

Zolpidem dependence case series: possible neurobiological mechanisms and clinical management

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Zolpidem is a short-acting imidazopyridine hypnotic that is an agonist at the γ -aminobutyric acid A type (GABA_A) receptor. It has been suggested that it acts selectively on α_1 subunit-containing GABA_A benzodiazepine (BZ₁) receptors presenting (contrary to classic benzodiazepines) low or no affinity for other subtypes. Therefore, it has been proposed that it lacks the benzodiazepines-like side-effects, having minimal abuse and dependence potential. Nevertheless, there is a considerable number of zolpidem dependence case reports in the literature. We present eight cases of zolpidem abuse and dependence without criminal record, without history of substance abuse (except for one alcohol abuser), with minor psychiatric disorders, who took zolpidem after physicians prescription in order to deal with their insomnia. However, they became zolpidem abusers not craving its sedative, but its anxiolytic and stimulating action, which helped them to cope with everyday activities. It is possible that, in the high doses that our patients used, zolpidem abandons its selectivity for BZ₁ receptors and demonstrates all the actions of classic benzodiazepines. Molecular biology, via possible mutations on GABA receptors, may provide some answers as to why our eight patients (who did not differ much from the thousands of insomniacs who use zolpidem) and other zolpidem abusers, raised the dose progressively, and sought something from the drug other than hypnotic action.

Key words: abuse, case series, clinical management, dependence, neurobiological mechanisms, zolpidem

Introduction

Zolpidem is an imidazopyridine agent that is an agonist at the benzodiazepine receptor component of the γ -aminobutyric acid (GABA)_A-receptor complex. It seems likely that zolpidem, similar to other agonists at this complex, enhances the inhibitory effects of GABA on neuronal excitation (Holm and Goa, 2000).

Differing in structure from the benzodiazepines, it is strongly sedative in its action, with only minor anxiolytic, myorelaxant and anticonvulsant properties. Zolpidem has been marketed in Europe since 1987; in April 1992, it was approved by the US Food and Drug Administration. It is a hypnotic agent, which has been shown to be effective in inducing and maintaining sleep in adults (Salva and Costa, 1995).

Zolpidem is one of the most commonly prescribed hypnotics (Rush *et al.*, 1999) because of its rapid onset, short duration of action, its ability to reduce sleep latency and, above all, the lack of certain side-effects such as alteration of sleep stages (Merlotti *et al.*, 1989), withdrawal effects, impairment of psychomotor function, next day memory impairment and, finally, its minimal

abuse and dependence potential, when administered at clinically relevant doses (Langtry and Benfield, 1990; Salva and Costa, 1995; Holm and Goa, 2000).

It has been suggested that these advantages result largely from the selective binding of zolpidem for the central benzodiazepine α_1 subunit-containing receptors, located within the γ -aminobutyric acid receptor-chloride ionophore supramolecular complex (BZ₁ subtype receptor) (Benavides *et al.*, 1990; Korpi *et al.*, 1997; Lancel, 1999; Mitler, 2000).

On the other hand, following the mid-1980s, many scientists have had differing opinions. Studies on primates revealed that the effects of zolpidem were similar to those of benzodiazepine agonists triazolam and zaleplon, and physical dependence appeared to develop after high doses (Weerts *et al.*, 1998). Studies on humans revealed that, despite its somewhat unique benzodiazepine-receptor binding profile, the acute behavioural effects of zolpidem and its abuse potential are generally similar to those of triazolam; both drugs increased subject ratings on items thought to measure abuse potential (Evans *et al.*, 1990; Rush *et al.*, 1999). Additionally, many researchers have suggested that zolpidem

