

'Z-trip'? A Comprehensive Overview and a Case-series of Zolpidem Misuse

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Although believed safer compared to short-acting benzodiazepines (BZD), in the past few years a growing concern has developed relating to the abuse of Z-drugs, and specifically of zolpidem. Here we aim to review the evidence for the misuse of zolpidem and describe several related cases collected in Italy. A comprehensive overview is here carried by using several databases, and by combining the search strategy of free text terms and exploding a range of MESH headings relating to the topics of Zolpidem and Abuse and/or Misuse as follows: ((*Zolpidem*[Title/Abstract]) AND (*Abuse*[Title/Abstract] OR (*Misuse*[Title/Abstract]))), without time and/or language restrictions. Furthermore, a case series of 8 cases of zolpidem misuse and/or abuse, collected in different Italian psychiatric settings (psychiatric public hospital, psychiatric private rehabilitation clinic, and private practice), have been here described. According to our findings, zolpidem should be prescribed with the same caution as BZDs, especially in patients with a history of drug abuse or in the elderly. Behavioural modifications, including bizarre behaviours, psychomotor agitation, sleep-related complex behaviours have been reported. Monitoring of zolpidem use in selected populations is warranted. Psychiatrists and physicians should be aware of the misuse potential of zolpidem and adopt measures restricting its use.

KEY WORDS: Zolpidem; Z drugs; Drug misuse; Drug prescription misuse; Hallucinations.

INTRODUCTION

Background

Z-drugs (i.e., zaleplon, zolpidem, and zopiclone) were introduced in the 1980s for the treatment of insomnia, with the aim of overcoming some of the disadvantages of benzodiazepines (BZDs), such as next day sedation and daytime sleepiness, but also dependence and withdrawal syndrome [1-3]. However, although believed to own a fa-

vorable and safer profile compared to short-acting BZDs [2,4-6], in the past few years a growing concern has developed relating to the abuse of Z-drugs [3,6,7]. This was consistent with an increased prevalence of Z-drugs, which steadily rose, e.g., in the United States from 0.05% in 1999–2000 to 0.47% in 2013–2014, by reflecting absolute and relative increases of +0.42% and +840% [8]. Moreover, even if guidelines recommend a short-term use (no more than 4 weeks), Z-drugs have been demonstrated to be associated with an increased risk of chronic use [2,9-11].

Pharmacology, Pharmacokinetics and Pharmacodynamics

Together with the other Z-drugs, zolpidem is a γ -amino-butyric acid (GABA)_A receptor agonist, which selectively

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binds to the α_1 (hypnotic) subunit [3,6,12], specifically involved in the sleep regulation [3,8]. The standard oral dose is 10 mg taken at bedtime, even though a lower dose of 5 mg is recommended in the elderly. It does exist in a controlled-release formulation in tablets of 6.5 or 12.5 mg [12]. Treatment duration commonly ranges from 1 to 6 months, depending on patient age, comorbidities, and type of pharmacokinetic preparation (immediate- or extended-release) [13]. Rapid metabolism and lack of active metabolites of zolpidem prevent the accumulation of potentially toxic compounds [12]. Nonetheless, a withdrawal syndrome, including symptoms such as worsening of insomnia, headaches or myalgia, confusion, and severe anxiety, restlessness, and irritability, has been reported after stopping Z-drugs, except for zaleplon [14].

The Abuse of Zolpidem, Not a 'So Safe' Drug

Considered the frequency of zolpidem abuse and dependence similar to that of BZDs, zolpidem was transferred to Schedule IV of the 1971 Convention (i.e., for drugs inducing dependence such as BZDs) in 2001 [12,15]. In fact, despite the minimal abuse potential showed by initial reports, zolpidem abuse and dependence have been increasingly recorded in multiple case reports and case series [14,16,17], especially at very high doses, amongst subjects with a history of drug and/or alcohol addiction, and through idiosyncratic intake modalities [2,17-25]. A second subset of individuals abusing or depending on Z-drugs include female patients with psychiatric comorbidities and/or pain syndromes, who were originally started with these molecules for insomnia but who developed tolerance and withdrawal phenomena [17,18,22,24,26-28]. More recently, after the request to reassess the addictive potential of zolpidem during the post marketing period from 1993 to 2002, the Committee for Narcotics and Psychotropic Drugs modified the French monograph on zolpidem, considering that the "*pharmacodependence may develop even at therapeutic doses, and/or for patients who do not show an individualized risk factor*" [29]. A UK-internet-based questionnaire relating to the abuse/misuse of BZDs and Z-drugs reported, amongst the main motivations for their consumption, to induce sleep (66.4%), to cope with stress (37.1%) and/or to get high (31.0%); the same survey reported that the medications were mainly obtained from healthcare professionals (55.2%), friends/family (39.7%)

or multiple sources (31%) [30]. Relating to drug-related fatalities, despite Z-drugs show a low fatal toxicity index, in a UK review of fatalities recorded from 1983 to 1999, zolpidem and zopiclone caused around 2 deaths per million prescriptions in England and Scotland (compared with around 7 for BZDs and around 150 for barbiturates) [31]. Moreover, Z-drugs, together with BZDs, were found as the most commonly detected substances in all suicidal cases from the Cause of Death Registers in Norway and Sweden [32]. Similarly, in Australia, zolpidem was detected in 90 post-mortem blood above 1,000 ng/ml (therapeutic C_{max} 100–200 ng/ml), mainly in combination with alcohol, antidepressants, BZDs and opioids [13].

Pharmacovigilance Studies

Pharmacovigilance data have shown the potential for abuse and addiction associated with zolpidem. After assessing the potential of abuse, dependence, and withdrawal of Z-drugs, through the analysis of datasets of adverse drug reactions provided by the European Medicines Agency, it has been demonstrated that zolpidem is more frequently involved in both misuse/abuse and withdrawal issues [33]. Interestingly, it was identified together with a range of both prescription and recreational psychotropics [33]. According to the 'Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse' (OPPIDUM) national survey, among all drug addict patients included the number of patients using zolpidem increased from < 1% (10 patients/1,462 in the 1998 survey) to 4% since 2001 (112 patients/2,858). Using the national sample cohort database of the Korea National Health Insurance Corporation between 2002 and 2013, the usage of zolpidem in the outpatient setting appeared to be dramatically increased by approximately 18 times after its market authorization (1,181 in 2002 vs. 21,399 in 2013), being treatment duration in 8.3% of episodes exceeded 30 days out of 75,087 zolpidem users and zolpidem prescription exceeding 30 days highest in patients aged 65 years and older and tertiary centres [27]. Similarly, according to the data from a tertiary deaddiction center in southern India, zolpidem was the most commonly reported drug together with alprazolam and nitrazepam in patients presenting with a BZDs/Z-drug dependence [34]. More recently, the Zolpidem and the Reinforcement of the Regulation of prescription Orders

(ZORRO) study, supported by the French National Agency for Medicines and Health Products Safety, which evaluates the overall impact of the new regulatory framework since 2017, requiring zolpidem to be prescribed on special secure prescription pads, analysing the number of consumers involved, the type of consumption (i.e., chronic use vs. occasional use, problematic consumption vs. nonproblematic use) and the consumption of other sedative molecules [35].

Effects Related With the Abuse/Dependence of Zolpidem

High-dose (600–2,000 mg daily) zolpidem use was associated with psychostimulant effects, such as feelings of well-being, euphoria (“high”), energy, alertness, sociability, talkativeness [23,29,36]. Moreover, other unexpected effects, such as sleepwalking, sleep-driving, sleep-related eating disorders or engaging in other activities while not fully awake, were reported [36–39]. These findings induced the Food and Drug Administration (FDA), in a recent Drug Safety Communication [37], to require a stronger warning related to those complex sleep behaviours occurring after Z-drugs intake, by adding a contraindication in prescribing these drugs in patients who have already experienced an episode of complex sleep behaviours due to resulting serious injuries and fatalities. Furthermore, delusions and psychotic experiences were also reported following high-dose use of zolpidem [23,40]. Finally, intense craving, inability to stop use and withdrawal were associated with long-term high dose zolpidem consumption [29,36].

