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CASE REPORT

Zolpidem-Induced Sleepwalking, Sleep Related Eating Disorder, and Sleep-Driving: Fluorine-18-Flourodeoxyglucose Positron Emission Tomography Analysis, and a Literature Review of Other Unexpected Clinical Effects of Zolpidem

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Zolpidem is a hypnotic which acts at the $GABA_A$ receptor and is indicated for short-term insomnia. Sleep related disorders including somnambulism, sleep related eating and sleep-driving have been reported with zolpidem. A 51-year-old insomniac who used zolpidem 10 mg nightly starting at 44 years of age is described. A few weeks after starting zolpidem she began walking, eating, and had one episode of driving while asleep. Episodes of sleep related eating, sleepwalking, and sleeptalking occurred 3 nights per week, 1 to 2 h after sleep onset. After her evaluation, the patient's zolpidem was gradually discontinued, and all sleep related activities immediately ceased. An 18F-FDG-PET was obtained 2 months after discontinuation of zolpidem. The following day, FDG was administered 1 h after oral administration of 10 mg zolpidem, and then a second PET was performed. We report the results and a review of the literature regarding other unintended effects seen with zolpidem use.

Keywords: Zolpidem, fluorine-18-flourodeoxyglucose positron emission tomography, sleep related eating disorder, sleepwalking, sleep-driving

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Sleepwalking or somnambulism, is a parasomnia consisting of a series of complex behaviors usually initiated during arousals from slow wave sleep and commonly culminate in walking with an altered state of consciousness and impaired judgment.[1] Sleep related eating disorder (SRED) consists of recurrent episodes of involuntary eating during arousals from sleep.[1] Parasomnias such as sleepwalking, SRED, and sleep-driving can coexist and are rare side effects of zolpidem. In a 2005 National Institutes of Health consensus statement for the treatment of chronic insomnia in adults zolpidem was considered a hypnotic with limited risk.[2] Two post-marketing studies of zolpidem reported sleepwalking incidences of 7 of 1972 patients (0.3%)[3] and 1 of 96 patients (1%).[4] We present a patient with zolpidem-induced sleepwalking, SRED, and sleep-driving. A fluorine-18-flourodeoxyglucose positron emission tomography (18F-FDG-PET) was obtained one month after discontinuation of zolpidem. A second 18F-FDG-PET was acquired the following day, 1 h after oral administration of zolpidem 10 mg (Figure 1). The cerebral glucose metabolism rates of the 2 studies were then compared, using statistical parametric mapping analysis. We also review the literature regarding unintended effects of zolpidem use.

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CASE REPORT

The patient is a 51-year-old African American woman with past medical history of hypertension, mild obstructive sleep apnea, hyperlipidemia, and depression. Previous diagnostic polysomnogram revealed an apnea-hypopnea index of 10 events/h. Medications included paroxetine 20 mg once a day, extended release metoprolol 25 mg twice per day, and simvastatin 40 mg once a day. History for alcohol, tobacco, or illicit drug use was negative. The patient reported no personal or family history of sleepwalking or other parasomnias. The patient did not have a history of daytime eating disorder. At age 44 the patient was started on non-extended release zolpidem 10 mg at bedtime for insomnia. A few weeks after starting zolpidem. she began sleep related walking, eating, and one episode of driving.

Episodes of sleepwalking, SRED, and sleeptalking occurred 3 nights per week, 1-2 h after sleep onset. The patient would speak incoherently using short phrases with her eyes closed and would then open her eyes when questioned by her husband. She would also leave her bedroom to go to her kitchen where she would eat a loaf of bread, cold cereal, or leftover food. The following morning she would have abdominal fullness, find her kitchen messy, and have complete amnesia for the event. The patient would also leave her home and walk on her front porch or on her front lawn. As a preventive measure, she installed nocturnal alarms on her doors to wake her or her family from sleep if she opened one. Other reported events included one occasion of urination in the hallway, and one episode when the patient drove her automobile 10 miles from her home and

