The Role of Zolpidem in Treating Neurological Disabilities After Stroke, Trauma, and Hypoxia: Evidence Review and Clinical Trial Justification

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Abstract

During 15 years 23 clinical reports and 6 studies have demonstrated associations between sub-sedative doses of zolpidem and recoveries from brain damage due to strokes, trauma and hypoxia. Clinical findings include unexpected awakenings from vegetative states and regressions of stroke symptoms after dosing that disappear during elimination and reappear on repeat dosing. Initially SPECT scans showed improved perfusion within, around and distant from infarctions. Then PET scans and EEG detected renewed metabolic and neuronal activity. Placebo or a similar, GABA-ergic, sedative zopiclone has no such effect. The effect appears only several months after the injury, reflecting recent evidence in mice of substantial differences between the states of GABA receptors in acute and chronic repair phases of recovery. Zolpidem's good safety record and rapid absorption further indicate a need for more clinical trials.

Introduction

Over 15 years ago in South Africa, 30-year old Louis Viljoen, was in a vegetative state 3 years after a road traffic accident. He was given the sedative zolpidem one evening because he was thrashing about in his cot. Some twenty minutes later, to the bystanders' amazement, he suddenly became conscious and greeted his mother with the words 'Hello

Mom'.[1] This became a cause celebre and led to brain scans in Louis and other patients with brain damage to find any detectable changes that might explain this paradoxical reaction to a sedative.[2] Until then it was assumed that brain infarctions contained only irretrievably dead tissue, but the single-photon emission computed tomography (SPECT) scans in this first and later studies showed increased blood flow in parts of the infarctions, suggesting that fresh neuronal activity was occurring in these areas.[3] These startling reports caused others in several countries to try zolpidem in other patients with brain damage, often using positron emission tomography (PET) or electroencephalography (EEG) to show whether zolpidem was in fact inducing fresh neuronal activity, and they achieved similar results.[4-9,11-29,32] Individual reports continue to appear and more systematic investigations have extended to six published controlled clinical trials.[31-36]

This effect of zolpidem occurs at sub-sedative doses, so if new formulations can be developed that sustain it at that level, they could provide a uniquely effective treatment for established brain damage.

History of zolpidem as a treatment for brain damage

Reports of brain SPECT scanning results in three cases by Clauss et al in 2000[1], 2001[2] and 2004[3] prompted several more.[4-9] In 2009 Whyte et al wrote of their experience of a prospective, placebo-controlled trial in 18 patients with disorders of consciousness (DOC) in which they found one who responded to zolpidem.[10] More reports of studies in individual patients appeared[11-20] including one using magneto-encephalography (M-EEG) to detect activity within the infarcted area of a patient who suffered from aphasia.[19] Under double-blind conditions they compared zolpidem with placebo and another gamma amino butyric acid (GABA) agonist zopiclone, neither of which caused the increased intra-infarction activity or the relief from aphasia that were seen after zolpidem.

In 2011 Nyakala et al reported a clinical trial that included patients with strokes.[31] They enrolled 23 patients with injuries caused by: stroke 12, trauma 7, anaphylactic hypoxia 2,

drug overdose 1, birth injury decades before 1. Four patients suffered from disorders of consciousness (DOC) and 19 who were neurologically disabled but conscious. Clinical improvements were observed mostly in speech, limb function and balance assessed by the Tinetti Falls Efficacy Scale (TFES) which improved 11·3% overall (p = 0.0001). Ten of the 23 showed improvements in blindly-read SPECT scans and their mean change in TFES was 19·4% compared with 5·08% in the other 13 (p = 0·0081), implying a correlation between improved SPECT scans and clinical improvements.

Williams et al described three patients who had baseline total Coma Recovery Scale-Revised (CRS-R) scores ranging from 10–15 before zolpidem that rose to a ceiling total score of 23 after it. [32] This reflected improvements in all subscales, including recovery of functional movements, consistent communication, and elements of executive function. Additional changes included recovery of fluent verbal communication, writing and complex organized movements such as assembling block structures to match arbitrary configurations. Maximal total CRS-R scores consistently appeared within 1h after drug administration and apparently for longer duration after the second dose of the day than the corresponding first dose. These clinical improvements correlated with EEG changes in cortical areas.