Aim of the Study

The present research study aims at critically describing a case series of zolpidem abuse and misuse, collected in different (clinical and forensic) settings in Italy by a working team of professionals working in the field of addiction psychiatry and medicine.

MATERIALS AND METHODS

A preliminary comprehensive literature overview has been here carried out in order to better deepen the pharmacological properties and addictive potential of zolpidem amongst both vulnerable (e.g., polydrug abusers) and not vulnerable people. Studies were identified searching the electronic databases MEDLINE/PubMed

and Scopus. A combined search strategy of free text terms and exploded MESH headings for the topics of Zolpidem and Abuse and/or Misuse as following: ((*Zolpidem*[Title/Abstract]) AND ((*Abuse*[Title/Abstract]) OR (*Misuse*[Title/Abstract])), without time and/or language restrictions, through November 15, 2019. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field and or manual search. The following exclusion criteria have been applied: a) not human studies; b) studies on zolpidem without data on potential abuse, misuse and/or dependence. Identified studies were independently reviewed for eligibility by 2 authors (SC and LO) in a two-step-based process; a first screening was performed based on title and abstract while full texts were retrieved for the second screening. At both stages, disagreements by reviewers were resolved by consensus. Data were extracted by two authors (SC and LO) and supervised by a third author (DDB) using an ad-hoc developed data extraction spreadsheet. With the initial set of keywords, after excluding duplicate papers, by integrating all databases, some 214 studies were identified. Of these, 9 were excluded because without full-text, 51 papers because not human studies, 15 because not written in English, whilst 94 because not consistent/pertinent with the aims of the review. Of these remaining some 45 relevant studies. Table 1 summarizes the main findings of studies here retrieved.

Subsequently, a full description of 7 clinical cases of zolpidem abuse and/or misuse has been here provided, following the CARE (CAse REport) Statement, Checklist and Guidelines [41]. All patients here described gave written consent for the publication of the presented findings. Table 2 summarizes all clinically relevant data of clinical cases here described.

Case History

Case 1. Nocturnal dissociative effects and diurnal hyperactivity in a dysthymic young adult man

A 25-year-old unmarried male, university student presented to a private practice psychiatric setting following the suggestion by his general practitioner (GP) physician after he was discharged by a psychiatric ward due to a suicidal behaviour occurring during a severe depressive episode. He described a previous cannabis use disorder, at age 16. He did not report any other substances of

Table 1. Overview of literature cases of zolpidem abuse/misuse: summary of the main findings

Study	Type of study (country)	Sample features (gender, age, psychiatric history)	Zolpidem (dosage, ROA)	Drugs/substances in combination (if any)	Clinical effects reported	Treatment
Bajaji <i>et al.</i> (2019) [65]	Case report (India)	n = 1, M, 45 yr, AUD	2,400 mg/d, OS	Alcohol	Anxiolytic and anti-craving alcohol withdrawal	Propranolol (20–40 mg/d)
Kim <i>et al.</i> (2019) [38]	Case report (Korea)	n = 1, F, 69 yr, primary insomnia	50–60 mg/d, OS	A liquid analgesic containing acetaminophen 200 mg, ethenzamide 100 mg, caffeine 30 mg and chlorpheniramine 2 mg	Aid to manage headache and insomnia	QUE (100 mg/d), melatonin (2 mg/d), acetaminophen (650 mg/d)
Lugoboni <i>et al.</i> (2019) [22]	Retrospective cohort study (Italy)	n = 107 (M = 51, F = 56); 44 ± 11 yr AUD (n = 15); OUD (n = 3), CoUD (n = 7); CUD (n = 3)	NA for each patient; available for 10 subjects (M = 8, F = 2); 10–1,800 mg/d, OS	BZDs, alcohol, methadone or other drugs of abuse (undefined number)	NA	NA
Sabe <i>et al.</i> (2019) [23]	Case report (Switzerland)	n = 1, F, 47 yr, insomnia secondary to ankylosing spondylitis	120 mg/d, OS	Oxazepam	Irritability, aggressive behaviours, hypersexuality, disinhibition, megalomania and persecution delusions	HALO (5 mg im), LOR (2 mg im), OLA (10 mg/d), OXA (15 mg/d)
Chiario <i>et al.</i> (2018) [52]	Case report (Switzerland)	n = 1, F, 70 yr, primary insomnia and PTSD	1,200 mg/d, OS	None	Anxiolytic, relaxing effect, aid to coping stress related PTSD	SER (75 mg/d), CLO (2 mg/d), PRE (150 mg/d)
Ohshima <i>et al.</i> (2018) [39]	Case report (Japan)	n = 1, M, 29 yr, primary insomnia	1,200 mg/d, OS	None	Anterograde amnesia, increased energy, sociable	Chlorpromazine (125 mg/d), CLO (6 mg/d)
Chattopadhyay <i>et al.</i> (2017) [36]	Case report (India)	n = 1, M, 33 yr, none	1,700 mg/d, OS	Nicotine, quetiapine	Euphoria, 'high', sociable and talkative, nocturnal overeating	Unspecified
Majumder <i>et al.</i> (2017) [98]	Case report (India)	n = 1, M, 36 yr, MDD	160–240 mg/d, OS	None	Euphoria	NA
Ahmadi (2016) [63]	Case report (Iran)	n = 1, M, 20 yr, substance-induced mood disorder	100–200 mg/d, OS	Cannabis, alcohol	Aggressive behaviour, obsession, anxiety, depression after zolpidem withdrawal	Unspecified
Haji Seyed Javadi <i>et al.</i> (2014) [91]	Case report (Iran)	n = 1, F, 30 yr, dysthymic disorder and chronic secondary insomnia	100–150 mg/d, OS	None	Hyperactivity, increased energy, mood enhancement, seizure episode after zolpidem withdrawal	VEN (75 mg TID), CLO (1 mg/d), QUE (25 mg/d)
Mohapatra <i>et al.</i> (2014) [68]	Case report (India)	n = 1, M, 33 yr, none	300 mg/d, OS	None	Enjoying the 'high'	NA
Pourshams and Malakouti (2014) [50]	Case report (Iran)	n = 1, F, 62 yr, MDD and OUD	570 mg/d, OS	Opium combined with zolpidem (relaxing and euphoric effects)	Sleep, depressive and anxiety improvement	GABA (900 mg/d), SER (200 mg/d), TRA (100 mg/d)
Eslami-Shahrbabaki <i>et al.</i> (2014) [40]	Case report (Iran)	n = 1, M, 27 yr, schizophrenia and primary insomnia	500 mg/d, OS	None	Social withdrawal, suspicious, aggressive behaviour, psychotic symptoms, hallucinations	RIS (2 mg TID), BIP (2 mg BID), TRA (100 mg/d)