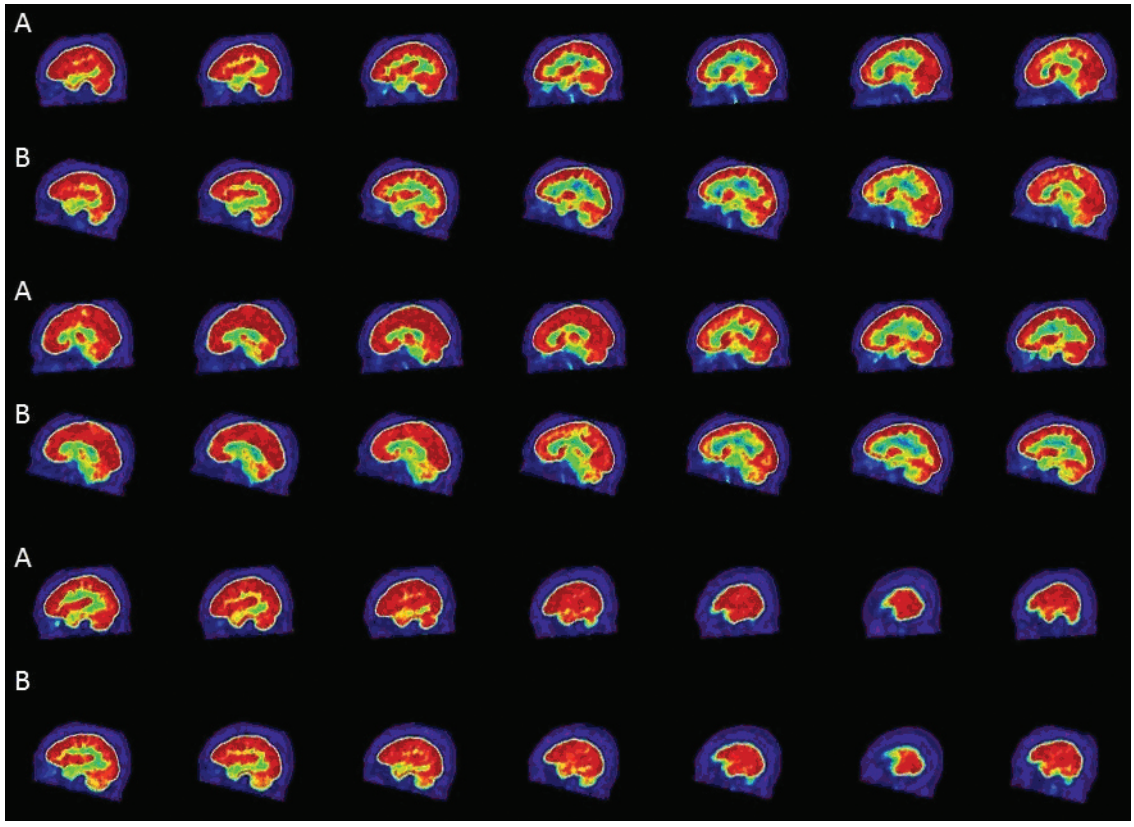

Figure 1—18-fluorine-flourodeoxyglucose-positron emission tomography (18F-FDG-PET) of a patient with zolpidem induced sleepwalking, sleep related eating disorder, and sleep-driving. A: 18F-FDG-PET off zolpidem. B: 18F-FDG-PET on zolpidem. FDG was administered to patient 1 h after ingestion of 10 mg zolpidem. Statistical parametric mapping comparison of the 2 sequences shows no significant differences.

was found asleep behind the wheel by police. She had a vague recollection of this event, but thought that she was dreaming. After her evaluation, the patient's zolpidem was gradually withdrawn; all sleep related activities immediately ceased and have not recurred during 6 months of follow-up.

18F-FDG-PET Analysis

The first PET study in our patient was performed after discontinuation of zolpidem for 2 months. A second PET study FDG was administered 1 h after the administration of 10 mg zolpidem. The patient was asleep in the scanner during both PET studies. Statistical parametric mapping comparison between our patient's 2 studies demonstrated no significant differences (Figure 1).

DISCUSSION

Zolpidem is an imidazopyridine drug indicated for short-term insomnia at a dosage usually ranging from 5 to 10 mg per day.[5] Though considered a non-benzodiazepine since its imidazopyridine structure differs from benzodiazepine fusion of benzene and diazepine, zolpidem is a benzodiazepine receptor agonist with high binding affinity for the $GABA_A$ (gamma-amino butyric acid type A) receptor expressing the α_1 subunit. Benzodiazepines and benzodiazepine receptor agonists like zolpidem bind to the $GABA_A$ receptor at sites that are distinct from the GABA binding site, thereby allosterically affecting the activity of the ligand-operated chloride channel.

GABA is the main inhibitory neurotransmitters in the mammalian central nervous system (CNS). $GABA_A$ receptors exist as pentameric protein complexes, assembled from a combination of at least 19 subunits from 7 distinct gene families (α, β, γ, δ, ε, θ, and π). Synaptic $GABA_A$ receptors are responsible for modulating benzodiazepine sensitivity and typically contain $\alpha_{1,2,3,\text{or }5}$, $\beta_{2\text{ or }3}$, and the γ_2 subunits.[6] $GABA_A$ receptor sensitivity to benzodiazepines is mediated through α subunits. Benzodiazepines bind to synaptic $GABA_A$ receptors containing α_1, α_2, α_3, or α_5 subunits with comparable affinity. The $GABA_A$ receptor expressing the α_1 subunit corresponds to the benzodiazepine ω_1 receptor.[7] $GABA_A$ receptors containing the α_1, α_2, α_3, or α_5 subunits correspond to ω_2 benzodiazepine receptors. The ω_3 benzodiazepine receptor is not related to the $GABA_A$ receptor. Extrasynaptic $GABA_A$ receptors are primarily composed of $\alpha_{4\text{-}6}$ subunits in combination with δ subunits, and are insensitive to benzodiazepines. The current benzodiazepine receptor nomenclature (ω_1, ω_2, and ω_3) replaced the previous anatomical localization classification (central benzodiazepine receptor type 1, central BZ-1; central benzodiazepine receptor type 2, central BZ-2; and peripheral benzodiazepine receptor type 3, BZ3) because of the existence of "central" benzodiazepine receptors with peripheral localization, and "peripheral" benzodiazepine receptors with central localization.