Du et al[12] had assessed the effects of zolpidem in seven patients by PET and Cerebral State Index (CSI) and continued onto a much larger study in 165 patients in 2013 in which they used SPECT scans and CSI.[33] 127 patients remained after their first dose and were given 1 x 10mg daily for one week. In both brain contre-coup contusion and space-occupying brain compression groups mean CSI increased and mean burst suppression was reduced ($P < 0.05$) and cerebral perfusion in SPECT scans improved. They concluded that while cortex lesions responded, brain stem injuries did not.

Whyte et al investigated a further 84 patients with DOC in Minimally Conscious States (MCS) due to a variety of causes.[34] Their double-blind, placebo-controlled, multi-centre trial found

four ‘definite responders’, a 4·8% response rate, although assessors of their patients reported detecting some response in 33%.

Thonnard et al recruited a group of 60 patients with chronic (> 4 weeks’ duration) MCS in an open prospective study using the Coma Recovery Scale (CRS).[35] They detected signs of arousal in 12 patients, but found no statistically significant change overall. One patient had a significantly improved diagnosis, but that did not reappear on repeated dosing. They concluded that the remarkable cases in the literature represent only occasional responders. Their result may have been affected by including some patients who were less than four months from their injury since the centre in South Africa that investigated the first patient has found that patients do not respond if their injury was less than four months old (Nel HW Personal communication). Thonnard’s group later published a more positive outcome in a study of three patients who were all responders.[36] It was a study using placebo and healthy controls and assessments by the CRS and FluoroDeoxyGlucose PET (FDG-PET). Behaviorally, all patients recovered functional communication after administration of zolpidem (i.e., emergence from the MCS). FDG-PET showed increased metabolism in dorsolateral prefrontal and meso-frontal cortices after zolpidem, but not after placebo.

Purpose

This review aims to show whether there is sufficient evidence to justify the large cost of further clinical trials. This depends upon

- Safety
- Number and Quality of responses
- Proportion of responders
- Whether there are effective ways of measuring responses and
- Whether there is any other equivalent treatment

Methods

One of us (RC) has monitored the literature on brain damage and zolpidem for many years, accumulating a database available on-line.[17] The main search strategy for this review focused on PUB Med and Medline databases with the help of the postgraduate library of the Royal Surrey County Hospital and internet search engines using a series of word groups, eg: 'zolpidem brain damage', 'zolpidem stroke', zolpidem stroke reversal', ' zolpidem vegetative state' and 'zolpidem rehabilitation'. When this produced a report of the use of zolpidem in any form of brain injury, both acute and established, it was accepted for further scrutiny if the name of a journal was listed on the SciJournal Impact factor list. It was then checked for an established method for monitoring brain activity, namely: positron emission tomography (PET) electroencephalography (EEG) and its magnetic equivalent (M-EEG) and magnetic resonance imaging (MRI). We also accepted studies using the less established Cerebral State Monitor (CSM) when it was used to detect cerebral activity. All comments by researchers were noted and quoted references followed up if they were not already in our list, an iteration that detected two further reports. Major journal websites were also visited and searched by the same method.

Findings

The searches produced the list of publications in Tables 1 and 2 where they are classified in three categories. Reports of individual cases presented at scientific meetings were excluded because it appeared that they were published subsequently.

Category A. Six studies with defined groups of patients, laboratory assessments of brain function and a blinding element such as the study that required the assessors of SPECT scans to remain unaware of the dose and patients' clinical histories.[31] They are listed in Table 1 and include the one negative study that we found.

Category B. Also listed in Table 1, four reports of open studies that used placebos, or another comparator, and occasionally healthy volunteer controls, but which are not double-blind, mainly due to the manifest sedative effect of zolpidem at higher doses.

Category C and C+. 23 Reports of individuals' responses listed in Table 2. C+ reports meet the criteria for 'n-of-1' studies as listed by Glasziou et al when they proposed the criteria by which alternatives to strict, double-blind trials may identified.[38] They are: uniqueness of effect, timing with regard to dose and duration, repeated effect after each dose, and a double-blind procedure. C reports lack the last criterion but include sufficient correlations between dose and effect to make a zolpidem-induced effect probable. Ten of the 23 clinical findings were supported by positive brain function investigations.

