

Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study

Marie Thonnard, MSc¹
Olivia Gosseries, PhD¹
Athena Demertzi, PhD
Zulay Lugo, MD, MSc
Audrey Vanhaudenhuyse, PhD
Marie-Aurélié Bruno, PhD
Camille Chatelle, PhD
Aurore Thibaut, MSc
Vanessa Charland-Verville, MSc
Dina Habbal, MSc
Caroline Schnakers, PhD
Steven Laureys, MD, PhD

Coma Science Group, Cyclotron Research Center & Neurology Department, University and University Hospital of Liège, Liège, Belgium

Correspondence to: Steven Laureys
E-mail: steven.laureys@ulg.ac.be

Summary

Zolpidem has been reported as an “awakening drug” in some patients with disorders of consciousness (DOC). We here present the results of a prospective open-label study in chronic DOC patients. Sixty patients (35±15 years; 18 females; mean time since insult ± SD: 4±5.5 years; 31 with traumatic etiology) with a diagnosis of vegetative state/unresponsive wakefulness syndrome (n=28) or minimally conscious state (n=32) were behaviorally assessed using the Coma Recovery Scale-Revised (CRS-R) before and one hour after administration of 10 mg of zolpidem. At the group level, the diagnosis did not change after intake of zolpidem (p=0.10) and CRS-R total scores decreased (p=0.01). Twelve patients (20%) showed improved behaviors and/or CRS-R total scores after zolpidem administration but in only one patient was the diagnosis after zolpidem intake found to show a significant improvement (functional object use), which suggested a change of diagnosis. However, in this patient, a double-blind placebo-controlled trial was performed in order to better specify the effects of zolpidem, but the patient, on this trial, failed to show any clinical improvements. The present open-label study therefore failed to show any clinically significant improvement (i.e., change of

diagnosis) in any of the 60 studied chronic DOC patients.

KEY WORDS: disorders of consciousness, minimally conscious state, treatment, vegetative state, zolpidem

Introduction

Zolpidem is often reported, particularly in the non-scientific literature (e.g., Interlandi, 2011), as a “miracle drug” that awakens patients with disorders of consciousness (DOC). As a consequence, families of patients with DOC are likely to invest much hope in this drug. However, the proportion of DOC patients in whom zolpidem produces such an effect is not well documented. Currently, patients with DOC are increasingly well defined, especially since the publication, in 2002, of diagnostic criteria for the minimally conscious state [MCS - presence of limited but clear signs of consciousness without effective communication (Giacino et al., 2002)] and the vegetative state, recently renamed unresponsive wakefulness syndrome [VS/UWS – wakefulness without signs of awareness (Laureys et al., 2010)]. However, there are no evidence-based recommendations regarding pharmacological treatment capable of improving the level of consciousness in DOC patients (Demertzi et al., 2008).

A number of studies, essentially case reports, have nevertheless reported zolpidem as a possible treatment, found to result in a transient recovery of consciousness in some DOC patients (Table I, over). Whereas zolpidem, an imidazopyridine, is generally used as a sedative-hypnotic drug, it seems that it occasionally produces, temporarily, a surprising paradoxical effect on the level of consciousness in some DOC patients, irrespective of whether they have a traumatic or a non-traumatic etiology (Gosseries et al., 2013). A wide range of behavioral improvements have been reported including the emergence of visual pursuit, command following, verbalizations, functional communication, motor improvements (e.g., ability to walk) and/or cognitive (e.g., reading, counting, writing) improvements (Brefel-Courbon et al., 2007; Clauss and Nel, 2006; Clauss et al., 2000; Cohen and Duong, 2008; Shames and Ring, 2008; Whyte and Myers, 2009) (Table I). Despite the existence of numerous case reports about zolpidem in DOC, only Whyte and Myers (2009) have investigated the incidence of responders among DOC patients (11). In their study, only one out of 15 patients evolved from VS/UWS to MCS (6.7% responder rate) and demonstrated behavioral

¹ M.T. and O.G. contributed equally to this work.