Zolpidem was developed as a drug with a structure different from benzodiazepines, allowing affinity for only a given subset of central benzodiazepine receptors resulting in hypnotic properties without additional anticonvulsant and myorelaxant properties of benzodiazepines. In contrast to benzodiazepines

like clonazepam, diazepam and flunitrazepam, which lack selectivity for the ω_1, ω_2, or ω_3 benzodiazepine receptor subtypes; zolpidem has a high affinity for ω_1.[8]

A possible explanation for zolpidem-induced nocturnal events is that after an arousal from sleep into wakefulness, nocturnal activity (i.e., walking, eating, or driving) occurred and was subsequently not recalled after returning to sleep because of the sedation-mediated amnestic properties of zolpidem. Another possibility is that an arousal occurred out of slow wave sleep with the parasomnia occurring in electroencephalographically verifiable sleep. We felt our patient experienced the later, given her incoherent interactions with her husband during her nocturnal events. Patients who do not recall waking events on zolpidem are typically cognitively functional, and retain the ability to speak in coherent short phrases.[9]

Sleepwalking is a relatively common condition affecting 10% of adults.[1] Recently hotels across the United Kingdom reported an increase in the number of hotel guests found to be sleepwalking.[10] Though the incidence of zolpidem induced sleepwalking has been reported to be low, it is possible that many cases of unexplained sleepwalking may be secondary to zolpidem given its widespread use.[3,4]

Along with sleepwalking, SRED, and sleep-driving parasomnias, zolpidem has been anecdotally reported to produce a range of unexpected beneficial effects. These include improvement in the following conditions: post-stroke Broca's aphasia; blepharospasm; quadriparesis of central pontine myelinolysis; catatonia of schizoaffective disorder; dementia with apraxia; post-anoxic minimally conscious states; bradykinesia, akinesia, and dystonia in Parkinson disease; post-levodopa dyskinesias in Parkinson disease; vertical saccadic eye movements and parkinsonism in progressive supranuclear palsy; restless legs syndrome; post-anoxic spasticity; and spinocerebellar ataxia (Table S1 summarizes the available reports of improvement in varied neurological conditions with zolpidem use). Effects were usually noted within 30 min of ingestion of the non-extended release formulation and lasted for 2 to 4 h, corresponding with a time to peak plasma contraction of approximately 1.2 h and a half-life of approximately 2.5 h.

Zolpidem effects might be mediated through its anti-anxiety effects, its benzodiazepine receptor agonist properties, its GABAergic activity, or some combination of all three. For example, symptoms of Parkinson disease worsen with anxiety. The improvement noted in Parkinson disease with zolpidem use may be secondary to its anxiolytic effect through a GABAergic effect on the limbic system or elsewhere. The improvement seen in blepharospasm, catatonia, and restless legs syndrome may be caused by the benzodiazepine ω_1 receptor agonist activity of zolpidem. However, opposing this theory of purely benzodiazepine agonist mediated effects, is that parasomnias like sleepwalking are often treated with benzodiazepines like clonazepam; yet zolpidem seems to induce parasomnias in a susceptible subpopulation.

The action of zolpidem via synaptic $GABA_A$ receptors with α1 subunits may produce different clinical responses depending upon regional distribution of receptor subtypes. Benzodiazepines bind to all the synaptic $GABA_A$ receptors, which are expressed throughout the nervous system. Even though zolpidem is a preferred α_1 agonist, α_1 subunits are expressed widely throughout the CNS.[11] Benzodiazepine-insensitive extrasynaptic $GABA_A$ receptors containing $\alpha_{4\text{-}6}$ subunits show much more regional specificity than benzodiazepine-sensitive synaptic $GABA_A$ receptors containing $\alpha_{1,\,2,\,3,\,\text{or}\,5}$.

Zolpidem has a less recognized but limited binding affinity to ω_2 benzodiazepine receptors. ω_1 and ω_2 receptors are also widely expressed throughout the human brain.[12] At higher doses these lower binding affinities may be expressed resulting in unexpected clinical outcomes. For example, anecdotally there appears to be differential efficacy of high dose zolpidem (70 mg/d) for blepharospasm, and low dose zolpidem (5-10 mg/d) for parkinsonian features. (Surprisingly at the high doses used by Garretto et. al for blepharospasm and Evidente for early onset Parkinson disease, 5 of 6 patients reported no somnolence, and only one patient had to discontinue the medication secondary to drug-induced diarrhea.[13,14] Somnolence was overcome with slow dose titration.)