Discussion

The reports provided a wide range of causes of brain damage, including trauma, hypoxia, encephalitis and meningitis. Early SPECT scan studies[3] showed increased cerebral blood flow within, adjacent to and remote from infarctions after zolpidem, which correlated with clinical improvements, suggesting that parts of tissue assumed to be irretrievably dead had been activated, as well as more distant areas. This possibility was confirmed in later trials by PET detecting metabolic changes[6,7,12,33,36] and EEG,[4, 6,18,21,32,33,34,37] magnetic resonance imaging (MRI)[26,32,37] and M-EEG[19] investigations detecting new neuronal activity. This evidence indicates that further definitive clinical trials are justified, depending upon: safety, the uniqueness and extent of the benefit for individual patients, the proportion of responders, and practical issues such as maintaining the effect when dosing must clearly remain below sedative levels.

Safety. In general an increased mortality risk, similar to smoking, has been reported in patients who use hypnotics including zolpidem[39] but it is not known if this is due to the sedation itself, the population that uses sedatives or whether it applies to patients who have

suffered brain damage. Overall, zolpidem has been used by millions over several decades during which it has gained an exceptional safety record, even in overdose, as surveyed by Wyss et al.[42] They reported that even with forty fold the normal 10mg dose no severe symptoms occurred in patients with zolpidem single-drug poisonings, while with triazolam coma was encountered in four cases (11%) and with midazolam also four cases (10%). Reports of adverse events are rare. For example Krystal et al reported that there were no serious adverse events in a thousand patients who took 12.5mg zolpidem for sleep at night for six months.[40] Clearly at higher doses zolpidem will sedate a patient, which might lead to falls in elderly patients, but there has been no evidence that it presents a greater risk in patients with brain damage. However, sedation may mask any beneficial effect and one report of that has appeared.[41] Chronic use as a sedative has engendered occasional reports of effects that disturb patients with low risk of life-threatening implications, such as antegrade amnesia, sleepwalking and hallucinations. They have not been reported in patients with brain damage.

Abrupt withdrawal of high long-term doses has produced a few reports of epileptic seizures. One was a 50 year old woman who took normal doses daily for five years then, due to tolerance, her dose was increased to 450mg per day in divided doses.[43] She abstained for 12 hours and then suffered an epileptic fit that she survived without permanent injury. Two reports were found of an epileptic seizure after long term high doses of zolpidem[44, 45] and one of a dependence syndrome in two patients with severe personality disorders who were also dependent on other drugs.[46] A 40 year old psychiatric patient taking zolpidem for spino-cerebellar ataxia was reported in 2011 to have escalated her daily dose to 1000mg, but she developed withdrawal seizures when some doses were missed.[47] These are rare cases, all of which were associated with personality disorders.

In zolpidem-brain damage studies Whyte et al[34] recorded adverse events in their cohort of 84 DOC patients in vegetative states of which only one was severe, a case of agitation that resolved as zolpidem was eliminated. Other events, more often seen in the active than

placebo group, were mild and self limiting, consisting mainly of sedation. This accords with Nel's experience of using zolpidem in over 1000 patients suffering from brain injuries (personal communication); nevertheless it would seem necessary to examine the safety of chronic use in any further clinical trials that take place.

Uniqueness. Zolpidem appears to have a unique effect. Other molecules are associated with arousal effects in patients with brain damage but reports are sparse and they are less practical. Baclofen, an agonist via the GABA 1B receptor, has engendered sporadic reports of improved consciousness in vegetative state patients, but only when the route of administration was intrathecal.[8,48] Zolpidem would be more practical due to its rapid absorption by mouth or sublingually. Amantadine has produced a faster rate of recovery in the acute phase after injury, but 'whether treatment with amantadine, as compared with placebo, improves the long-term outcome or simply accelerates recovery en route to an equivalent level of function remains unknown'.[49] This may be explained by the fact that zolpidem acts on the GABA-1A omega 1 subtype receptor while zopiclone, a GABA-ergic agonist on the omega 2 subtype, has had no effect in zolpidem responders (Nel HW, personal communication) and in one crossover study using M-EEG.[19]

