Awakened by a sleeping pill

Characteristic changes in brain activity accompany the paradoxical increase in alertness observed in some patients with severe brain injury when they are treated with the sleeping pill zolpidem.

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Image Brain activity in a patient with severe brain injury before (blue) and after (red) zolpidem
alpha 1) which are expressed on inhibitory neurons in the globus pallidus. Schiff and Posner therefore proposed that zolpidem blocks the inhibitory inputs from this structure to the thalamus, thus allowing the thalamus to excite the cortex and help restore cognitive and motor functions.

Although functional improvement following zolpidem is well documented, it is also rare. Now, Williams et al.—who are based at various institutions in Belgium and the US—offer significant insights into the zolpidem paradox based on a study of three severe brain injury patients with strong arousal responses to the drug. The three patients, who had each experienced brain injury via a different mechanism, were tested on and off zolpidem using electrodes attached to the scalp to measure changes in the brain's electrical activity. Off zolpidem, all three showed strong brain waves with an unusually low frequency (between 6 and 10 Hertz), which were most prominent over fronto-central regions of the scalp, and which were highly coherent within and between hemispheres. Zolpidem sharply reduced the strength and coherence of the 6-10 Hz activity, and led to an increase in the average frequencies of brain waves (15-30 Hz). These changes correlated with the improvements in alertness seen in the patients.

By linking their clinical observations to in vitro and in vivo neurophysiology studies, Williams et al. reasoned that the 6-10 Hz oscillations probably arise from the intrinsic membrane properties of the damaged neurons in the cortex. They suggest that the brain waves become coherent because those brain areas with residual electrical activity that remain connected will have a tendency to begin firing together at a common frequency. They therefore interpret the coherent 6-10 Hz brain waves as a marker of reserve capacity that could be recruited to restore function, for example, through the use of drugs such as amantidine and zolpidem, or devices such as deep brain stimulation and transcranial magnetic stimulation. Zolpidem probably works by breaking up the coherence in the network through the mechanism outlined above. Williams et al. thus offer new insights into the therapeutic use of zolpidem and suggest a potential diagnostic and prognostic brain wave signature that is easy to measure.

Along with the scientific findings, other lessons can be learned from this study. The integration of clinical practice, pharmacology, formal behavioral testing and basic neurophysiological reasoning into an informative observational study establishes a paradigm which others in clinical neuroscience should emulate. These findings also support the need for a larger clinical trial to evaluate the effects of zolpidem on the recovery of brain function in patients with severe brain injury. Given that zolpidem is only effective in a small number of patients, and there is extensive variation in the expression of GABA receptor subtypes between individuals (Kang et al., 2011), these studies should include genetic profiling. Future work will help to identify those patients most likely to benefit from zolpidem and the best therapeutic regimen to use, as well as the diagnostic and prognostic value of the 6-10 Hz brain waves.

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