Table 1 – Pharmacological studies on zolpidem in post-comatose patients with disorders of consciousness.

Type of study	n (etiology)	Diagnosis	Time since insult	Dose	Main results	MRI or CT of zolpidem responders
Williams et al., 2013						
EEG case study	3 (TBI, stroke, TBI/hypoxic)	MCS	5, 6, 9 y	10 mg	Behavioral improvements: verbal fluency, functional use of objects, functional communication. EEG: ↓ of power and coherence at ~6-10 Hz and ↑ in power at ~15-30 Hz. Changes in brain metabolism (PET): ↑ in anterior forebrain with the largest ↑ in the lateral frontal cortex	Unavailable
Du et al., 2013						
Cohort study using SPECT	127 [brain contrecoup contusion, primary brainstem injury, space-occupying brain compression injury and secondary brainstem injury]	VS/UWS (N.B.: no behavioral standard)	Unavailable	10 mg	↑ cerebral state index, ↑ cerebral perfusion, ↓ burst suppression in contrecoup contusion and space-occupying compression group. No changes in primary and secondary brainstem injury groups	Unavailable
Machado et al., 2011						
Case study	1 (stroke)	VS/UWS	5 y	10 mg	Signs of arousal (eye movements and yawns), heart rate ↑, EEG changes from subdelta band to the lower delta frequency range	Lesions in rostral part of the pons, mesencephalon and both thalami
Snyman et al., 2010						
Double-blind placebo-controlled randomized trial	3 pediatrics (1 TBI)	VS/UWS	2, 14, 13 y	0.14-0.2 mg/kg	No change of RLAS scores, ↑ CNCS scores (reduced responsiveness)	(No responder)
Whyte & Myers, 2009						
Multi-centric, double-blind, randomized study	15 (8 TBI)	VS/UWS, MCS	3 m-23 y	10 mg	1 responder to treatment (VS/UWS to MCS), ↑ CRS-R score, visual pursuit, response to command	Bilateral temporal lobe contusion, intraventricular hemorrhage
Cohen & Duong, 2008						
Case study	1 (anoxic)	MCS	8 m	5-20 mg	↑ lucidity, ↑ interactions, ↑ verbal and social responses	Unavailable
Shames & Ring, 2008						
Case study	1 (anoxic)	MCS	18 m	10 mg	↑ lucidity, ↑ RLAS score, ↑ verbal communication, reading, counting, verbal production, self-feeding	Mild ventricular dilatation

Abbreviations: n=number of patients; TBI=traumatic brain injury; VS/UWS=vegetative state/unresponsive wakefulness syndrome; MCS=minimally conscious state; ↑=increase; ↓=decrease; y=year(s); m=month(s); EEG=electroencephalogram; SPECT=single photon emission computed tomography; CRS-R=Coma Recovery Scale-Revised; RLAS=Rancho Los Amigos Scale; GCS=Glasgow Coma Scale; CNCS=Coma/Near Coma Scale; PET=positron emission tomography

Table 1 (cont.) – Pharmacological studies on zolpidem in post-comatose patients with disorders of consciousness.

Type of study	n (etiology)	Diagnosis	Time since insult	Dose	Main results	MRI or CT of zolpidem responders
Singh et al., 2008						
Double-blind case study	1 (TBI)	MCS	4 y	10 mg	No effect on tests with instructions which ↑ in complexity	(No responder)
Lo et al., 2008						
Double-blind case study	2 (anoxic)	VS/UWS	±1 m	10 mg	No arousal improvement, no recovery of consciousness, no ↑ GCS score	(No responder)
Brefel-Courbon et al., 2007						
Double-blind, placebo-controlled randomized case study	1 (anoxic)	MCS	2 y	20 mg	↑ arousal, ↑ motor and neuropsychological performance (functional communication, eating, walking, reading and repeating words)	Unavailable
Clauss & Nel, 2006						
Case studies	3 (2 TBI)	VS/UWS	3-5 y	10 mg	↑ arousal, ↑ GCS and RLAS scores	Unavailable
Clauss et al., 2000						
Case study	1 (TBI)	'Semi-comatose'	3 y	10 mg	Verbal response after 15 min, talking, answering simple questions, spontaneous interaction, counting, writing	Hemorrhage in left lentiform nucleus, thalamus and cerebellar peduncles. Intra-ventricular blood in occipital horn of lateral ventricles, lesion in brainstem

