

Zolpidem and restoration of consciousness – fact or fiction?

To the Editor: Recently the magical effect of zolpidem in bringing people in a vegetative state back to life was proclaimed in the general media. Since then physicians, including paediatricians, have been flooded by hopeful individuals seeking treatment for a wide variety of cerebral pathologies. Looking at three recent publications on this topic, all may not be as it was made out to be.

Zolpidem is a short-acting non-benzodiazepine gamma-aminobutyric acid agonist hypnotic approved for the treatment of insomnia. It has been shown to have a paradoxical effect in some patients with disorders of consciousness, leading to improvement of arousal and cognitive abilities. It has been suggested, and partly proven, that zolpidem disinhibits the globus pallidus interna, and in that way increases the thalamic excitatory role on the frontal lobes.

After a cerebral insult, patients may stay in a prolonged period of unconsciousness. They usually evolve from a comatose state to a vegetative state (eyes open but only showing reflex behaviours) to a minimally conscious state (MCS). This state is characterised by inconsistent reproducible evidence of awareness. If these are present without command following, it is classified as MCS-, and with command following as MCS+. From a research perspective, emergence from an MCS is characterised by recovery of functional communication and/or functional object use.^[3]

Several case studies have shown that zolpidem effected impressive recoveries in patients with severe brain damage of various causes. However, this effect occurs in only 5 - 7% of patients. It is important to realise that there is not always significant functional recovery; patients may regain the ability to follow simple commands, recognise objects and regain some communication, but unfortunately the effect lasts for about 4 hours (the half-life is 2.4 hours) and is often followed by increased somnolence.

The only placebo-controlled, double blind, single-dose crossover study was published last year.^[1] A very complex research design, involving a cohort of 84 participants (>18 years of age) with traumatic and non-traumatic disorders of consciousness of at least 4 months' duration, found that only 4.8% responded to zolpidem. In this study, all responders were male with a median age of 34 years. Responders could not be distinguished in advance from non-responders, although those

who did improve were more likely to have some signs of consciousness at baseline. The effect was usually apparent by the first hour after drug administration, but was already diminished or absent after one further hour. Side-effects were rated as mild and no intervention was required. Post-response somnolence was seen in several participants. While 10 mg was the dose used in this study, other studies have shown an increased effect with 20 mg. In one study a responder had been treated (on a three times a day dose) for more than 9 years without habituation.^[2] The majority of persons who benefitted from zolpidem required other medications such as amantadine and lamotrigene to improve function.

Conclusions:

- There are no scientific data to support the use of zolpidem in children for restoration of consciousness.
- There is a small chance ($\pm 5\%$) that patients in a vegetative state will respond favourably.
- The effect of zolpidem is specific for patients in an MCS (probably MCS+) and has not been shown for all neurological conditions.
- Even in those patients who respond, functioning may not be completely restored.
- Lifelong treatment appears to be necessary, with multiple doses daily. There is no evidence whether it could be addictive or not.
- In patients in a vegetative state or MCS, it may be worthwhile to consider one dose of 10 mg zolpidem to establish whether or not there is a response.

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*Naidoo R, Muckart D. The wrong and wounding road: Paediatric polytrauma admitted to a level I trauma intensive care unit over a 5-year period. *S Afr Med J* 2015;105(10):823-826. [<http://dx.doi.org/10.7196/SAMJnew.8090>]

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*Stein C, Wallis L, Adetunji O. Meeting national response time targets for priority 1 incidents in an urban emergency medical services system in South Africa: More ambulances won't help. *S Afr Med J* 2015;105(10):840-844. [<http://dx.doi.org/10.7196/SAMJnew.8273>]