A review of the evidence of zolpidem efficacy in neurological disability after brain damage due to stroke, trauma and hypoxia: A justification of further clinical trials

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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 single-photon emission computed tomography scans showed improved perfusion within, around and distant from infarctions. Then positron emission tomography scans and electroencephalography detected renewed metabolic and neuronal activity. Placebo or a similar, gamma-aminobutyric acid (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.

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, Gamma-Aminobutyric Acid; MCS, Minimally Conscious State; M-EEG, Magneto-Encephalography; MRI, Magnetic Resonance Image; MSN, Median Spiny Neurones; PET, Positron Emission Tomography; PVS, Persistent Vegetative State; RLAC, Rancho Los Amigos Cognitive scores; SPECT, Single-photon emission computed tomography; TFES, Tinetti Falls Efficacy Scale; 99mTc HMPAO, Technetium hexamethylpropyleneamine oxime

**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 célèbre and led to brain scans in Louis and other patients with brain damage to find any detectable change 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 others to investigate further [4–9]. In 2009, Whyte et al. wrote of their experience of a prospective, placebo-controlled trial in 18 patients with disorders of consciousness (DOCs) 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-aminobutyric acid (GABA) agonist zopiclone, neither of which caused the increased intra-infarction
activity or the relief from aphasia that were seen after zolpidem administration.

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 and birth injury decades before 1. Four patients suffered from DOCs, and 19 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 suffered from DOC with total Coma Recovery Scale-Revised (CRS-R) scores ranging from 10 to 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]. One hundred and twenty-seven patients remained after their first dose and were given 1×10 mg daily for one week. In both brain contrecoup 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, multicentre 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 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). Behaviourally, all patients recovered functional communication after the administration of zolpidem (i.e., emergence from the MCS). FDG-PET showed increased metabolism in dorsolateral prefrontal and meso-frontal cortices after zolpidem administration, 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 online [17]. The main search strategy for this review focused on PUBMed 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, e.g. ‘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, PET and 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 into 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
Table I. Published reports of controlled trials of zolpidem in post-acute brain damage.

| Report category | 1st Author | Year | Injury type | n | % response | Method of assessment | Result and authors' comment |
|-----------------|------------|------|-------------|---|------------|----------------------|-----------------------------|
| B 12            | Du B       | 2008 | Various     | 7 | 0          | PET scans and cerebral state monitor index (CSI) | Evidence of arousal in PET and CSI |
| B 10            | Whyte J    | 2009 | PVS cases of different causes | 15 | 6.7 | CRS-R assessments. | 1/15 had a 'clinically significant response, which altered his assessment from the vegetative state to minimally conscious' |
| B 15            | Manzi G    | 2010 | Prospective PVS of various causes occurring 4 weeks previously <100 on Barthel Index | 15 | 0 | Coma Recovery Scale | No effect detected after 1 × 10 mg dose for 7 days. Injuries were only 4 weeks previously, so patients were not in the repair phase as defined by Steinberg et al. [57]. 11% in mean reduction of TFES score (p = 0.0001) in all patients; divided between a) the 10/23 who had improved SPECT scans plus a 19.4% improvement in TFES and b) non-SPECT responders with a 5% mean improvement (p = 0.0081), indicating that those who had SPECT scan activation had better TFES scores. |
| A 20            | Nyakala NE | 2010 | Stroke 12, TBI 7 Hypoxia from Anaphylaxis 2 Drug overdose 1 Birth injury 1 | 23 | 43 | Blinoly-read SPECT scans. Tinetti Falls Efficacy Scale (TFES) | Signs of arousal. Behavioural improvements: verbal fluency, functional use of objects, functional communication correlating with reduction in pathological slow-wave activity. Changes in brain metabolism (PET) in anterior forebrain with the largest in the lateral frontal cortex. 127 patients remained after 1st dose. Given 1 × 10 mg daily for 1 week. In two groups: patients with contre-coup lesions and symptoms of brain compression due to space occupying lesions. CSI increased and burst suppression reduced (p < 0.05) and SPECT perfusion increased. No response seen in brain stem injuries. A 5% response rate. 1 case of agitation otherwise occasional somnolence and some mild, transient adverse events only. |
| A 32            | Williams ST | 2013 | TBI, Stroke, TBI/hypoxic in MCS | 3 | NA | EEG of power and coherence at ~6–10 Hz and in power at ~15–30 Hz. PET | 12/60 showed some improvement or change in CRS scale but no change in diagnosis. Study included patients 4 weeks after they had been injured when zolpidem often does not have its effect until at least 12 weeks. Patients recovered functional communication after zolpidem but not placebo. |
| A 33            | Du B       | 2013 | PVS of various causes divided into 4 groups by SPECT scan evidence of brain damage areas | 165 | NA2 | Scans at 1 h post dose. Tc-ECD SPECT CSM | Yawning in 7/8 patients indicating activation. EEG activation in cortical areas. Vagolytic chronotropic cardiac effect without increased vagomotor sympathetic tone. |
| A 34            | Whyte J    | 2014 | MCS of various causes. | 84 | 5 | Double-blind and placebo-controlled. Clinical signs of lighter consciousness in 4/84 patients vis the CRS-R | 19% response rate. 1 case of agitation otherwise occasional somnolence and some mild, transient adverse events only. |
| B 35            | Thonnard M | 2014 | Various. 52% traumatic. | 60 | 20 | Coma Recovery Scale-Revised | 12/60 showed some improvement or change in CRS scale but no change in diagnosis. Study included patients 4 weeks after they had been injured when zolpidem often does not have its effect until at least 12 weeks. Patients recovered functional communication after zolpidem but not placebo. |
| A 35            | Chatelle C | 2014 | MCS due to Hypoxia | 3 | NA1 | Coma Recovery Scale-Revised (CRS-R Giacino et al 2004) FDG PET | Patients compared with 8 placebo controlled subjects. 1 patient reported in ref 17 |
| A 36            | Machado C  | 2014 | PVS due to post-anoxic encephalopathy. Central transcortical hemiation. Hydrocephalus. Basilar artery stroke | 7 | NA1 | CRS-R MRI EEG | Yawning in 7/8 patients indicating activation. EEG activation in cortical areas. Vagolytic chronotropic cardiac effect without increased vagomotor sympathetic tone. |