The potential clinical significance of preferred $GABA_A$ α_1 subunit/ω_1 receptor activation is unclear. For example, it was previously thought that zolpidem did not possess significant myorelaxant properties similar to benzodiazepines. However, anecdotal reports of efficacy for zolpidem in post-anoxic spasticity, parkinsonian dyskinesias/tremors, blepharospasm, and restless legs syndrome provides anecdotal evidence to the contrary. Zolpidem may affect many neurological diseases through binding at a variety of locations simultaneously (Figure 2). Zolpidem binding at one anatomical location is unlikely to explain all of its myriad effects. Also, electrophysiological studies suggest that different GABA subunit combinations may mediate different physiological and pharmacological properties of the ligand-operated ion channel.[11] Therefore, even though zolpidem has a high affinity for $GABA_A$ receptors with the α_1 subunit, different pharmacological responses may results from different subunit combinations with the α_1 subunit. As a result, clinical efficacy in a given disease is difficult to correlate with binding and receptor activation at a single $GABA_A$/benzodiazepine receptor type, at a single anatomic site, or at a single dose.

An intriguing theory on the etiology of sleepwalking and SRED concerns the presence of theoretical *cerebral pattern generators* (CPGs).[15,16] CPG are thought to be neuronal collections in the brain, brainstem or spinal cord that can potentially control innate motor behaviors essential for survival like feeding and locomotion. Diffuse zolpidem cortical binding may cause release of CPGs associated with evolutionarily conserved motor patterns such as walking and eating, leading to subsequent disorders of arousal like somnambulism and SRED. Since some CPGs may reside in the cortex, zolpidem use also release cortical patterns associated with overlearned behaviors, such as driving.

In an attempt to identify zolpidem-induced changes in cerebral glucose metabolic rates, an 18F-FDG-PET was performed in our patient on and off zolpidem. Gillin et al. compared the effects of 10 mg zolpidem and placebo on cerebral glucose metabolic rates in 12 young normal volunteers (mean age: 22.5 y) using 18F-FDG-PET.[17] In that study FDG was administered about 1 h after oral administration of zolpidem while the patient was in electroencephalographically (EEG) verifiable stage 2 sleep and at a time of expected zolpidem peak concentrations (1.2 ± 0.2 h)