Abbreviations: n=number of patients; TBI=traumatic brain injury; VS/UWS=vegetative state/unresponsive wakefulness syndrome; MCS=minimally conscious state; ↑=increase; ↓=decrease; y=year(s); m=month(s); EEG=electroencephalogram; SPECT=single photon emission computed tomography; CRS-R=Coma Recovery Scale-Revised; RLAS=Rancho Los Amigos Scale; GCS=Glasgow Coma Scale; CNCS=Coma/Near Coma Scale

improvements, namely visual pursuit and response to command.

The numerous case reports present in the literature may result in overestimation of the rate of patients in whom zolpidem works as a “waking up pill”. On the other hand, only one study has assessed the responder rate in a small sample. The aim of the present prospective, uncontrolled, unblinded study was thus to estimate the frequency of beneficial clinical changes after zolpidem intake and to characterize these changes in a larger cohort of chronic DOC patients.

Materials and methods

We prospectively enrolled patients with chronic (>4 weeks post injury) VS/UWS or MCS. The patients underwent repeated (≥5) standardized behavioral assessments using the Coma Recovery Scale-Revised [CRS-R, (4)], administered by trained examiners over a one-week period. The CRS-R was also administered before and one hour after (considering the approximate moment

of the peak plasma concentration) a single dose of zolpidem (10 mg administered orally or via a feeding tube). If the clinical diagnosis, according to the CRS-R results, improved in the open-label zolpidem trial, a double-blind placebo-controlled trial was performed in order to confirm the improvement. Informed consent was obtained from each participant's legally authorized representative. Statistical analyses were performed on diagnosis and CRS-R total scores using non-parametric statistics (Wilcoxon's signed rank test, SPSS 16.0, 2007, SPSS Inc.). Data were corrected for multiple comparisons (Bonferroni's correction, $p < 0.05$, one-tailed).

Results

Sixty patients (18 females, mean age±SD: 36±14 years) with a diagnosis of VS/UWS (n=28, 47%) or MCS (n=32, 53%) were assessed between four weeks and 26 years post-injury (mean time since injury±SD: 4±5.5 years). The etiology was traumatic in 31 (52%) and non-traumatic in 29 (48%) patients [i.e., anoxic encephalopathy

(n=18), hemorrhagic or ischemic stroke (n=6), metabolic encephalopathy (n=2) and mixed etiology (n= 3)]. At the group level, the diagnosis did not change after zolpidem intake ($z=-1.7$, $p=0.10$, $r=0.15$) and CRS-R total scores decreased [pre-zolpidem median=7, post-zolpidem median=6, interquartile range (IQR)=1, $z=-2.7$, $p=0.01$, $r=0.24$, Fig. 1], and the CRS-R subscores showed no significant change pre- versus post-zolpidem. However, at the individual level, 12 patients showed improved behaviors and/or increased CRS-R total scores after zolpidem (Table II). Of these 12 patients, four (2 traumatic brain injury, 1 anoxia and 1 metabolic etiology, with different patterns of regional brain damage) showed improvements not observed in any other CRS-R assessments performed outside the zolpidem trial (e.g., reproducible command following, object recognition, vocalization; Table II). However, in only one of these patients did the improvement suggest a change of diagnosis. Patient n. 45, a 30-year-old man who suffered a traumatic brain injury nine years before the study, was diagnosed as MCS on the basis of all the pre-zolpidem CRS-R assessments. He presented conscious behaviors such as command following, object recognition and visual pursuit. However, he showed functional use of objects only on the post-zolpidem CRS-R assessment, which thus suggests that he emerged from MCS. A double-blind placebo-controlled study was consequently performed, which, however, failed to confirm the clinical improvement; i.e., there was no increase in any of his CRS-R subscores and, therefore, no change of diagnosis.