Table 1 Examples of zolpidem dependence from the published literature

	Cases	Diagnosis	Dose (mg)	Withdrawal Symptoms	Dependence
Cavallaro <i>et al.</i> (1993)	2	A: Personality disorder B: Depression, insomnia	100 80	A: Anxiety, tremor B: Anxiety	Yes Yes
Gericke <i>et al.</i> (1994)	1	Depression	280	Epileptic seizures	Yes
Watsky (1996)	1	Insomnia	10	Hyperventilation, tense and angry feelings, cramping muscles	No
Hofmann <i>et al.</i> (1998)	1	Carcinophobia, insomnia	400	Restlessness, agitation	Yes
Ravishankar and Carnwath (1998)	2	A. Depression B. Not described	200 100	A: Nightmares, tremors, panic attacks B: Anxiety, panic attacks	Yes Yes
Courtet <i>et al.</i> (1999)	7	Depression, personality disorders, substance abuse, schizophrenia, hypochondriasis	60–800	1: Grand mal 2: Anxiety 4: No	Yes
Aragona (2000)	1	Insomnia	600	Epileptic attack	Yes
Golden <i>et al.</i> (2000)	1	Insomnia	40	Anxiety, agitation, poor concentration	Yes
Madrak <i>et al.</i> (2001)	1	Depression	100	No	Yes

impairs not only performance, but also memory in normal therapeutic doses (Berlin *et al.*, 1993; Rush and Griffiths, 1996; Rush *et al.*, 1998; Mintzer and Griffiths, 1999).

Throughout the years of its use, zolpidem has become a controversial issue, especially concerning its abuse and dependence potential. Supplementary to the studies reported above, many cases of zolpidem abuse arose shortly after its introduction. Some authors believe that the cases of dependence reported worldwide are few (only 15 since 1993), and most of them had other substance abuse histories (Soyka *et al.*, 2000). To our knowledge, there are five cases published in Greece (Sakkas *et al.*, 1999; Vartzopoulos *et al.*, 2000) and we now report a further eight cases, who additionally had no history of substance abuse (except for one who had been abusing alcohol for only 1 year), giving a total of 13 in a country of only 10 million inhabitants.

A number of cases of zolpidem dependence from the published literature and their main features are presented in Table 1.

Case reports

We present the cases of eight individuals with zolpidem dependence, and without a criminal record, who started using the drug after medical prescription for the treatment of insomnia.

Case 1

A 28-year-old single, unemployed woman, without personal or family history of psychiatric disorder, developed mild depressive syndrome with anxiety and vigorous initial insomnia after the death of her mother. Her general practitioner prescribed bromazepam and 10 mg zolpidem. After 1 month, the patient was using 10–15 tablets (100–150 mg) per day divided into two doses and, 1 month later, 30 tablets per day. She became a regular user of the substance for a period of 2 years. Under intoxication, she developed symptoms such as hyperactivity, euphoria, childish behaviour and impairment of anterograde memory. She reported that she was using zolpidem for stimulation reasons, trying to cope with her depressive mood and her daily activities. She never used zolpidem as a sedative drug. The patient visited psychiatrists, who prescribed various sedative and antidepressant medications, and tried them for some days but stopped, insisting that they were ineffective. She preferred zolpidem because of its quick effect on her psychopathology. On occasion, she abruptly disrupted abusing

zolpidem trying to get rid of the habit without any experience of withdrawal symptoms. She contacted the Drug Addiction Unit of the Psychiatric Clinic of Athens University Medical School asking for help. According to the DSM-IV criteria, she was diagnosed as having a dysthymic disorder and entered the psychotherapeutic program for detoxification. After three meetings, the patient abandoned the effort.

Case 2

A 35-year-old divorced, unemployed woman contacted the same drug clinic with a zolpidem dependence problem. She had a history of onychophagia, eating disorders and impulsive suicide attempts. She had no history of substance abuse. One year previously, because of family and financial problems, the patient developed anxiety, dysphoric mood and intense initial insomnia. She took zolpidem and, after 1 month, she was taking 10–15 tablets per day divided into two or three doses. She was using zolpidem for stimulation purposes in order to face her daily activities. The substance intoxication brought her energy, euphoria, mild dysarthria, hyperactivity, impulsive behaviour and sometimes anterograde memory impairment. The patient following the treatment program of the Drug Clinic, stopped taking the drug without having any withdrawal symptoms and started therapy with fluoxetine 20 mg twice daily. After 6 months, she is still in abstinence from zolpidem.