Table 1. Continued 1

Study	Type of study (country)	Sample features (gender, age, psychiatric history)	Zolpidem (dosage, ROA)	Drugs/substances in combination (if any)	Clinical effects reported	Treatment
Heydari and Isfeevajani (2013) [67]	Case report (Iran)	n = 1, M, 32 yr, OUD	1,110–1,400 mg/d, OS	Diphenoxylate	Euphoria, to manage tics	Unspecified
Fernandes <i>et al.</i> (2013) [49]	Case report (India)	n = 1, F, 72 yr, primary insomnia	300 mg/d, OS	None	Diurnal sedation, mood swings, euphoria, dysphoria, increased energy	GABA (1,200 mg/d)
Liappas <i>et al.</i> (2013) [62]	Case series (Greece)	n = 3 A: M, 30 yr, CoUD B: F, 35 yr, onychophagia, ED and impulsive SA C: M, 42 yr, primary insomnia	A: 200–300 mg/d, OS B: 100–150 mg/d, OS C: 30–300 mg/day, OS	A: cocaine (3–4 g/d) B: none C: none	A: zolpidem as aid to manage cocaine craving, pathological gambler, hyperactive, excitement, childish behaviour, logorrhea, euphoria B: stimulant effect euphoria, mild dysarthria, hyperactivity, impulsive behaviour, anterograde memory impairment C: amnesia, memory blanks, confusion, energy to deal with his everyday problems, hyperactivity, euphoria	A: FLU (20 mg BID) B: FLU (20 mg BID) C: FLU (20 mg TID)
Chen <i>et al.</i> (2012) [92]	Case report (Taiwan)	n = 1, F, 53 yr, MDD	100–160 mg/d, OS	None	Energy, daytime vitality, anxiety control	PAR (60 mg/d), FLUN (1 mg/d), QUE (200 mg/d)
Hsu and Chiu (2013) [97]	Case report (Taiwan)	n = 1, M, 29 yr, MDD and history of hypnotic abuse	40 mg/d, IV	Not current	Dangerous driving, bizarre and impulsive behaviour	MIR (30 mg/d), oral zolpidem (20 mg/d)
Keuroghlian <i>et al.</i> (2012) [72]	Case report (USA)	n = 1, M, 34 yr, primary insomnia	100–200 mg/d, OS	Alcohol	Grand mal seizure after zolpidem withdrawal	Chlordiazepoxide (unspecified dosage)
Kummer <i>et al.</i> (2012) [73]	Case report (Poland)	n = 2 A: F, 21 yr, primary insomnia B: F, 28 yr, primary insomnia	10–15 mg/d, OS	Occasionally alcohol and cannabis	Pleasant visual (pseudo) hallucinations, diplopia, mild agitation, logorrhea	Unspecified
Chien <i>et al.</i> (2011) [96]	Case report (Taiwan)	n = 1, M, 25 yr, MDD	300–500 mg/d, OS	None	Helped against depression, euphoria	NA
Kinnan <i>et al.</i> (2011) [66]	Case report (USA)	n = 1, M, 27 yr, Schizoaffective disorder	10 mg/d, OS	None	Baseline hypomania turned into a manic state	NA
Oulis <i>et al.</i> (2011) [88]	Case report (Greece)	n = 1, F, 49 yr, dysthymic disorder	1,500 mg/d, OS	None	"Find relief from psychological difficulties", "Gain strength in facing everyday professional and familial burdens"	PRE (450–900 mg/d)
Wang <i>et al.</i> (2011) [90]	Case report (Taiwan)	n = 2 A: F, 43 yr, dysthymic disorder B: F, 35 yr, MDD	A: 200–400 mg/d, OS B: 400–500 mg/d, OS	None	Euphoria, relaxing effect	A: LOR (2 mg/d), ALP (0.5 mg/d) B: CLO (unspecified dosage)

Table 1. Continued 2

Study	Type of study (country)	Sample features (gender, age, psychiatric history)	Zolpidem (dosage, ROA)	Drugs/substances in combination (if any)	Clinical effects reported	Treatment
Spyridi <i>et al.</i> (2009) [48]	Case report (NA)	n = 1, M, 78 yr, BZD dependence	300 mg/d, OS	BZDs	Anxiolytic effect, energy	VA (unspecified dosage), MIR (unspecified dosage), QUE (unspecified dosage)
	Case report (Greece)	n = 1, M, 78 yr, primary insomnia	300 mg/d, OS	None	Euphoria, dysphoria, increased energy, insomnia	VA (1,000 mg/d), MIR (45 mg/d), QUE (100 mg/d)
Jana <i>et al.</i> (2008) [61]	Case report (India)	n = 1, M, 33 yr, OUD	100–150 mg/d, OS	None	Felt energetic, active and happy	NA
Licata <i>et al.</i> (2008) [57]	Double-blind, placebo-controlled, crossover, pilot study (USA)	n = 7, F, 27 ± 5 yr, healthy	10 mg/d, OS	None	Subjects effects characteristic of hypnotic drugs, reduced rating of drug 'liking', 'willing to take again', 'willing to pay for' vs. placebo	NA
Svitek <i>et al.</i> (2008) [56]	Case report (Germany)	n = 1, M, 27 yr, none	800 mg/d, OS	None	Relaxed, pleasantly, stimulated and able to manage his daily activities	NA
Askwel (2007) [100]	Case report (USA)	n = 1, F, 30 yr, pregnant, primary insomnia	1,000 mg/d, OS	None	Not reported	Not reported
Benyamina <i>et al.</i> (2007) [60]	Case report (France)	n = 1, F, NA, SUD	30–50 mg/4–5 times a week, IV	Alcohol, cannabis	Alcoholic inebriety, more powerful sensations, euphoria	PAR (40 mg/d)
Djezzar <i>et al.</i> (2006) [59]	Case report (France)	n = 1, M, 38 yr, OUD	1,000 mg/d, OS	Dextromoramide	Euphoria, sensation of increased intellectual efficiency without dysphoric or sedative effect	NA
Quaglio <i>et al.</i> (2005) [55]	Case report (Italy)	n = 1, F, 39 yr, OCD, MDD	400–800 mg/d, OS	None	Anxiolytic and euphoric effect	NA
Hill <i>et al.</i> (2004) [47]	Case report (USA)	n = 1, F, 67 yr, none	10 mg/d	None	Manic state with insomnia and paranoid delusions	NA
Rappa <i>et al.</i> (2004) [89]	Case report (USA)	n = 1, M, 46 yr, stress-related insomnia	400 mg/d, OS	Tramadol (100 mg QID)	"Cut some after-work anxieties"	DIA (10 mg/d), atenolol (25 mg/d), melazodone (600 mg/d)

Table 1. Continued 3

Study	Type of study (country)	Sample features (gender, age, psychiatric history)	Zolpidem (dosage, ROA)	Drugs/substances in combination (if any)	Clinical effects reported	Treatment
Liappas <i>et al.</i> (2003) [53]	Case series (Greece)	n = 8 A: F, 28 yr, dysthymic disorder B: F, 35 yr, onychophagia, ED and impulsive SA C: M, 29 yr, avoidant personality disorder, anxious-depressive disorder D: F, 80 yr, anxious-depressive disorder and insomnia E: F, 35 yr, primary insomnia and AUD F: F, 33 yr, primary insomnia G: F, 46 yr, dysthymic disorder, severe insomnia and BZD abuse H: F, 30 yr, dysthymic disorder	A: 100–150 mg/d, OS B: 100–150 mg/d, OS C: 100–300 mg/d, OS D: 100 mg/d, OS E: 450 mg/d, OS F: 600 mg/d, OS G: 200 mg/d, OS H: 300 mg/d, OS	None but D (alcohol consumption), F (cannabis)	A: hyperactivity, euphoria, childish behaviour, anterograde memory impairment B: hyperactivity, euphoria, impulsive behaviour, anterograde memory impairment C: hyperactivity, euphoria, impulsive behaviour, anterograde memory impairment, irritability, dysarthria D: anxiolytic effect, compulsive zolpidem craving E: mood enhancement, relaxing effect, sleep aid, anxiolytic effect F: euphoria, self-confidence, sense of grandiosity, traffic accidents G: anterograde memory impairment, confusion, mood elevation H: stimulation, exaltation, epileptic seizures after abrupt discontinuation	A: not specified, drop-out B: FLU (20 mg BID) C: VEN (75 mg BID)
Liappas <i>et al.</i> (2002) [58]	Case report (Greece)	n = 1, M, 30 yr, CoUD and secondary insomnia	300 mg/d, OS	Cocaine	Euphoria, hyperactivity, childish behaviour, logorrhea, anti-craving cocaine	FLU (20 mg BID)
Madrak and Rosenberg (2001) [46]	Case report	n = 1, F, 67 yr, MDD	100 mg/d, OS	Alcohol, barbiturate and BZD dependence	Unspecified	Chlordiazepoxide (300 mg/d)
Aragona (2000) [102]	Case report (Italy)	n = 1, F, 43 yr, primary insomnia	450–600 mg/d, OS	None	Epileptic seizures after abrupt discontinuation	Not reported
Golden and Vagnoni (2000) [70]	Case report (USA)	n = 1, M, 39 yr, primary insomnia	40 mg/d, OS	Occasional alcohol consumption	Hyperactivity, increased alertness	Chlordiazepoxide (unspecified dosage)