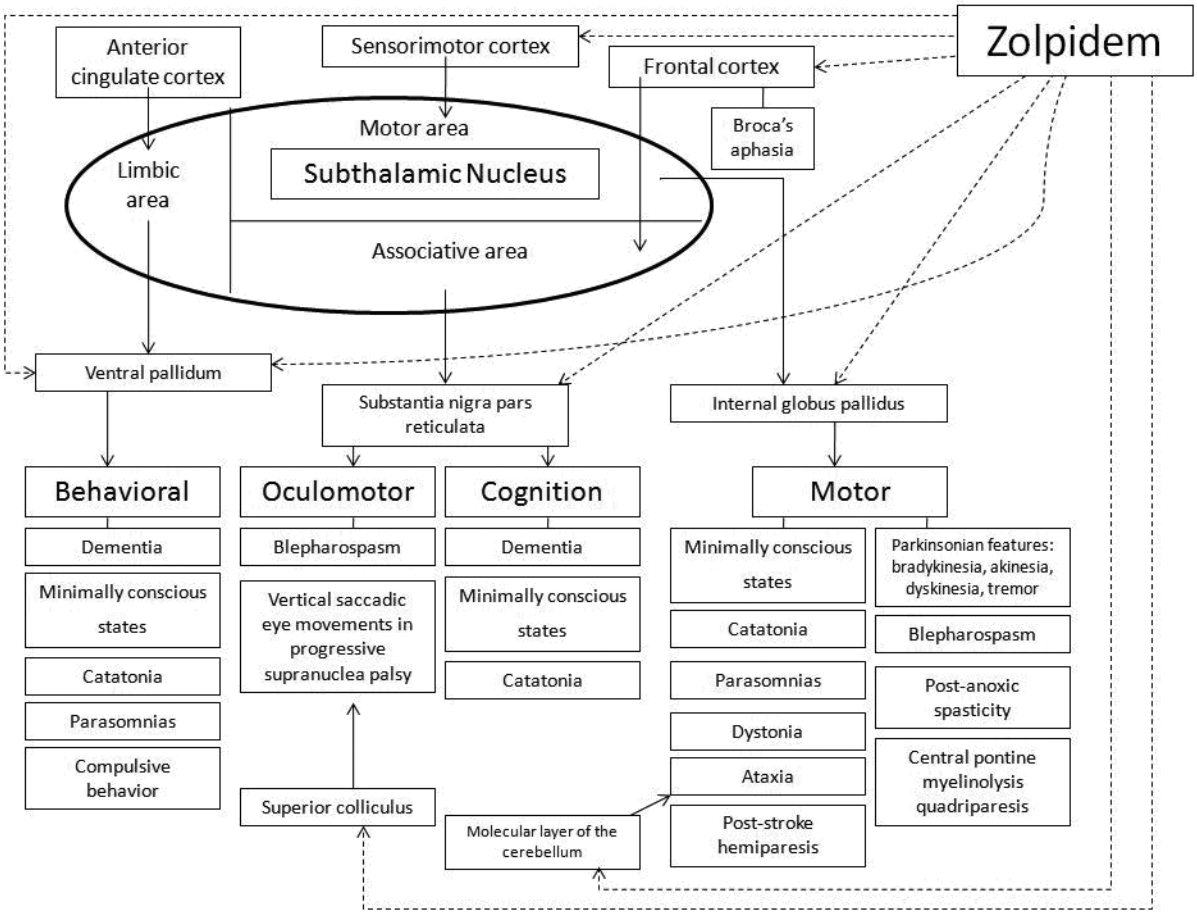

Figure 2—Regional distribution of zolpidem binding, and the potential clinical consequences. Zolpidem is a benzodiazepine receptor agonist with high binding affinity for the $GABA_A$ (gamma-amino butyric acid type A) receptor expressing the α_1 subunit. Benzodiazepines and benzodiazepine receptor agonists like zolpidem bind to the $GABA_A$ receptor at sites that are distinct from the GABA binding site, thereby allosterically affecting the channel. $GABA_A$ receptor sensitivity to benzodiazepines is mediated through α subunits. Zolpidem's action via synaptic $GABA_A$ receptors with α1 subunits may produce different clinical responses depending upon regional distribution of receptor subtypes. Benzodiazepines bind to all the synaptic $GABA_A$ receptors, which are expressed throughout the nervous system. Even though zolpidem is a preferred α_1 agonist, α_1 subunits are expressed widely throughout the CNS. Given zolpidem's many binding sites, the improvement noted across a range of neurological disorders are difficult to localize to binding at a single anatomic location. $GABA_A$ α_1 subunits/ω_1 benzodiazepine receptors are widely distributed throughout the central nervous system, in many more areas than indicated in this simple schematic figure.

in plasma (and presumably brain). Gillin et al. found that across all cortical areas glucose metabolic rates were not significantly different on placebo versus zolpidem. Our patient's results were similar to those seen in Gillin's normal volunteers.

Compared to wake, whole brain cortical glucose metabolic rates decrease in NREM and REM stage sleep.[18] One would expect a decline in cortical glucose metabolic rate with the use of sleep-inducing hypnotics like zolpidem. However, our results, along with those of Gillin show otherwise. The reasons for this are unknown.

One possible explanation may be that PET is too insensitive a tool to detect subtle localized or generalized glucose metabolic rate differences on and off zolpidem in the normal brain. If such differences could be identified, then patients who are susceptible to developing parasomnias could be identified prior to use. More importantly, this may also provide insight into other extraordinary anecdotal effects of zolpidem.

A limitation of our PET analysis was that the scan was not performed in EEG verified slow wave sleep (SWS), when parasomnias are thought to emerge. Future 18F-FDG-PET studies in patients with zolpidem induced parasomnias could be attempted during EEG verified SWS on and off zolpidem to identify differences in glucose metabolic rates not seen in our analysis. However, this may prove to be difficult given the variable presence of SWS and the need to wait 1 h after FDG injection prior to the PET scan. By the time the patient receives the FDG injection and the scan is performed, the patient may no longer be in SWS. And though parasomnias tend to emerge in SWS, they can potentially arise from any NREM stage.

Temporal resolution is not a major limitation of PET studies in that in order to scan a brain the cortical area is divided into thirds and scanned in 3 successive 5-min sessions that are then compiled together to form an entire cortical scan. As a result, the PET findings in any particular cortical area are an estimation of glucose metabolic rate over a five minute time window. Despite this small time window, 18F-FDG-PET findings would be difficult to correlate with a particular arousal in a period of SWS. Similar studies may be performed on and off medica-

tion in NREM and REM to assess differences in brain cortical glucose metabolic rates, though the procedural limitations described above would still apply.