Discussion

The aim of this prospective uncontrolled study was to estimate the frequency of beneficial clinical changes after zolpidem intake and to characterize these changes in a large population of chronic DOC patients. Overall, zolpidem intake did not induce a beneficial effect in chronic DOC patients. On the contrary, zolpidem led to decreased CRS-R total scores. At the individual level, however, 12 patients showed an increase of CRS-R total scores compared to the pre-zolpidem baseline CRS-R assessment. Some might argue that these slight improvements could have been the result of spontaneous fluctuations of vigilance and responsiveness, which are well known to occur in patients with DOC. Therefore, we also compared the post-zolpidem status to the best clinical status during the one week of repeated CRS-R assessments. Only four patients (6.7% of the present cohort) showed some functional improvements. Although this responder rate is identical to the 6.7% obtained by Whyte and Myers (2009), it is important to note that, contrary to our study, the clinical improvements observed in one of Whyte and Myers' patients resulted in a change of diagnosis. Indeed, the positive changes observed in our patients did not, ultimately, result in a change of diagnosis. This result also conflicts with previous reports of changes of diagnosis after zolpidem intake in some patients (e.g., Brefel-Courbon et al., 2007;

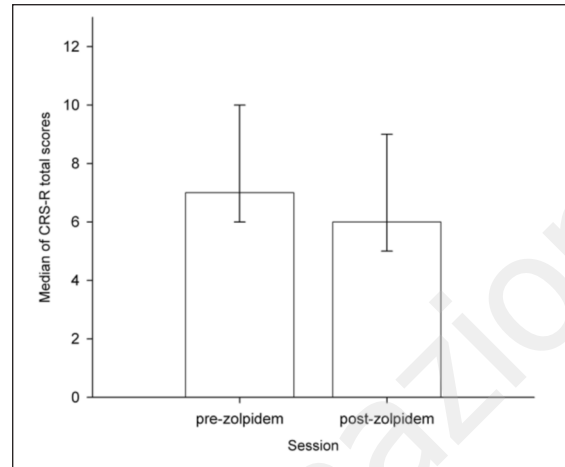


Figure 1 - Significant decrease of CRS-R total scores (ranging from 0 to 23) after zolpidem intake (interquartile range represented by errors bars) in the entire sample (n=60).

Clauss and Nel, 2006; Clauss et al., 2000; Shames and Ring, 2008); indeed, although one of our patients did show a significant improvement, the follow-up double-blind placebo-controlled trial failed to confirm the zolpidem effect. Instead of having an all-or-none effect, zolpidem seems to have a gradual effect, not necessarily sufficient to justify a change of diagnosis. Given the current results, it is important to temper the enthusiasm in the media about zolpidem as a "miracle awakening pill". Extraordinary cases with regained speech or other impressive effects exist and are reported in the literature, but they seem to be exceptions rather than the rule. Families of patients have to be informed that this treatment possibility exists but, as clinicians, we should properly inform patients' relatives about the low responder rate, and the sometimes limited clinical improvements observed.