Table 1. Continued 4

Study	Type of study (country)	Sample features (gender, age, psychiatric history)	Zolpidem (dosage, ROA)	Drugs/substances in combination (if any)	Clinical effects reported	Treatment
Vartzopoulos <i>et al.</i> (2000) [71]	Case series (Greece)	n = 4 A: F, 42 yr, borderline personality disorder B: F, 30 yr, histrionic personality disorder C: F, 26 yr, borderline personality disorder, AUD D: M, 33 yr, dysthymia, borderline personality disorder	A: 300 mg/d, OS B: 400–500 mg/d, OS C: 160–200 mg/d, OS D: 120 mg/d, OS	A: BZD B: none C: alcohol D: cannabis	A: anxiolytic effect B: anxiolytic effect C: anti-craving alcohol withdrawal, anxiolytic effect D: relaxing and anxiolytic effect	A: unspecified B: unspecified C: unspecified D: unspecified
Ravishankar and Carnwath (1998) [103]	Case report (UK)	n = 2 A: NA, NA, MDD B: NA, NA, none	A: 200 mg/d, OS B: 100 mg/d, OS	NA	NA	NA
Gericke and Ludolph (1994) [95]	Case report (Germany)	n = 1, M, 33 yr, MDD	280 mg/d, OS	None	Generalized tonic-clonic seizure, anterograde memory impairment	NA
Cavallaro <i>et al.</i> (1993) [45]	Case report (Italy)	n = 2 A: F, 60 yr, personality disorder	A: 100 mg/d, OS	NA	A: dysarthria, confusion, disinhibition, anterograde amnesia; withdrawal syndrome described B: withdrawal syndrome described	A: IV chloridesmethyl diazepam (5 mg/d), flunitrazepam (20 mg/d), CLO (2 mg/d) B: DIA (4 mg/d)
Sullivan <i>et al.</i> (1993) [69]	Case report (UK)	B: F, 31 yr, MDD n = 1, M, 17 yr, NA	B: 80 mg/d, OS 450 mg/d, OS	Alcohol	Euphoria	Unspecified

Values are presented as mean \pm standard deviation.

ALP, alprazolam; AUD, Alcohol Use Disorder; BZDs, benzodiazepines; BID, two times daily; BIP, biperidene; CLO, clonazepam; CoUD, cocaine use disorder; CUD, cannabis use disorder; DIA, diazepam; ED, eating disorders; F, female; FLU, fluoxetine; FLUN, flunitrazepam; HALO, haloperidol; GABA, gabapentin; IV, intravenous; LOR, lorazepam; M, male; MDD, Major Depressive Disorder; MIR, mirtazapine; NA, not available; OCD, obsessive-compulsive disorder; OLA, olanzapine; OS, oral; OUD, opioid use disorder; OXA, oxazepam; PAR, paroxetine; PRE, pregabalin; QUE, quetiapine; RIS, risperidone; ROA, route of administration; SA, suicide attempt; SER, sertraline; SUD, substance use disorder; TID, three times daily; TRA, trazodone; VA, valproic acid; VEN, venlafaxine; PTSD, posttraumatic stress disorder; QID, quater in die.

Table 2. Description of clinical cases

Patient	Socio-demographic features	Psychiatric history	Zolpidem (dosage, ROA)	Drugs/substances in combination (if any)	Clinical effects reported	Treatment
Case 1	25 yr, M, unmarried, university student	Dysthymic disorder, previous SA (n = 1), previous CUID	200 mg/d, OS	None	Sedative (taken at bedtime) whilst euphoria and increased energy (if taken during the day) Strange and bizarre nocturnal behaviour	SER 150 mg/d BUP 300 mg/d QUE 25 mg/d
Case 2	28 yr, F, married, housewife	MDD, previous physical and psychological abuse, previous SA (n = 3)	80 mg/d, OS	None	Dissociative effects, imperative hallucinations, amnesia	SER 150 mg/d TRA 100 mg/d MEL 3 mg/d
Case 3	35 yr, M, unmarried, general manager	ADHD, Narcissistic personality disorder, CoUD	300 mg/d, OS 30 mg/d, IV	Cocaine	Euphoria, 'high', hyperactivity	GABA 900 mg/d BUP 150 mg/d MEL 5 mg/d
Case 4	56 yr, F, married, unemployed	Previous BZD dependence, GAD, previous physical and psychological abuse, previous SA (n = 1)	300 mg/d, OS	None	Anxiolysis, anxiety, mood and sleep improvement	TRA 100 mg/d PRE 300 mg/d Baclofen 10 mg/d MEL 2 mg/d
Case 5	52 yr, F, unmarried, general manager	Primary insomnia; Narcissistic personality disorder and a cyclothymic temperament	450 mg/d, OS	None	Hyperactivity, euphoria, work efficiency, increased levels of work competence	PRE 300 mg/d BUP 150 mg/d TRA 150 mg/d
Case 6	23 yr, F, unmarried, unemployed	Primary insomnia	30 mg/d, OS	Alcohol	Sexual disinhibition, hyperactivity, euphoria	TRA 50 mg/d
Case 7	36 yr, M, inmate, unemployed	Antisocial personality disorder, previous AUD, impulse dyscontrol	240 mg/d, OS	None	Mood elevation, euphoria, loquacity, sexual disinhibition	FLU 20 mg/d GABA 900 mg/d
Case 8	47 yr, F, unmarried, unemployed	MDD, personality disorder, zolpidem-induced epileptic seizures	120 – 140 mg/d, OS	None	Anxiolysis, mood enhancement	OLA 2.5 mg/d

AUD, alcohol use disorder; BZDs, benzodiazepines; CoUD, cocaine use disorder; CUID, cannabis use disorder; F, female; FLU, fluoxetine; GABA, gabapentin; GAD, Generalized Anxiety Disorder; IV, intravenous; M, male; MDD, Major Depressive Disorder; OLA, olanzapine; OS, oral; PRE, pregabalin; QUE, quetiapine; ROA, route of administration; SA, suicide attempt; SER, sertraline; TRA, trazodone; ADHD, attention deficit hyperactivity disorder; BUP, bupropion; MEL, melatonin.

abuse. He started Engineering at the University but, after the first year of study, he began to manifest a progressive social withdrawal, accompanied by low mood, sleep disturbances with apathy, anhedonia, poor life expectations, feelings of hopelessness and inability, poor concentration and attention, difficulty in studying and suicidal ideation. During the Christmas period, when he came back to home, he decided to attempt suicide by means of defenestration, but he was promptly stopped by his father. Then, he was admitted to the emergency room (ER) of the local hospital and was visited by a psychiatrist who decided for the admittance to the psychiatric ward. At the time of admission, complete blood count, biochemistry test, thyroid test, as well as electrocardiography (ECG) and urine test were in normal range. Urine screening test was negative for any investigated substances. After 14 days, he was discharged with a Diagnosis of “*Suicide attempt in severe depressive episode*” and prescribed the following therapy: sertraline 100 mg/day and zolpidem 10 mg/day at bedtime. Subsequently, he was followed up by a public service of Mental Health for approximately two years and started psychodynamic psychological sessions one weekly. Following the retirement of his psychiatrist, he decided to turn to a private practice psychiatrist, suggested by his GP. After a psychiatric evaluation in a private practice setting, he was diagnosed with “*Persistent Depressive Disorder (Dysthymia), with intermittent major depressive episodes, with current moderate episode*” (300.4), according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [42]. He reported a current low mood with anhedonia, apathy, low self-esteem, severe insomnia (initial and lacunar), poor concentration, hopelessness feelings which greatly determined a clinically significant distress and impairment in social, family, occupational and study functioning. After the first psychiatric evaluation, it was suggested to optimize the therapy by an adequate sertraline dosage up to 200 mg/day and by adding bupropion 150 mg/day in the morning. It was proposed to change zolpidem with melatonin up to 30 drops/day at bedtime, as the patient referred a persistent severe insomnia accompanied by a great diurnal asthenia and poor concentration and attention. During the subsequent psychiatric visits, he reported a mood improvement and an increase of daily energy, motivation and a greater proactivity associated with a major loquacity and mood elevation. However, after 6 months, he asked for a further