Single photon emission computed tomography (SPECT) studies have been used successfully to show increased cerebral blood flow in a range of cortical areas after zolpidem administration despite a more limited spatial resolution than PET. SPECT has been used to show increased regional blood flow in the frontal cortex in Broca aphasia, the cerebellum in spinocerebellar ataxia, and the contralateral hemisphere in hemiparetic patients.[19-21] In normal baboon models, SPECT has been used to demonstrate that zolpidem does not cause changes in regional cerebral blood flow in normal baboons. However, in baboons with cortical injuries, zolpidem increased blood flow to the injured areas.[22] Zolpidem mediated increase in regional cerebral blood flow to injured cortical areas on SPECT was attenuated by the use of flumazenil, a benzodiazepine receptor antagonist.[23] The baboon studies correlate to the case report of Brefel-Courbon et al. of a patient in a post-anoxic minimally conscious state showing arousal on clinical exam and increased cerebral glucose metabolism on 18F-FDG-PET in the bilateral post-rolandic territories and frontal lobes after zolpidem administration.[24] The normal baboon SPECT study findings also correlate with the 18F-FDG-PET findings in our neurologically intact patient and Gillin's normal volunteer cohort.[17]

To date no large scale randomized controlled trials exist assessing the efficacy of zolpidem for aphasia, blepharospasm, catatonia, central pontine myelinolysis, dementia with apraxia, Parkinson disease, progressive supranuclear palsy, restless legs syndrome, post-anoxic spasticity, or spinocerebellar ataxia. The clinical benefit of zolpidem for patients in minimally conscious states is currently being explored in clinical trials.[25] These results may also help to further understand sleep-wake mechanisms and the function of hypnotics.

The anecdotal benefits of zolpidem have provided hope that damage to brain tissue after strokes anoxic insults previously thought to be permanent may actually be reversible. Zolpidem may reactivate cortical areas that have undergone injury-induced dormancy, or there may be more redundancy built into our brains than previously believed, e.g. CPGs. GABAergic hypnotics like zolpidem through diffuse cortical binding may somehow unmask this redundancy.

Future studies may also shed light on whether different susceptibilities to zolpidem induced parasomnias and its other effects may depend upon the formulation used. For example, Chiang et al. reported 2 patients who experienced zolpidem induced sleepwalking and SRED on only the extended release formulation and not the non-extended release formulation.[26] Validation of these anecdotal findings and investigations into the new sublingual formulation of zolpidem may provide insight into how formulation dependent pharmacokinetics may influence an individual's susceptibility to zolpidem-induced parasomnias.[27]

Investigations into the mechanisms of action of GABAergic induced parasomnias may overturn therapeutic nihilism for a variety of neurological disease. Capitalizing upon zolpidem's myriad anecdotal serendipitous effects, basic science research using animal models of non–sleep-wake related neurological disorders may provide us with a of understanding how the brain reorganizes itself after injury. Also genetic analysis of individual patients may also provide insight into potentially identifiable pharmacogenetic vulnerabilities/susceptibilities. These exciting and unexplored avenues of research may be used in the treatment of disease previously thought untreatable.

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DISCLOSURE STATEMENT

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Table S1—Zolpidem: A Spectrum of Unintended Effects and Potential Uses. SRED: sleep-related eating disorder.

Reference	Age, sex, and clinical state	Dose	Description of response
Aphasia			
Cohen et al. 2004[19]	52, female, stroke of left insula, putamen, and superior temporal gyrus with resultant Broca aphasia	Zolpidem 10 mg once/d Time to response: 20 minutes Duration of response: unknown	Patient regained effective speech, naming, and repetition.
Blepharospasm, Meige syndrome (oromandibular dystonia and blepharospasm)			
Garretto et al. 2004[13]	Three patients Patient 1: 57, woman, Meige syndrome Patient 2: 63, male, blepharospasm Patient 3: 66, male, Meige syndrome	Patient 1: Zolpidem 10 mg every 2-3 h (70 mg/d) Time to response: 30 min Duration of response: 3 h Patient 2: Zolpidem 10 mg 3 times/d Time to response: 20-30 min Duration of response: 3 h Patient 3: Zolpidem 10 mg twice a day Time to response: 30 min Duration of response: 3 h	Blepharospasm improved in all 3. Effect on oromandibular dystonia in the 2 patients with Meige syndrome was not mentioned.
Catatonia			
Thomas et al. 1997[28]	21, woman, schizoaffective disorder. One month after discontinuation of haloperidol, patient developed severe oppositional behavior, mutism, staring, posturing, and refusal of food.	Zolpidem 10 mg once/d Time to response: 15 min Duration of response: 4 h	All behavior and motor symptoms resolved on zolpidem.
Central pontine myelinolysis			
Wang et al. 2007[29]	51, female, post-surgical complication resulting in central pontine myelinolysis with spastic quadriparesis and pseudobulbar palsy	Zolpidem 10 mg once/d Time to response: 20 min Duration of response: 4 h	Regained facial expression, effective speech, and smooth limb movements
Compulsive behavior while awake			
Tsia et al. 2007[30]	Three previously healthy patients Patient 1: 34, female Patient 2: 40, female Patient 3: 50, female	Zolpidem 10 mg once/d All 3 patients exhibited compulsive behaviors (cleaning, shopping, and eating) with anterograde amnesia for the events.	Events were not considered to be sleepwalking because patients were able to communicate fluently and perform normally beyond the compulsive activity. Events stopped with cessation of zolpidem in all 3 patients.
Dementia with apraxia			
Jarry et al. 2002[31]	60, woman, alcoholic, reduced cognition, memory loss, apraxia, inability to join in conversation	Zolpidem 10 mg once/d Time to response: 45-60 min Duration of response: 3 h	Improvement in cognition and praxis. Regained the ability to perform simple chores around the home.
Minimally conscious states			
Claus et al. 2000[32]	28, male, motor vehicle accident resulting in post-anoxic minimally conscious state	Zolpidem 10 mg once/d, Time to response: 15 min Duration of response not explicitly stated	Interacted spontaneously and responded to simple questions with short appropriate answers