Case 3

A 29-year-old single man, working as a hairdresser, was hospitalized in the psychiatric clinic of Athens University for anxiety, mild depression and zolpidem dependence. He had no history of substance abuse. During the past 20 years, he had reported anxiety, fits of violence, sleep disturbance, depressive-like and phobic symptoms, and somatoform disorders. He was characterized as an avoidant personality, who had twice displayed impulsive self-destructive behaviour and he had once been hospitalized in a private psychiatric clinic. Three years previously, he visited a psychiatrist who prescribed fluvoxamine, alprazolam and 10 mg zolpidem. Within a period of 1 year, he gradually increased the zolpidem dose to 100–200, or even 300 mg daily. Under the toxic activity of the substance, he developed impulsive and demanding behaviour with hyperactivity, euphoria, anterograde memory disorders, dysarthria and irritability. He used zolpidem in order to obtain energy and cope with everyday

problems. In the university clinic, the patient abruptly stopped the use of the substance without any withdrawal symptoms and was given 75 mg venflaxine twice daily as medication. After 2 months hospitalization, his condition improved drastically and, subsequently, he has been examined on a regular basis. He later had about 10 relapses, during which he used 10–15 tablets of zolpidem for 1 or 2 days, without having withdrawal symptoms upon giving up the drug. The relapses always correlate with the need of the patient to function properly in his family and social life under difficult and demanding conditions.

Case 4

An 80-year-old single woman, without major somatic problems and without history of psychiatric disorders or substance abuse, developed mild depressive syndrome and intense insomnia. She was treated by a psychiatrist with 150 mg venflaxine and 10 mg zolpidem. Two months later, she discontinued the antidepressant drug by herself and raised the dose of zolpidem up to 100 mg per day. She claimed that zolpidem made her calm, good tempered and able to sleep better. When she reduced the dose to 20 mg, after pressure from her relatives, she complained of discomfort, irritability, and agitation, and increased the drug dose again. For the next two months, she replaced the pills with one glass of traditional Greek alcohol drink (tsipouro, 40% volume) in the morning and one at noon, although she had never consumed alcohol before. After that, she continued to take 100 mg zolpidem daily without being able to control this abuse.

Case 5

A 35-year-old single, unemployed waiter, living with his mother, with a history of 1.5 years of alcohol abuse approximately 10 years ago, started to use zolpidem after the sudden death of his brother because of initial insomnia. Within 3 months, he increased the daily dose up to 25 tablets, because he claimed that the drug improved his mood, vanished unpleasant thoughts, relaxed him and helped him to sleep. Over the next 4 months, the patient was taking 35–45 tablets per day. He was spending his time in bed watching television without any other interest or occupation. He did not appear depressed and hid the abuse from his family. After five years of abuse and without any withdrawal symptoms, he himself asked to be hospitalized. Ten days later, he gave up the use of zolpidem. One month later, he had a relapse and again started to take 35 tablets daily. He justified his behaviour saying that the use helped him to control his anxiety, his aggression, and the frustration of his social and financial problems. He then reduced zolpidem to 5 tablets a day and, at the same time, he was prescribed 20 mg paroxetine, 20 mg clobazam and 20 mg propranolol. Currently, he is in full abstinence.

Case 6

A 33-year-old secretary started taking zolpidem for insomnia 4 years ago. At this time, she was very anxious, and she also started taking zolpidem in the morning. She felt not only calmer, but she also reported that zolpidem induced a feeling of exaltation. The drug stimulated her, gave her self-confidence, and a sense of grandiosity. Therefore, every morning, she started taking 1–2 tablets of zolpidem. Progressively, after some months, tolerance to the drug forced her to increase the dosage of her morning intake. Thus, she ended up taking 600 mg daily for the last 6 months.

However, although she ingested 60 tablets every morning, she did not feel as good as she had done initially. On the other hand, when the dosage of zolpidem increased, the patient was involved in a number of traffic accidents. She had experienced instability, dizziness and a craving for other psychotropic substances, such as marijuana. She started smoking marijuana, for the first time in her life, in order to augment the effect of zolpidem; however, she was not involved in marijuana smoking on a regular basis.

Case 7

A 46-year-old married nurse was a benzodiazepine abuser after medical prescription (600 mg temazepam daily) from the age of 30 years for 8 years because of dysthymic disorder and serious insomnia (iatrogenic user). Subsequently, she became a bromazepam abuser for 7 years and, in the last year, she has been dependent on zolpidem. She uses the substance in order to combat her sleep problems and the symptoms of dysthymia. She ingests up to 20 tablets daily in divided doses. Quite often, under drug intoxication, she complains of anterograde memory impairment and confusion. After the first visit to the detoxication program, she rejected the terms of the treatment and left.