help in sleep regulation by asking how many zolpidem pills he could theoretically take to achieve a better sleep and solve his chronic insomnia, as he confessed to have self-titrated zolpidem dosage (previously prescribed) for his resistant insomnia up to 200 mg/day in divided dosages (oral intake). He clearly reported that zolpidem taken at bedtime functioned as sleep aid, whilst zolpidem taken during the day gave it an increased energy and mood elevation. However, despite this initial enhancing effect, he was out of control as he needed ever increasing zolpidem dosages in order to obtain the same sleep regularity. He did not report any further adverse events following zolpidem intake. However, the day before the psychiatric control, his GP reported to his psychiatrist that the patient manifested a strange and bizarre nocturnal behaviour a few days before, as reported by his parents who found their son sleepwalking in the middle of a trafficked and risky road near to their house. They reported that when they tried to call their son, he was unresponsive, mute, staring in a state like a dissociative episode. The day after the episode, the patient did not remember that episode. After clearly talking and explaining the addictive potential of zolpidem to the patient, the psychiatrist suggested to gradually discontinue zolpidem and modify the psychopharmacological treatment through a planned psychiatric hospitalization. The treatment consisting in progressively prescribing quetiapine 25–50 mg/day bedtime and completely and temporarily switching zolpidem to diazepam (ratio 2:1, i.e., 200 mg of zolpidem converted to 100 mg of diazepam) over a 60-days hospitalization in a private practice clinic for detoxification and rehabilitation. During these two months, diazepam was progressively de-titrated until a complete discontinuation. The patient is still taking sertraline 150 mg/day, bupropion 300 mg/day and quetiapine 25 mg/day at bedtime. After a follow-up of 1 year, the patient referred a complete sleep restoration and clinical remission of depressive episode, denied any suicidal ideation and/or behaviour and continued psychodynamic psychotherapy one session weekly.

Case 2. Dissociative and amnesic effects in a postpartum depression woman

A 28-year-old married woman, housewife, presented into a private practice psychiatric setting following the suggestion by her psychotherapist due to the emergence of a severe depressive episode with psychotic features oc-

curing 3 months after her delivery. The patient had no a previous psychiatric history except a history of reiterate physical and psychological abuse occurring during her infantile period and a previous suicide attempt at 13 age. The patient is of Bolivian origin and she transferred to Italy at 18 age, after having met her future Italian husband in Bolivia. Family psychiatric history positive for mood disorder not elsewhere specified (mother and sister). She reported a first healthy pregnancy and vaginal delivery without perinatal complications at 25 years old. During the post-partum period, she did not describe any mood swings, sleep disturbances and/or other signs of post-partum psychopathological issues. Whilst during the second pregnancy, occurring at age 27, she firstly described the occurrence of the first signs of an antenatal depression, characterized by a low mood, easy irritability, inability to cope with daily duties and in assisting her first son, inversion in wake-sleep rhythms (since forth month of pregnancy) and a pre-eclampsia at the seventh month of pregnancy. She did not ask for any psychological support and/or psychiatric consultation, preferring not talking with anyone (neither family members) about her condition. After her (caesarean) delivery, she started to progressively manifest low mood, irritability, verbal aggressive behaviours towards her son and daughter, sleep disturbances (severe insomnia), accompanied by suicidal and homicidal ideation (towards her son and daughter) and disorganized and bizarre behaviour with auditory (imperative) hallucinations and grief feelings. After the emergence of these symptoms, her husband decided to ask for a psychological support for her wife (started in May 2018). After three psychological sessions, the psychotherapist suggested a psychiatric consultation, mainly due to the emergence of suicidal and homicidal ideation. After a first psychiatric evaluation, she was diagnosed with “*Major Depressive Disorder (MDD), current single severe episode, with psychotic features*” (296.24), according to the DSM-5 [42]. She was treated with sertraline (50–100 mg/day) and olanzapine 2.5 mg/day bedtime, until the next psychiatric visit (after 21 days). During the second psychiatric visit, she described a mood improvement without suicidal and/or homicidal ideation, even though she reported the persistence of a severe insomnia and referred to have discontinued olanzapine without medical consultation (due to the occurrence of side effects, i.e. excessive diurnal somnolence, persistent headache and dif-

ficulty in waking up at night if the child was crying). Meanwhile, without asking for her physician or psychiatrist, she took zolpidem which was prescribed to her mother-in-law with great benefit in sleep regulation. She asked for a zolpidem prescription and it was adjusted sertraline dosage at 150 mg/day with a significant clinical remission in mood and sleep, at third visit (after 45 days: HAM_D < 7). After 3 months, she went to a psychiatric follow-up together with her husband and, after the pressure of her relatives, she reported a zolpidem abuse occurring during the last month (up to 80 mg/day). Her husband reported that she was found sleepwalking aimlessly with a knife in her hand in the kitchen during a night. She was completely absent, mute, unresponsive to verbal and nociceptive stimuli in a state like a dissociative state. She referred a total amnesia of the episode. Her husband reported she presented a similar episode some weeks after her second delivery, when she spontaneously took zolpidem 10 mg/day which was prescribed to her mother-in-law. The treatment consisting in progressively prescribing trazodone 100 mg/day bedtime and switching zolpidem to diazepam (ratio 2:1, i.e., 80 mg of zolpidem converted to 40 mg of diazepam). During the subsequent two months, diazepam was progressively de-titrated until complete discontinuation. The patient is still taking sertraline 150 mg/day, melatonin 30 drops bedtime and trazodone 100 mg/day. After a follow-up of 1 year, the patient referred a complete clinical remission of depressive episode and sleep disturbances, denied any suicidal and/or homicidal ideation and/or behaviour and continued psychodynamic psychotherapy one session weekly.

Case 3. Psychostimulant and euphoric effects in a poly-drug abuser man

A 35-year-old unmarried male, general manager, was admitted to a private psychiatric rehabilitation clinic for dual diagnoses and substance and/or alcohol use disorders, for a detoxification programme due to its current cocaine use disorder associated with a recent zolpidem dependence. He reported a previous and long history of polydrug abuse (i.e., cannabis, cocaine, and psychostimulants) and a previous abuse and misuse of prescription-only drugs (i.e., quetiapine, olanzapine). He was referred to a private psychiatric clinic because of restlessness, irritability, myalgia, verbal aggression, severe insomnia and muscle cramps due to the withdrawal of daily use of zol-