In conclusion, no change in outcome was observed after zolpidem administration even in DOC patients who transiently showed some increased alertness. Only a small minority of our patients showed partial beneficial effects after zolpidem (4/60; 6.7% of the present cohort), and the observed clinical changes did not lead to a change in diagnosis in any of the cases included in this study. However, these partial beneficial effects, although not significant, suggest that the effect in DOC patients does not seem to be bimodal, but rather more subtle and possibly gradual in some patients. Therefore, in order to more precisely characterize and understand the effects of zolpidem, we suggest that, in the future, the positive behavioral changes observed should be classified as small (i.e., increase in arousal), medium (i.e., improved responsiveness but same diagnosis) or significant (i.e., change of diagnosis). Recent case-report studies have used neuroimaging and electroencephalography techniques to document the effect of zolpidem (Machado et al., 2013; Snyman et al., 2010; Williams et al., 2013). Further studies should focus on large patient series aiming to identify the characteristics of

Table II – Data regarding 12 out of 60 DOC patients who showed improved behaviors and/or increased CRS-R total scores after zolpidem administration.

Patient	Age	Etiology	Time since injury	Diagnosis (CRS-R total score)			Improvements compared with pre-zolpidem baseline	Improvements compared with one-week baseline assessments
				All CRS-R	Pre-zolpidem	Post-zolpidem		
45*†	30	TBI	9 y	MCS (14)	MCS (9)	EMCS (17)	<ul style="list-style-type: none"> • Reproducible command following • Object localization • Functional use of objects 	<ul style="list-style-type: none"> • Functional use of objects
52*	48	Anoxia	1 y	MCS (10)	MCS (7)	MCS (12)	<ul style="list-style-type: none"> • Reproducible command following • Object recognition 	<ul style="list-style-type: none"> • Reproducible command following • Object recognition
4*	21	TBI	5 y	MCS (10)	MCS (8)	MCS (14)	<ul style="list-style-type: none"> • Systematic command following • Automatic motor reaction • Vocalization • Intentional communication 	<ul style="list-style-type: none"> • Intentional communication
15*	53	Metabolic	1 y	MCS (15)	MCS (15)	MCS (16)	<ul style="list-style-type: none"> • Object localization • Automatic motor reaction 	<ul style="list-style-type: none"> • Object localization
19	20	TBI	3.5 y	MCS (10)	MCS (10)	MCS (10)	<ul style="list-style-type: none"> • Auditory startle 	-
59	24	TBI	3 y	MCS (10)	MCS (9)	MCS (11)	<ul style="list-style-type: none"> • Reproducible command following 	-
9	23	TBI	1 y	MCS (10)	MCS (11)	MCS (10)	<ul style="list-style-type: none"> • Vocalization 	-
58	24	TBI	9 m	MCS (10)	VS/UWS (8)	MCS (11)	<ul style="list-style-type: none"> • Automatic motor reaction 	-
46	67	Stroke	4 y	MCS (4)	VS/UWS (4)	VS/UWS (5)	<ul style="list-style-type: none"> • Eye opening without stimulation 	-
50	22	TBI	6 m	VS/UWS (8)	VS/UWS (6)	VS/UWS (7)	<ul style="list-style-type: none"> • Auditory startle 	-
21	19	TBI	9 m	MCS (11)	MCS (11)	MCS (11)	<ul style="list-style-type: none"> • Vocalization 	-
53	49	Anoxia	8 y	VS/UWS (6)	VS/UWS (4)	VS/UWS (3)	<ul style="list-style-type: none"> • Eye opening without stimulation 	-

* Patients (n=4) showing improvements post-zolpidem compared to all CRS-R assessments.

† In this patient, a placebo-controlled double-blind zolpidem trial failed to show any clinical improvement.

Abbreviations: TBI=traumatic brain injury; VS/UWS=vegetative state/unresponsive wakefulness syndrome; MCS=minimally conscious state; EMCS=emergence from minimally conscious state; CRS-R=Coma Recovery Scale-Revised; y=year(s); m=month(s)

zolpidem responders using clinical, functional neuroimaging and electrophysiological techniques in order to better understand the precise underlying mechanisms of action of the effect of zolpidem in patients with DOC (Schiff, 2010).

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