Case 8

A 30-year-old divorced, unemployed woman, with no history of substance abuse, developed dysthymic disorder with severe sleep disturbance, 3 years ago, after the death of her mother. She began treatment for insomnia with zolpidem after medical prescription. During a period of a few months, the patient consumed approximately 300 mg daily and, for the next 2.5 years became a zolpidem abuser. The drug enabled her to confront everyday problems. Although she took the major quantity of the drug in her effort to fall asleep, she received stimulation and exaltation, instead of sedation. The patient unsuccessfully attempted to discontinue use and she was hospitalized because of epileptic seizures as a result of the drug suspension.

Discussion

During the last decade, the nonbenzodiazepine hypnotic zolpidem was considered to be a novel solution for the treatment of insomnia, because it was suggested that it maintained the beneficial characteristics of benzodiazepines as far as the reduction of sleep latency and sleep maintenance are concerned, without having their side-effects. It was suggested that zolpidem lacked anxiolytic, anticonvulsant and myorelaxant action, hardly caused memory impairment and, most importantly, had minimal abuse and dependence potential, which is a major drawback of benzodiazepines. Additionally, it could be terminated abruptly without any withdrawal symptoms (Langtry and Benfield, 1990; Salva and Costa, 1995; Holm and Goa, 2000).

The cases that we have presented are in disagreement with the theory above and, even though they are outnumbered by the number of people who are treated with zolpidem, they have certain traits that lead us to make some interesting conjectures.

Five of the patients had memory disturbances, a side-effect that is described in the literature to occur even in therapeutic doses (Berlin *et al.*, 1993; Rush *et al.*, 1998; Mintzer and Griffiths, 1999) much lower than the doses that our patients used, a fact that

reinforces our hypothesis that, at high doses of the substance, memory impairment is a very frequent phenomenon.

All of our patients used the drug (under their own doctor's prescription) to cope with everyday activities, receiving anxiolytic action from it. To our knowledge, such a number of cases of zolpidem abuse in the same place and time has never previously been presented in the literature, where the substance is needed to overcome daily social, professional and family problems. Thus, anxiolytic action is observed, which is demonstrated in this unique way in our patients.

The majority of the cases were single or divorced individuals, who suffered from insomnia as a result of a minor psychiatric disorder (mild depression, dysthymia or anxiety).

Only one of the patients had history of alcohol abuse, contrary to other authors' assumptions that a high risk of zolpidem dependence occurs mainly among people with a history of alcohol or other substance abuse. The characteristics of our cases lead us to speculate that the risk of zolpidem dependence exists for a significant portion (possibly larger than previously thought) of its users.

All of the patients experienced euphoria and exaltation instead of sedation with the use of high doses of the drug. This is discrepant with the suggested selectivity of zolpidem for the α_1 subunits of the GABA_A receptors, which are claimed to be responsible only for sedative action.

As mentioned above, zolpidem has been suggested to have selective action on GABA_A receptors with α_1 subunits, opposite to benzodiazepines which do not present selectivity, and also to bind to α_2 , α_3 and α_5 subunits. The α_1 subunit-containing receptors are located in most regions of the brain and it is presumed that their activation has hypnotic results. The α_2 subunit-receptors are enriched in the amygdala, the region that strongly contributes to the anxiolytic action of benzodiazepines. The hippocampus, which is involved in many integrative functions of the brain, such as learning and memory, is enriched in α_5 subunit-containing receptors (Korpi *et al.*, 1997). Zolpidem was believed to have low affinity for α_2/α_3 receptors, and an even lower affinity for α_5 subunit-containing receptors, therefore having minor anxiolytic action and minimal activity on memory functions (Benavides *et al.*, 1990; Korpi *et al.*, 1997; Lancel, 1999; Mitler, 2000; Holm and Goa, 2000).

Our patients reported anxiolysis and memory disturbance as well, after using zolpidem. It is possible that the drug in high doses, such as those taken by our patients, could induce these effects by losing its selectivity and by acting also in α_2 , α_3 , and α_5 subunit-containing GABA_A receptors. This suggestion has been made by others (Göder *et al.*, 2001) and, additionally, even before the first cases of zolpidem dependence had been brought to light, researchers claimed non-selectivity for the action of zolpidem at benzodiazepine receptors (Byrnes *et al.*, 1992).

