the dose progressively and seek from the drug something other than hypnotic effect. Changes in the expression of genes encoding various α or γ subunits of the GABAA receptor complex can impact receptor affinity, to the point that the benzodiazepine site can lose its activity, thus resulting in differences of sensitivity. This sort of mutation could be a risk factor for zolpidem abuse [60–62].

This assumption that each individual presents with a specific susceptibility has been confirmed by Meram

[63], who reported that in cases of extreme intoxication, there seemed to be no apparent correlation between clinical symptoms and ingested dose.

While the existence of previous dependence or psychiatric disease was often reported as a risk factor for abuse, our survey has outlined abuse, dependence and withdrawal syndrome in patients without evidence of abuse or psychiatric disorder. It is probable that the 'reward' effect leads predisposed individuals, notably those with personality disorders and a history of substance abuse, to drug-seeking behaviour and subsequent ingestion of high doses. The resulting dependence could then be explained by the loss of its specific receptor affinity on high dose levels.

Pharmacodependence management is difficult. Successful detoxification with a benzodiazepine has been reported. Liappas [24] has described three patients treated with fluoxetine; zolpidem consumption resulted in a reduction of the activity of the serotonergic system in the hippocampus, striatum and frontal cortex, which was compensated by decreasing the reuptake of serotonin in the treatment of zolpidem abuse by selective serotonin reuptake inhibitors. The efficacy of this kind of medication used for the abuse of a GABAergic agonist suggests a serotonergic and GABAergic system interaction.

The number of reported cases of zolpidem abuse or dependence is small compared with the widespread use of the drug. This low incidence is due to a continued unawareness of clinicians and patients of the potential for abuse of zolpidem, even if it concerns only a small proportion of patients.

Nevertheless, we need to remember that practitioners do not report as often as they should. In fact, the drug is routinely used as long-term treatment (almost never reported), and a certain level of overdosing is accepted by medical professionals: this explains the low rate of reports.

Conclusion

This study adds to the growing evidence that zolpidem presents a potential for abuse for some users and that these patients do not differ *a priori* from the thousands of insomniacs who use zolpidem. As a consequence, physicians should always keep this effect in mind:

- Zolpidem should be used with caution for patients with a previous history of substance abuse.
- Pharmacodependence must be dealt with as soon as an increase of the initial doses is observed. If the practitioner notices this behaviour, he must immediately

begin to decrease the dose because, as we reported, this increase takes place rapidly in a matter of a few months.

- Zolpidem dependence syndrome must be identified despite the lack of an official description: high doses, the patient's psychological status, manipulative behaviour such as lying in order to obtain an increased supply of medication, should alert physicians. Reported paradoxical effects such as stimulant actions are also a major feature.

The French monograph on zolpidem was comprehensively modified by the health authorities in 2004. In particular, it includes the following sentence: 'Pharmacodependence may develop even at therapeutic doses, and/or for patients who do not show an individualized risk factor'.

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