Reference	Age, sex, and clinical state	Dose	Description of response
Claus et al. 2006[33]	Three patients: Patient L: 31, male, Patient N: 31, male, Patient G: 29, male. All 3 had motor vehicle accidents resulting in post-anoxic minimally conscious state	Doses unknown. Time to response: L: 20-30 min, N: 1 h; G: 20-30 min. Duration of response was 4 h for all 3 patients.	L: meaningful interactions/ conversations with caregivers, purposeful response to stimuli, voluntary behavior. N: Cessation of random screaming episodes. Watched television and laughed at funny scenes. Stated his name and age. G: Meaningful interactions with caregivers. Lifted hands, counted to 5, and smiled on command.
Brefel-Courbon et al. 2007[24]	48, male, suicide attempt by hanging resulting in post-anoxic encephalopathy with minimally conscious state	Zolpidem 10 mg once/d Time to response: 20 min Duration of response: 2-3 h	Increased arousal; communicated with family; swallowed food; moved spontaneously in bed
Cohen et al. 2008[34]	35, male, cardiac arrest resulting in post-anoxic encephalopathy with minimally conscious state	Zolpidem 5 mg once a day → 10 mg in the morning and 5 mg in the evening → 10 mg twice/d, Time to response: 1 h Duration of response: 3-6 h depending on dosing	Zolpidem 5 mg once a day: Increased arousal and more interactive with caregivers. Could toss a football Zolpidem 10 mg/ 5 mg: Walked with assistance Zolpidem 10 mg/ 10 mg: Spoke more frequently and fluently. Walked unassisted.
Shames et al. 2008[35]	50, woman, cardiac arrest resulting in post-anoxic encephalopathy with minimally conscious state	Zolpidem 10 mg once/d Time to response: 30 min Duration of response: 3 h	Increased arousal. Alert and oriented to self and place. Cessation of athetoid movements. Regained full voluntary movements of all 4 extremities.
Parkinson disease, Parkinsonian features			
Daniele et al. 1997[36]	10 patients, mean age 69.9	Zolpidem 10 mg once/d In the responders (6/10 patients): Time to response: 45-60 min Duration of response: 2-4 h	6/10 patients showed motor improvement in facial expression, rigidity, akinesia, bradykinesia, posture and gait
Ruzicka et al. 2000[37]	45, female, Parkinson disease with generalized choreic dyskinesia post-levodopa administration	Zolpidem 5 mg per day Time to response: 30 min Duration of response: 2 h	Limb and trunk dyskinesia ceased on zolpidem
Farver et al. 2001[38]	31, male, schizoaffective disorder, illicit substance abuse (cocaine, amphetamines, marijuana) Patient developed parkinsonian rest tremor on antipsychotic medications. Tremor failed to respond to lowering the antipsychotic dose, adding anticholinergic or dopaminergic medications, or switching to novel antipsychotics.	Zolpidem 5 mg 4 times/d	The patient's tremors resolved within 1 month of zolpidem. With withdrawal of zolpidem the tremors returned. They ceased once again when zolpidem was restarted.