pidem 300 mg/day, as he was unable to find someone who repetitively prescribes the drug to him, and for managing his cocaine dependence as well. He reported cocaine consumption since age 21, on a weekend basis and for recreational motivation. Then, he described a pathological and greater cocaine intake at age 31, for supporting the “*weight of responsibilities and the increased workload*”. However, he rapidly developed an increscent insomnia and he was prescribed zolpidem 10 mg/day at bedtime by his GP. He reported to have experienced euphoric mood after the first oral zolpidem intake and subsequently he self-administered higher dosages of zolpidem for treating his chronic insomnia in the next months. He reported to take zolpidem in order to ‘get high’ and balance the effect of cocaine. Then he tried to take zolpidem during the day and experimented the effect when combined with cocaine, after reading online some psychonauts’ suggestions. Subsequently, he described euphoric and disinhibiting effects if he took zolpidem during the day, with an enhancing cocaine effect when combined (particularly, higher levels of concentration and efficiency, a great mental lucidity and hyperactivity). He tried intravenously zolpidem administration as well at 30 mg/day with a “*greater mood enhancement and energy*”. However, he gradually developed a severe worsening of his insomnia, hence, he gradually increased zolpidem dosage up to 300 mg/day mainly at bedtime. At the time of admission, complete blood count, biochemistry test, thyroid test, as well as ECG and urine test were in normal range. Urine screening test was positive for cocaine. He had no history of other medical conditions. Family history for substance and/or alcohol use disorder and/or psychiatric disorder was negative. He was diagnosed with “*Attention Deficit/Hyperactivity Disorder (ADHD)* (314.01); *Narcissistic Personality Disorder* (301.81); *Cocaine Use Disorder*” (304.20) and “*sedative, hypnotic or anxiolytic use disorder*” (304.10), according to the DSM-5 [42]. The treatment consisting in progressively switching zolpidem to diazepam (ratio 2:1, i.e., 300 mg of zolpidem converted to 150 mg of diazepam). During the hospitalization, diazepam was progressively de-titrated until a complete discontinuation. At the discharge, the patient was managed with gabapentin 900/day ter in die, bupropion 150 mg/day and melatonin 50 drops/day at bedtime. The patient was followed up by a psychiatrist working in a local Addiction Service, but it was referred that he drop-

ped out after 7 months. There are no further psychiatric records about his current clinical situation.

Case 4. Zolpidem abuse of a woman who cannot “face the day”

In April 2015, a 56-year-old woman was admitted to the Day Hospital for drug addiction of Policlinico Agostino Gemelli, Rome, Italy, due to a drug-resistant insomnia. During the last 6 months, she took 300 mg/die of oral zolpidem prescribed by her GP and stolen also from her husband. The clinical history of the patient showed BZDs addiction and a previous suicide attempt at age 13, as a result of a child abuse. According to her psychiatric history, she was not followed by public psychiatric services but she was followed by a private psychotherapist for many years. She had a diagnosis of Hashimoto’s thyroiditis, treated with 100 µg/die of levotiroxine, an irritable bowel syndrome and a chronic osteoarticular pain caused by a psoriatic arthritis (not pharmacologically treated). She usually smoked an average of 20 cigarettes/day. Three years before the admission at our Day Hospital, she started a self-administration of big amounts of drugs (BDZs and zolpidem) in the attempt to manage what she referred to be a “*great and intolerable stress*” caused by her work environment. She also described previous severe episodes of panic attack and agoraphobia. Moreover, she referred an increased feeling of anxiety, tension and frustration which reached a state of apathy and depersonalization, mainly related to work perceived stress. At the beginning of 2013, she was admitted to the ER two times due to lipothymic episodes and loss of consciousness not caused by any cardiovascular or neurological disorders. At the admission, she was verbose, anxious and the mood was slightly dysphoric; she referred to take 30 or 40 mg of zolpidem every 3 hours (also during the night) in order to reduce stress, anxiety, insomnia and “*to face the day*”, she also referred that when she did not take zolpidem for more than 4 hours she had shivers, generous sweating, vertigoes, confusion, general weakness, nausea, increasing of anxiety and of insomnia. Personality tests (MMPI-2, HAM-A, HAM-D) showed high level of anxiety, hypochondria and narcissistic traits. Her clinical condition presented the criteria for a “*Generalized Anxiety Disorder*” (300.02), according to the DSM-5 criteria [42] with important autonomic hyperarousal and other physical conditions that may be as-

sociated with stress. It has been planned a daily hospitalization for two weeks to gradually reduce the zolpidem intake. During the treatment, appropriate tests, to exclude an organic cause, was performed: TSH, FT3, FT4, electrolytes and inflammatory indexes, hepatic indexes and ammonium blood levels were normal. At the beginning, zolpidem administration was reduced at 150 mg/day for three days, in addition to pregabalin 150 mg/day, then followed by a reduction of 20–30 mg/day combined with intravenous trazodone 50 mg, glutathione 600 mg and piridinol 2 mg to decrease potential withdrawal symptoms. Three days after starting the treatment, the patients referred central-type insomnia, confusion and gastrointestinal symptoms. During the next days, the patient was able to reduce zolpidem from 1–2 pills/day to a complete interruption at day 14 with a good psycho-physical balance and a partial improvement of insomnia. In the meantime, oral therapy was modified with trazodone 100 mg/day, baclofene 10 mg/day, melatonin 2 mg at bedtime and pregabalin 300 mg/day. Three months after the discharge, the therapy was gradually reduced until the complete interruption and without relapses at the follow-up visits (last follow-up visit: one year after discharge).

Case 5. A general manager woman who tries to continuously be getting 'high'

A 52-year-old unmarried woman was admitted to the Psychiatric Day Hospital of the National Health Services (NHS) of the Department of Mental Health of Viterbo, Italy due to an acute insomnia and Z-drugs abuse. She reported a consumption of 450 mg/day of tartrate zolpidem in drops (one bottle and half) bedtime. She does not report any impairment in social and work functioning, despite the high-dose abuse of zolpidem. She is a successful general manager of a famous and important multinational company which requires high levels of competence and work efficiency. Therefore, this work aspect may indeed explain the motivation of zolpidem abuse. In fact, she reported that "zolpidem is the only drug able to sleep induce overnight and get high and hyper-activity during the day". She previously took other hypnotics without the comparable efficacy of zolpidem. She asked for a psychiatric consultation due to the occurring need to constantly increase daily zolpidem dosage in order to reach the same effect. She developed a zolpidem tolerance. She attempted to self-reduce zolpidem dosage, but she devel-

oped a withdrawal syndrome characterized by vertigo, uncontrollable anger, great irritability and tremors. After a psychiatric visit and a clinical assessment (MMPI-2, TCI-R, BPRS), clinicians excluded any Axis-I psychiatric diagnosis. She presented a "Narcissistic Personality Disorder" (301.81) according to the DSM-5 [42] and a cyclothymic temperament, according to the *Temperament Evaluation Instrument of Memphis, Pisa, Paris and San Diego* (TEMPS-A) questionnaire [43]. The clinical history excluded any previous and/or concomitant alcohol- and/or substance use. Family history was negative for alcohol- and/or substance use or psychiatric disorder. The treatment included a multidisciplinary approach involving psychological support, Interpersonal therapy and Social Rhythms (IPSRT) psychoeducation and psychiatric rehabilitation as well as a pharmacological treatment. Psychopharmacological approach consisted in prescribing pregabalin 300 mg/day (150 mg bis in die), bupropion 150 mg/day and chlorhydrate trazodone (Contramid[®]) 150 mg/day bedtime, over a 4-week period. She progressively reduced zolpidem of 10 mg/day, up to reach a dosage of 150 mg/day. At the end of fourth week of hospitalization, zolpidem was completely switched to diazepam (ratio 2:1, i.e., 150 mg of zolpidem converted to 75 mg of diazepam). During the next three months, diazepam was progressively de-titrated until a complete discontinuation. The patient is still taking pregabalin 300 mg/day, bupropion 150 mg/day and trazodone 150 mg/day. She referred a regular sleep pattern and a good sleep hygiene after the IPSRT programme.

Case 6. Zolpidem abuse in a Chem-Sex setting by a young girl

A 23-year-old young woman was evaluated into a private practice outpatient service, because she manifested a progressive social withdrawal and apathy and her parents were worried about this behaviour. She was recently graduated in Biology and lives with her parents. She usually spent all day at the computer and watching TV. After a psychiatric visit, it was excluded any Axis-I psychiatric diagnosis and/or Personality Disorder, according to the DSM-5 [42]. The clinical history excluded any previous and/or concomitant alcohol- and/or substance use. The patient only reported an inversion of sleep-wake rhythms. Then, she was prescribed zolpidem 10 mg/day at bedtime. She continued to take zolpidem, even though she

did not present to the follow-up psychiatric visits. However, she occasionally telephoned to psychiatrist reporting a great wellbeing after intake of zolpidem, even though she sometimes manifested sporadic amnestic episodes. Subsequently, she reported to have self-administered zolpidem 30 mg/day associated with alcohol for recreational motivations, as trigger and disinhibition aid during Chem-Sex night parties. She described disinhibition, increased sociability and mood enhancement which gave her the courage to take sexy photos to be sent out to unknown people through web social networks (i.e., Tinder, Tango and Instagram) and then met up these people in order to have occasional unprotected sexual relations. The day after, she manifested several amnestic episodes and she was not able to describe what she did the night before. Due to the increasing guilt feelings and worrying morning amnesia, she was able to recall the psychiatrist in order to address the issue. The treatment included a psychodynamic psychotherapy together with a psychopharmacological approach consisting of trazodone 50 mg/day bedtime. During a follow-up period of one year, she did not report any abuse of alcohol and zolpidem and she is substantially clinically stable.