Defined in Methods. Categories A & B = Controlled trials with and without blinding. % responders: NA1 = Not applicable due to selection of known responders, NA2 due to lack of evidence of selection methods.
Published reports of new individual cases of zolpidem effect in post-acute brain damage.

**Result and authors**

Cessation of athetoid movements, regained speech although somewhat impaired in spasticity and global cognitive scores (RLAC)

Marked improvement in apathy but no significant effect in cognitive testing

Increased blood flow within infarctions that correlated with clinical improvements

Maintained on a dose of 2.5 mg 4 hourly 'without evidence of toxicity or tolerance'

Regained speech although somewhat fragmentary. Increased perfusion in infarction site indicated hypofunction of the frontal lobe.

Cessation of athetoid movements, regained speech and ability to perform various tasks including self-feeding

Cessation of disabling apathy...superior frontal region, "marked improvement in her neurological function."

No difference between zolpidem and placebo. Coincident with speech improvement. Marked improvement in apathy but no significant effect in cognitive testing

EEG Activation

Transient increased BOLD signal localized in the left frontal cortex and bilateral anterior cingulate areas, L thalamus and R head of caudate nucleus. Increased N-Acetyl-Aspartate, Glutamine-glutamate and lactate in same frontal region.

Case used to illustrate importance of noticing unexpected responses to treatment.