To our knowledge, there are no available studies containing high doses of zolpidem; apart from poisoning studies (Garnier *et al.*, 1994). Supratherapeutic doses should be tested because they are the ones that are usually involved in abuse.

The stimulating and euphoric effect of zolpidem on all of our patients could possibly be interpreted by the activity of the drug on dopaminergic pathways. There has been a considerable number of cases reported of psychotic reactions, agitation, disorientation, LSD-like induced symptoms in patients who have taken even therapeutic doses of zolpidem (Ansseau *et al.*, 1992; Iruela *et al.*,

1993; Pies, 1995; Hoyler *et al.*, 1996), which indicates a possible involvement of the drug with the dopaminergic system. An enforcing argument in this direction is that our fourth patient replaced zolpidem with alcohol in order to receive euphoria and pleasure; it has been suggested that ethanol induces euphoria through the release of activating neurotransmitters such as dopamine (Nutt, 1999).

Molecular biology could provide certain clues for the interpretation of the paradoxical manifestations after the use of zolpidem in a small amount of people (e.g. euphoria, memory impairment, anxiolysis and increased abuse and dependence potential). Many studies have revealed that mutations in the α_1 or γ subunits of the GABA_A receptor can result in alteration in affinity for several agonists, including zolpidem (Buhr *et al.*, 1997a,b). It is possible that such mutations may play a role as predisposing factors for zolpidem abuse. There is still much work to be done to fully comprehend GABA receptor structure and function until such theories are confirmed.

In conclusion, we note that the selectivity of zolpidem at BZ₁ GABA_A receptors may be challenged. Thus, less distinctive characteristics from benzodiazepines are attributed to zolpidem in comparison with previous theories. Whether only the α_1 receptor activation alone could be possibly responsible for euphoria and stimulation is another perspective and a subject for future studies. We report eight cases of ordinary individuals without a criminal record, without a history of substance abuse (except one) and with minor psychiatric disorders, who received zolpidem after medical prescription as a treatment for their insomnia. However, they used the drug for stimulation and anxiolysis rather than sedation, developing after a short period of time a serious dependence. Many questions remain to be answered and well-controlled studies need to be performed regarding the pharmacodynamics of zolpidem (including the structure, function and location of its receptors) and its abuse and dependence potential in relation to the genetic and psychological profile of its users.

Concerning the clinical praxis, we note that, in the literature, a considerably higher possibility of zolpidem dependence occurs in patients with a history of substance abuse. (Mitler, 2000; Soyka *et al.*, 2000; Vartzopoulos *et al.*, 2000; Göder *et al.*, 2001) However, only one of our patients has such a history, without ever being a street addict but, instead, an alcohol abuser for a certain period of time. All the more so, the common features of our cases are insomnia and mood disorders (dysthymia), which could possibly be considered as vulnerability factors for zolpidem abuse and dependence. Finally, our patients, except for one case with epileptic seizures, did not demonstrate withdrawal symptoms, apart from a craving for the drug.

Implications for clinical care

Prevention

Zolpidem dependence prevention initiates from the physician's caution as far as drug prescription is concerned, and his alertness and ability to apprehend the tendency of the patient to increase the initial dose. If the doctor notices such behaviour, he must gradually reduce the dose of the drug and finally stop prescribing it.

Recognition

To our knowledge, there is no official syndrome of zolpidem dependence described in the literature. However, it can be recognized from the high doses of the drug used on a regular basis

and the severe psychological dependence expressed by patients. Memory blanks, anterograde memory disturbance and euphoric-like symptomatology are also predominant characteristics (Courtet *et al.*, 1999).

Management

In most cases, somatic withdrawal symptoms did not occur, and the use of substitute medication was not necessary. If epileptic seizures, tremor, intense insomnia, anxiety or other severe psychosomatic symptoms are present, then the use of benzodiazepines seems to be beneficial (Cavallaro *et al.*, 1993; Watsky, 1996; Aragona, 2000).

The recognition and the treatment of the patient's psychopathological symptoms, which played a significant role (possibly aetiological) in the dependence, is of great importance in a successful management procedure.

If repeated relapses of zolpidem abuse occur, then the assistance of a specialist in a substance abuse clinic is necessary.

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