Extent. One reason for suggesting more studies is precisely a lack of systematic evidence of the extent of the beneficial effect for an individual patient who has brain damage. However, when that patient recovers speech, limb or cognitive function it has a profound effect on quality of life and may even include savings to the health service when for example improved limb function reduces dependence on walking aids or daily help in the home. In one long-term, documented patient the beneficial effect has also increased with duration of treatment. He was the index patient LV who was treated daily for nearly ten years who improved steadily without adverse effects apart from the expected sedation. After six years his SPECT scan prior to a dose of zolpidem was much improved compared with his first scan, pari passu with his improved clinical state.[51]

Another dimension of extent is the range of injuries that responds to zolpidem. To date it includes brain damage due to: trauma, hypoxia, stroke and encephalitis, a finding that suggests a trial in one category of injury could be relevant to the others. Other case reports have shown some effect in more chronic or conditions, namely: dementia,[26,52] spino-cerebellar ataxia,[47,53] dystonia,[54] Parkinson's Disease,[55] dyskinesia/akathisia[56] and progressive supranuclear palsy.[57] A possible explanation may lie in the wide distribution of GABA receptors in the brain since they would be involved in the pathology of all these diseases, an hypothesis recently supported by evidence from GABA-ergic models in mice where it was concluded that enhancing phasic GABA signalling during the repair phase is beneficial for stroke recovery while tonic GABA signalling in the acute phase is not.[57] This helps to explain the absence of clinical effects of zolpidem for some 4 months after injury and its relevance to the chronic phase after brain injury.

An argument against the case for further trials could be that the proportion of responders appears to be low. On the other hand, we believe that the considerable improvements in quality of life in those who do respond counters the low proportion argument. In deep states of unconsciousness Whyte et al found four responders in 84 DOC patients (4·8%).[34] Du et al reported significant improvements in CSI and Burst Suppression analyses of CSM recordings in their group of 165 patients (despite mean times from injury being only around nine weeks), but a subgroup of 38 patients with brain stem injuries did not respond.[33] Snyman et al had no responders clinically or in PET scans in 3 children who were in a persistent vegetative state (PVS).[16] Having treated over 1000 patients, Nel has found that the proportion of responders may be higher when injuries are less severe, ie around 25%(personal communication).

It is essential to include reliable assessments of brain activity to complement clinical evidence as they may point to a central mechanism of effect rather than a peripheral stimulus of some sort. SPECT scans show increased blood flow which implies neuronal activation.

The link is strengthened when the increase correlates with clinical improvements such as those found by Nyakala et al using the TFES.[31] PET scans detect changes in glucose metabolism and studies using 18FDG have shown similar results to 99TcHMPAO SPECT studies. Although they do not measure neuronal activation as such, they do indicate increased metabolic activity and it would be surprising if no such increase occurred in the presence of increased clinical activity.[35] Methods that show neuronal activity itself are EEG (including CSM/CSI[12]) and M-EEG[19], the first detected after zolpidem in several case reports[4,6,18,23,30] and three trials.[33,34,37] Such a wide range of evidence accords with increased brain activity in responders after zolpidem.

Mechanism of Action. Several hypotheses have been proposed to explain the mechanism of zolpidem's therapeutic effect after brain injury, from enhanced GABA-A receptor states and brain dormancy reversal[2] to mesocircuit models[3,60,61], but none has been confirmed beyond doubt. A viable theory must account for its GABA-ergic, inhibitory mechanism and the lack of the effect for some 4 months after the acute phase of a brain injury. Hui et al have investigated GABA receptor states in mice with surgically induced strokes.[58] In the repair phase, after 4 weeks from the injury, they found increased numbers of alpha1 subunit-containing GABA-A receptors that enhance phasic (synaptic) GABA signalling. According to Clarkson these receptors seem to oppose the suppressive tonic (extrasynaptic) GABA signalling that is known to suppress brain after stroke and thereby enhance clinical recovery.[59] In follow-on experiments, Hui et al applied sub-sedative levels of zolpidem in the both the tonic and repair phases of recovery and found only in the repair phase that zolpidem enhanced phasic signalling and dramatically improved the rate of recovery from stroke. They conclude that this identifies ‘a novel therapeutic strategy and pharmacological target for stroke.’ The mesocircuit theory is advocated by Schiff [60] and Schiff and Posner[61] which involves increased levels of metabolism in large areas of the brain during recoveries. Under normal circumstances, the median spiny neurones (MSN's) dis-inhibit the central thalamus via the globus pallidus interna (GPi) so when MSN activity is reduced as a consequence of brain injury, central thalamic activity is also reduced. Since zolpidem directly

inhibits the GPi, it can substitute for the normal inhibition of the GPi from MSN's which permits a more normal level of central thalamic activity. The GABA-A alpha-1 subunit is expressed in large quantities in the globus pallidus interna and experimental studies support this mechanism of action [62]. Hence, the number or concentration of GABA-A receptors may be a critical factor in determining who responds to zolpidem and if severe brain injuries incur fewer of them, it may explain the lower incidence of responders in that condition.