Reference	Age, sex, and clinical state	Dose	Description of response
Evidente 2002[14]	Three patients with X-linked early onset parkinsonism with dystonia (Lubag syndrome) Patient 1: 41, male Patient 2: 38, male Patient 3: 36, male	Patient 1: Zolpidem 10 mg every 2 h Time to response: 15 min Duration of response: 2 h Patient 2: Zolpidem 10 mg twice/d Time to response: 40 min Duration of response: 3 h Patient 3: Zolpidem 10 mg twice/d Time to response: 45 min Duration of response: 2 h	All three patients had improvement in dystonia and parkinsonism on zolpidem
Progressive supranuclear palsy (PSP)			
Daniele et al. 1999[39]	10 patients with PSP, mean age: unknown	Crossover trial: All patients received zolpidem 5 mg once a day, zolpidem 10 mg once a day, levodopa-carbidopa 250 mg-25 mg, and placebo. Time to response to zolpidem: 40-60 min Duration of response to zolpidem: 2 h	Zolpidem, unlike levodopa-carbidopa or placebo, improved saccadic eye movements in 4/10 patients on Zolpidem 10 mg/d
Mayr et al. 2002 [40]	61, male	Zolpidem 5 mg/d Time to response and duration of response: unknown	Patient showed improvement in vertical gaze palsy and parkinsonism. Patient showed response for 4 weeks. Second trial of zolpidem 2 months later showed no benefit.
Psychostimulant effect			
Gericke et al. 1994[41]	33, male, depression	Zolpidem 80 mg/d. Patient self-increased the dose from 10 mg per day due to insomnia and accidently discovered a stimulant effect at higher doses with improvement in depression. Time to stimulant response: 20 min Duration of response: 5-6 h	Generalized tonic-clonic seizure occurred at 80 mg per day.
Restless legs syndrome			
Bezerra et al. 2002[42]	8 patients, 3 male, Mean age: 50.8	Zolpidem 10 mg once/d Time to response: mean of 4 days Continued response on medication with no relapses	Positive response was noted in all patients, regardless of age and severity of restless legs syndrome
Sleepwalking with or without sleep related eating disorder (SRED)			
Sauvanet et al. 1988[4]	Post-marketing study showed 1 of 96 patients developed sleepwalking on zolpidem	Dose unknown	Data not available
Mendelson 1994[43]	20, male, participant in clinical study of nocturnal effects of sedative medications History of sleepwalking as a child.	Zolpidem 10 mg at bedtime before polysomnogram.	Investigator initiated auditory tone aroused patient out of stage 4 sleep. Patient stood up and walked on the bed. He was confused when sleep technician entered room and asked him to sit. He had vague memory of the events
Ganzoni et al. 1999[3]	Post-marketing study showed 7 of 1972 patients developed sleepwalking on zolpidem	Dose unknown	Data not available

Reference	Age, sex, and clinical state	Dose	Description of response
Harazin et al. 1999[44]	46, male, shift work related insomnia Negative history for sleepwalking	Zolpidem 10 mg at bedtime	Within 4 days of initiation of zolpidem he would arise at night to prepare a meal and eat it. He had no memory of the events. Medication was discontinued. Unknown whether events recurred off zolpidem.
Morgenthaler, et. al. 2002[45]	Five patients Mean age: 61.4, 3 male All 5 patients had restless legs syndrome, 3 had obstructive sleep apnea All 5 patients had a negative history for sleepwalking	Zolpidem 10-20 mg once/d	All exhibited sleepwalking and SRED 4/5 had vague memory of the events. Events ceased in all patients with zolpidem discontinuation
Sattar et al. 2003[46]	47, male, bipolar disorder. Negative history for sleepwalking.	Citalopram 40 mg once/d, valproic acid 250 mg twice/d, Zolpidem 5 mg at bedtime	Sleepwalking started when valproic acid was added to citalopram and zolpidem. He had no memory of the events. Events ceased when valproic acid was withdrawn and returned when valproic acid was restarted.
Sharma et al. 2005[47]	19, male, schizoaffective disorder Negative history for sleepwalking	Zolpidem 10 mg at bedtime	Within a few days of initiation of zolpidem he started to sleepwalk and talk incoherently. He had no memory of the events. Events ceased with zolpidem discontinuation.
Najjar 2007[48]	46, female, depression, obstructive sleep apnea on continuous positive airway pressure therapy Negative history for sleepwalking or parasomnias	Zolpidem extended-release form 6.25 mg once/d	Sleepwalking and SRED began immediately after initiation of zolpidem use and ceased immediately after it was discontinued.
Chiang et al. 2008[26]	Two patients: Patient 1: 75, female Patient 2: 70, female Both patients had restless legs syndrome, obstructive sleep apnea , and used continuous positive airway pressure therapy Both patients had a negative history for sleepwalking or SRED	Both patients had sleepwalking and SRED on zolpidem extended release 12.5 mg once/d. Neither patient experienced sleepwalking or SRED on the immediate release form of zolpidem.	Both patients experienced sleepwalking and SRED immediately after initiation of extended release zolpidem use and ceased immediately after it was discontinued
Sansone et al. 2008[49]	51, female,	Zolpidem 10 mg at bedtime	Arose at night to prepare a meal and eat it. She had no memory of the events. Events stopped with cessation of zolpidem.
Post-anoxic spasticity			
Shadan et al. 2004[50]	28, male, cardiac arrest resulting in post-anoxic spasticity	Zolpidem 10 mg once a day Time to response: 20 min Duration of response: 2-4 h	Decrease in muscle rigidity, spasticity and dystonic posturing
Spinocerebellar ataxia			
Claus et al. 2004[21]	5 members of a family, 3 male, Mean age: 33	Zolpidem 10 mg once/d Time to response: 1 h Duration of response: unknown	4/5 patients showed improvement of ataxia with zolpidem