**Table II. Published reports of new individual cases of zolpidem effect in post-acute brain damage.**

| Report type* Ref N° | 1st author | Year | Injury type | n | Method of assessment | Result and authors' comment |
|---------------------|------------|------|-------------|---|----------------------|-----------------------------|
| C 1                 | Clauss RP  | 2000 | TBI         | 1 | Clinical signs, SPECT | Arousal from a deep vegetative state |
| C 2                 | Clauss RP  | 2001 | PVS due to TBI(2) and hypoxia (1) | 2 | Glasgow Coma and Rancho Los Amigos Cognitive scores (RLAC) | Improvements in both scores after 3–6 years' daily treatment with zolpidem without adverse effects. Plus follow-up of 1 case in earlier report (ref 1) |
| C 3                 | Clauss RP  | 2004 | Severe aphasia post stroke | 3 | Clinical signs and RLAC | Increased blood flow within infarctions that correlated with clinical improvements |
| C+ 4                | Ginsberg DL | 2004 | Severe aphasia post stroke | 1 | SPECT EEG MRI | Marked improvement in aphasia |
| C 5                 | Shadan FF  | 2004 | Post-anoxic spasticity after cardiac arrest | 1 | Clinical signs over 4 years with 'marked improvement' in spasticity and global performance. | Maintained on a dose of 2.5 mg 4 hourly 'without evidence of toxicity or tolerance' |
| C 6                 | Cohen L    | 2004 | Post stroke aphasia | 1 | EEG PET | Regained speech although somewhat fragmentary. Increased perfusion in infarction site indicated hypofunction of the frontal lobe. |
| C+ 7                | Brefel-Courbon C | 2007 | Akinetic mutism | 1 | Motor and cognitive tests 18F-fluorodeoxyglucose and H2O18 PET | Transient cognitive and motor improvements Activation of anterior cingulate and orbitofrontal cortices after zolpidem not seen after placebo. |
| C 8                 | Shames JL  | 2008 | Severe anoxic brain injury | 1 | Clinical responses | Cessation of athetoid movements, regained speech and ability to perform various tasks including self-feeding |
| C 9                 | Singh R    | 2008 | MCS due to TBI | 1 | Clinical responses | No difference from baseline, some symptoms worse due to sedation. |
| C 10                | Cohen SI   | 2008 | Anoxic brain injury post cardiac arrest | 1 | Clinical responses | 'Dramatic increase in the level of alertness', including improved speech and gait. |
| C 11                | Adamiak G  | 2009 | Ischaemic stroke in cerebellum, hydrocephalus, brain stem damage | 1 | Clinical signs of recovery | |
| C 12                | Shyu C     | 2011 | Cerebellar mutism syndrome due to brain surgery in a child | 1 | Clinical signs of recovery | Recovery of speech |
| C+ 13               | Snyman N   | 2010 | Paediatric PVS of various cause | 3 | Rancho levels of cognitive functioning scale, the coma/near-coma scale and F (18)-FDG PET. | No difference between zolpidem and placebo. |
| C+ 14               | Hall SD    | 2010 | Post-stroke aphasia | 1 | Single-blind Magneto-encephalography and speech tests. | Fresh activity within an established infarction only after zolpidem and not zopiclone or placebo. Coincident with speech improvement. Marked improvement in apathy but no significant effect in cognitive testing |
| C+ 15               | Mathieu S  | 2011 | Apathy due to stroke and anoxic brain damage | 2 | Clinical signs | |
| C+ 16               | Machado C  | 2011 | PVS cause | 1 | Clinical signs EEG | EEG Activation |
| C+ 17               | Appu M     | 2013 | 16-year-old girl with anti-N-methyl-d-aspartate receptor encephalitis | 1 | Clinical signs | "marked improvement in her neurological function." |
| C+ 18               | Rodriguez-Rojas R | 2013 | PVS and a normal age-matched placebo control subject. | 1 | MRI BOLD and metabolite spectral signals |Transient increased BOLD signal localized in the left frontal cortex and bilateral anterior cingulate areas, L thalamus and R head of caudate nucleus. Increased N-Acetyl-Aspartate, Glutamine-glutamate and lactate in same frontal region. |
| C 19                | Isomura S  | 2013 | Fronto-Temporal Dementia with reduced brain perfusion. | 1 | Mini-Mental State Examination score was 21/30 with disturbances in orientation, attention, and calculation, while Frontal Assessment Battery score was 11/18 with signs of perseverance that indicated hypofunction of the frontal lobe. | |
| C 20                | Autret K   | 2013 | 'disabling apathy' after a stroke. | 1 | Double-blind and placebo-controlled dosing over 2 weeks using the Apathy Inventory and the Behavioral Dys-executive Syndrome Inventory. | ‘...dramatic improvement’. No adverse events. |
| C 21                | Kaufman KR | 2014 | Hypoxia post drug overdose and myocardial infarction | 1 | 9-year follow-up of clinical responses to 10 m ×3 daily that included talking to parents for first time in 4 years. | Required 20 mg dose for maximum effect which did not cause undue sedation. Patient also on lamotrigine and amantadine. |
| C 22                | Calabro RS | 2015 | Cardiac arrest hypoxia 3 y before | 1 | CRS-R MRI EEG | Response emerged only when dose reached 20 mg optimized at 30 mg without undue adverse event. |
| C 23                | Duraski SA | 2015 | PVS after hypoxic brain injury | 1 | Clinical signs | Case used to illustrate importance of noticing unexpected responses to treatment. |

*Defined in Methods. Categories: C+ = individual reports with blinding, C without blinding. n = number of patients.
histories. 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 are 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 be 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] 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 40-fold of the normal 10 mg 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 12.5 mg 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 450 mg 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 1000 mg, 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 counter 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, i.e. 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 [3,51,52], 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 (MSNs) disinhibit 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 Gpis, it can substitute for the normal inhibition of the Gpis from MSNs, 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. Thomnard et al. [35] do not report it in their 60 patients given 10 mg 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.

Declaration of interest

The authors report no declarations of interest.

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