Recommendations for further action. Due to the sedative action of zolpidem the main practical issue is to sustain the beneficial effect without somnolence. This appears to be feasible given the sparse mention of sedation or somnolence in the 23 case reports and 10 clinical studies. Whyte et al[33] give individual details of the arousal effect seen in their 84 patients and report that only one patient had somnolence that prevented assessments by the CRS-R; plus signs of decreased arousal twice in the two assessments per patient. Thonnard et al[35] do not report it in their 60 patients given 10mg doses, although none were responders. M-EEG, EEG and CSI findings were of activation rather than signs of sedation.[19,36,33] Avoiding sedation may be easier with newer formulations that use the sublingual route due to rapid onset of effect so that patients could take small top-up doses at intervals of 2-3 hours in similar fashion to asthmatics using inhalers.

However, no manufacturer is interested in developing this indication for zolpidem despite the extent of the evidence and the very large numbers of patients who could benefit. This might suggest that publicly funded studies should be done to define the quality and extent of the benefit, ideally in all three indications where numbers of patients are practical, namely stroke, trauma and hypoxia established for at least 4 months. It appears that other GABA-ergic sedatives do not have this effect so they would make useful positive controls more closely matching zolpidem than a non-sedative placebo. Funding limits may restrict the early trials to a moderate scale, enrolling some 50-60 patients, but enough to achieve a realistic estimate of the incidence of responders. If numbers have to be smaller, it would be appropriate to

show the existence of a beneficial effect with non-parametric statistical analysis rather than attempt to measure its extent. Trials would need clear entry criteria where patients have symptom complexes that can be measured reliably such as deficiencies in speech, hearing and balance, which implies patients with milder injuries who can comply with test procedures. That would complement Nel's finding after treating 1000 patients of higher response rates in milder cases for reasons unknown. We would recommend establishing the upper range of response rate because it would be most helpful to those making the decision to invest the large funds needed for full development. Another advantage of milder cases is that they may achieve a complete or almost complete resolution of symptoms, an advantage because it avoids a possible criticism of results from patients with severe PVS who may reach unprecedented levels of consciousness while not achieving full mobility or independence. Indeed if early studies could include assessments of dependence on helpers they would also indicate the likelihood of savings for health services and recouping the costs of development.

Conclusions

The extent of reports of clinical recoveries when patients with brain damage are given zolpidem indicates that further clinical trials of zolpidem are justified. Reports include evidence of renewed neuronal activity within infarctions that had been considered irretrievably dead, which implies recoveries beyond mere stimulation. The unique nature of the effect, a markedly positive risk-benefit ratio and the extent of the profound unmet need further indicate the urgency of continued development.

List of Acronyms

BOLD	Blood-Oxygen-Level Dependent contrast imaging in MRI
CRS	Coma Recovery Scale
CRS-R	Coma Recovery Scale Revised
CSI	Cerebral State Index
CSM	Cerebral State Monitor

DOC	Disorder of Consciousness
EEG	Electro Encephalography
FDG-PET	FluoroDeoxyGlucose- Positron Emission Tomography
FTD	Frontotemporal dementia
GABA	Gaba Amino Butyric Acid
MCS	Minimally Conscious State
M-EEG	Magneto Encephalography
MRI	Magnetic Resonance Image
MSN	Median Spiny Neurones
PET	Positron Emission Tomography
PVS	Persistent Vegetative Sate
RLAC	Rancho Los Amigos Cognitive scores
SPECT	Single-photon emission computed tomography
TFES	Tinetti Falls Efficacy Scale
99mTc HMPAO	Technetium hexamethylpropyleneamine oxime

Declarations of Interest

The authors report no declarations of interest.

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