Case 7. Euphoric effects in an antisocial personality disorder inmate man

A 36-year-old man, with a diagnosis of “*Antisocial personality disorder*” (301.7) [42], a previous history of alcohol use disorder, self-harm injuries, heteroaggressive behaviours and impulse dyscontrol was admitted to a prison due to possession of drugs of abuse. The police seized around 50 packages of tartrate zolpidem 10 mg at his home. He reported different ER accesses due to his impulsivity, aggressiveness and alcohol intoxication and several episodes of sexual disinhibition. During the psychiatric evaluation, he reported a chronic zolpidem dependence (240 mg/day at average, i.e., 30 mg every 3 hours) for recreational purpose as he described ‘high’ effects comparable to methylphenidate even though they last much longer. He manifested a mood elevation, euphoria, loquacity and he usually used this ‘high’ to have sex with different girls, occasionally met in the city clubs. The treatment included a switch change-over from zolpidem to diazepam (ratio 2:1, i.e., 240 mg of zolpidem equivalent to 120 g of diazepam) together with fluoxetine 20 mg/day and gabapentin 900 mg/day. Subsequently,

the patient progressively decreased diazepam (5 mg weekly) until a complete BZD discontinuation. The remission is currently complete, the patient mood is stable and in the last 6 months there were no episodes of aggressive behavior or impulse dyscontrol.

Case 8. A complex case of zolpidem abuse and withdrawal in a woman with MDD and personality disorder

A 47-year-old woman manifested three tonic seizures and was admitted to the ER. At the admission, she manifested cognitive impairment (i.e., confusion, time and space disorientation and lack of verbal expression). Brain computed tomography (CT), blood tests and ECG were normal. She did not manifest fever. During the 2-days of ER observation the patient presented further three episodes of tonic seizures, therefore, she was hospitalized at the neurology ward. Neurological examination and assessment were negative, except for lack of verbal expression, a confusing state, and spatial and time disorientation. EEG and magnetic resonance imaging (MRI) showed generic and non-specific alterations. Cerebrospinal fluid examination and serology were requested. Six days after the first epileptic seizure the patient underwent a psychiatric interview. She was described as a dysphoric and slightly agitated, with over-represented facial expressions and visual false perceptions. Olanzapine 2.5 mg/day was prescribed. Four days later, the psychiatric symptomatology improved. During the psychiatric interview, the patient reported that the public psychiatry service was taking care of her up to 8 months before the epileptic seizures and that she stopped all the treatment except zolpidem. However, she reported that, during the last months, she gradually increased the zolpidem dosages up to 120–140 mg/day. Two days before her hospitalization, she discontinued zolpidem intake because she could not afford it anymore. Fourteen days after epileptic seizures, cerebrospinal fluid examination and serology were normal, the control MRI was normal and the neurologists could not find any neurological possible cause of epileptic seizures, by supposing that they were most likely be induced by an abrupt zolpidem withdrawal. The patient was discharged with a diagnosis of “*sedative, hypnotic or anxiolytic use disorder*” (304.10) [42] and prescribed clonazepam 2.5 mg/day, olanzapine 2.5 mg/day and levetiracetam 1,500 mg/day. During the next seven months, the patients underwent a cognitive-behavioural

psychotherapy, the drugs dosages were gradually reduced until the complete interruption and she did not report any epileptic seizures. During the follow-up period, she did not report any epileptic seizures.

DISCUSSION

Zolpidem has been widely believed relatively safer and much tolerable compared to BDZs, not causing toxicity nor dependence and tolerance [27]. However, a growing plethora of studies demonstrated its potential of misuse and abuse (Table 1) associated with behavioral modifications, including bizarre behaviours, psychomotor agitation, sleep-related complex behaviours like sleep-eating, sleep-driving, sleep-shopping and sleep-conversations, often accompanied by amnesia for the episode [44]. According to the research studies so far published, there are at least two categories of zolpidem abusers who may experience compulsion and physical dependence [22]. A first category includes those subjects who firstly take zolpidem as hypnotic aid and then, due to the development of a tolerance to the sedative effect, progressively increase zolpidem dosage until becoming abusers and dependent; whilst a second category comprise those subjects, mainly with a concomitant and/or previous substance use disorder (SUD)/alcohol use disorder (AUD) or other dependence who take zolpidem due to recreational purposes [22]. Despite we agree with suggested categorization by Lugoboni *et al.* [22], we proposed three groups of subjects who abuse zolpidem, as following described. In fact, according to our clinical experience, within the first category, which comprise those “*subjects who seek hypnotic zolpidem effect*”, we could identify two sub-categories: the elderly (group A) and the females (group B). The elderly people seemed to firstly take zolpidem as sleep aid and then progressively increase doses as they experience anxiolytic effects, at supratherapeutic doses. In fact, the increasing risk of zolpidem overdose amongst the elderly, who usually manifest depressive symptoms accompanied with anxiety, may be easily explained by anxiolytic zolpidem effect at higher doses [38,45-52]. Conversely, female subjects who usually abuse zolpidem, are those suffering from iatrogenic insomnia or secondary to a minor psychiatric disorder (i.e., mild depression, dysthymia, or anxiety) (see Table 1) [53-57]. On the other hand, the second category (group C), which we may denominate “*subjects*

who seek euphoric and disinhibiting zolpidem effect”, is represented by younger subjects with severe dependence, who consume zolpidem at high supratherapeutic doses or intravenously, due to its paradoxical amphetamine/cocaine-like effect and, hence, mainly for recreational purposes [22,58-71]. Furthermore, zolpidem appears to be frequently consumed in association with other drugs of abuse (i.e., alcohol, cocaine, heroin, cannabis) or other prescription drugs (i.e., quetiapine, SSRIs, etc.) [22,46,50, 53,58,60,62,63,69-74]. In addition, it has been reported as well as an adjunctive substance to alcohol in drug-facilitated crimes [75] and some could argue that it may be added within the Chem-Sex parties, as reported in one of our clinical cases. Motivations may include strategy to cope with everyday activities, to overcome daily social, professional and family problems, anxiolytic effect and mood enhancement and psychostimulant potentiation. Sabe *et al.* [23] suggested that zolpidem dependence may develop for reaching a “*sedative or hypnotic effect*”, “*antidepressant-like effect, anxiolytic effect, or pleasant effect*” and “*being able to cope with everyday problems*”; or, finally, for the “*stimulation, euphoric or manic effect*”. Since zolpidem effect lasted no more than one hour, the subject usually repeats the intake in the daytime in order to maintain a basic euphoric effect [29].

From a pharmacological point of view, as previously described, zolpidem binds to the GABA_A receptor in a manner similar to that of BZDs, but unlike BZDs it exerts a more selectivity for the α_1 subunit, by enhancing GABA-mediated inhibition through allosteric modulation of the GABA_A receptor, at therapeutic doses [44]. A continuous zolpidem intake may induce adaptive changes in GABA_A receptors which could be responsible for the development of tolerance and dependence [51]. It has been demonstrated that α_1 subunits of GABA receptors are claimed to be responsible only for sedative activity and zolpidem shows a specific selectivity to α_1 subunits, at therapeutic dosages, opposite to BZDs which bind to α_2 , α_3 and α_5 subunits. Moreover, it has been demonstrated that α_2 subunits of GABA receptors are enriched in amygdala and were supposed to exert an anxiolytic activity which appeared not to be targeted by zolpidem at therapeutic dosages. Whilst it appeared that supratherapeutic doses of zolpidem may result in its binding in a less selective manner at GABA_A receptor which may determine a greater anxiolytic effect, by affecting also GABA_A receptors with

α_2 subunits. Furthermore, α_3 subunits of GABA_A receptor is supposed to exert an activity on memory function, and the hippocampus, which is involved in several integrative cerebral functions (i.e., learning and memory), is enriched in α_5 subunits of GABA_A receptor. Similarly, at supra-therapeutic doses, it has been supposed that zolpidem may lose its selectivity for α_1 subunits and exerts its activity also at α_2 , α_3 and α_5 subunits of GABA receptors which may cause memory impairment, i.e. amnesic episodes [53]; an anxiolytic effect, euphoria, exaltation, hyperactivity and stimulation; hence, zolpidem may be used to achieve these paradoxical effects and not for sedation [29]. Moreover, the stimulating and euphoric effect could be likely be explained by a dopaminergic activity of zolpidem as well [58,76] which may explain the occurrence of psychotic symptoms, psychomotor agitation and hallucinations in some clinical cases [23,40,77-80]. In fact, the "amphetamine/cocaine-like" zolpidem effect may be explained by its activity in increasing dopamine release through switching-off the firing of GABA neurons that tonically inhibit dopamine cell firing [81]. Moreover, it has been demonstrated that activity at α_1 subunits of GABA_A receptors in the ventral tegmental area may determine increased levels of dopamine and this may be of greater relevance for zolpidem which owns a high selectivity for α_1 subunits [39,82]. Amongst the most frequently described side effects following zolpidem abuse, sleep-walking and bizarre nocturnal behaviours like sleep-driving have been reported [83,84]. It has been supposed that zolpidem-induced sleep-walking may be explained by the desensitization of GABAergic receptors located on serotonergic neurons. In fact, zolpidem potentiates GABA_A receptors activity and, in turns, it enhances desensitization of these receptors which leads to decreased inhibitory drives and, hence, an increasing serotonergic activity. The excessive activation of GABA_A receptors, which may be possible at higher doses of zolpidem intake, may induce transient increase in serotonergic activity, which may result in an over behavioural reaction. According to this model, the delay between desensitization of GABA_A receptors and a compensatory decrease in serotonin release may determine these parasomnias [83].

Previous literature suggested that gabapentin may efficiently manage and treat alcohol withdrawal, cocaine dependence and BZDs dependence and detoxification as well as zolpidem abuse [49,50]. Gabapentin, by its

GABAergic activity (i.e., by binding subunits of L-type calcium channels), increases GABA synthesis, restores the feedback inhibition from the nucleus accumbens after an alteration occurring after a repeated drug use [84-86]. Similarly, pregabalin potently binds to the α_2 -delta regulatory subunit of voltage Ca⁺⁺ channels, thus inhibiting activity-dependent Ca⁺⁺ influx in presynaptic neurons, which results in a reduced release of excitatory neurotransmitters [87]. This activity may explain its efficacy in treating zolpidem dependence [52,88]. Overall, long-acting BZDs have been suggested as the ideal substitute for zolpidem (e.g., clonazepam, diazepam, chlorthalidoxepoxide) by using a cross-titration strategy with an adequate and equivalent diazepam dosage [39,45,46,52,53,67,72,89-91]. At the first step, a detoxification strategy based on a cross-titration with diazepam appeared to show the best outcomes in terms of safe detoxification and in ensuring a persistent zolpidem abstinence [92]. Furthermore, since melatonin and zolpidem share some neurochemical mechanisms in the brain, i.e., they interact with GABA and own similar behavioural properties (i.e., day-dependent anxiolytic activity), melatonin therapy has been recommended as well as possible aid to curtail zolpidem abuse [93,94]. Finally, it has been proposed a serotonin depletion hypothesis which may explain the efficacy of prescribing a SSRI or a serotonin antagonist-reuptake inhibitor (SARI), like trazodone, in managing zolpidem craving (Table 1) [60,62].

In our case clinical study, we described eight cases of oral zolpidem abuse (only in Case 3 an intravenous 30 mg/day zolpidem administration is reported). Zolpidem dosages ranging 30 to 450 mg daily. Three subjects were affected with a mood disorder (e.g., Dysthymic Disorder or MDD) accompanied with a secondary insomnia, which is comparable with clinical cases previously described [45,46,50,53,71,88,90-92,95-98]. Two cases reported previous traumatic experiences (physical and/or sexual and/or psychological abuse) which may partially explain zolpidem abuse as a tool to relieve and cope with stress-related disorders, as previously reported in literature [52,89]. A case involved a woman with a BZD dependence whilst in four cases here described, the subjects were affected with a Personality Disorder (mainly belonging to the 'Cluster B', i.e., Narcissistic [n = 2], Borderline [n = 1] and Antisocial [n = 1]), of which two with a current or previous SUD (e.g., a cocaine use disorder, n = 1) or AUD

($n = 1$), as previously described [22,45,48,60,62,63,71,97]. In one subject, zolpidem abuse was combined with alcohol intake within the Chem-Sex scenarios. Subjects here described reported dissociative experiences accompanied with amnesia and bizarre nocturnal behaviours, like sleep-walking and nocturnal overeating also at lower dosages (80–200 mg) whilst it has been reported euphoria, hyperactivation, hypervigilance, mental lucidity, increased energy and mood enhancement at higher dosages (> 200 mg/day). Subjects described more sedative and hypnotic effects at bedtime whilst mood enhancement and activating effects if zolpidem was diurnal administered. Zolpidem appears to be used as euphorizing agent also amongst those subjects not affected with any psychiatric disease and as aid to enhance the experienced relieving effect on their dysphoric and/or dysthymic states, or to cope with stressing daily professional activities, to reach a higher efficiency (as a performance enhancer). Due to this euphoric and performance enhancement experienced, most subjects here described gradually increased the prescribed zolpidem dose. According to the previous categorization of zolpidem abusers, one could argue that for those subjects “*who seek euphoric and disinhibiting zolpidem effect*”, the best psychopharmacological strategy could be a combination of GABAergic and dopaminergic agents (i.e., bupropion and gabapentin or pregabalin); in some cases, it could be effective integrate with a serotonergic agent (i.e., sertraline, fluoxetine). Whilst for those subjects “*who seek hypnotic/sedative/relaxing zolpidem effect*”, it could be recommended much more sedative agents (i.e., low-doses of trazodone, quetiapine, olanzapine).

CONCLUSIONS

Zolpidem should be prescribed with the same caution as BZD hypnotics, especially in patients with a history of drug abuse [17] or in the elderly (aged ≥ 65 years) [49-51]. Furthermore, some authors argued that gender may represent a susceptibility factor for developing a set of specific side effects as well as a great zolpidem abuse liability and vulnerability in the development of a withdrawal syndrome [54,99,100]. This aspect may be explained by the fact that there are significant sex-related differences in zolpidem clearance [101]. Finally, possible genetic mutations involving genes encoding different sub-

units of GABA_A receptors, may determine an individual variability in affinity receptor and explain why some patients progressively increase the dose and seek from the drug something other than hypnotic effect [29,102,103].

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Laura Orsolini, Angelo Bruschi, and Paolo Grandinetti conceived the topic of the manuscript, while Stefania Chiappini and Laura Orsolini carried out the main analysis. Roberta Testa, Domenico De Berardis, and Stefania Chiappini assisted in either screening of the studies or preparation of the attachments. Umberto Volpe served as study senior reviewer. Angelo Bruschi, Paolo Grandinetti, Alessandra Provenzano, and Laura Orsolini collected the clinical cases and discussed each other the main findings. All the co-authors substantially contributed to the present piece of work before approving it for final submission.

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