Author's reply: I thank Katz *et al* for their insightful comments on this complex topic. I am familiar with their work but, as they suspected, unfortunately removed their 2004 reference from the final version of my editorial because of space restrictions imposed by the *Journal*. In fact, I reluctantly removed an entire section concerning the value of predicting improvement based on early response in certain psychopathological domains. Katz *et al* appear to be one of the few groups to examine the issue of differential response in various domains in sufficient detail (Farabaugh *et al*, 2005). As they recognise, the purpose of an editorial is not to provide an exhaustive review but a synopsis of studies of outstanding interest. Since submitting this editorial a year ago, colleagues and I have nearly completed a more thorough review of this topic, including the work of the San Antonio group and the parallel research that challenges the delayed onset of antipsychotics (Agid *et al* 2003). I would very much welcome readers' observations regarding the rapidity and measurement of onset of action of mood stabilisers and electroconvulsive therapy, which have received relatively little attention to date.

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A. J. Mitchell Department of Liaison Psychiatry, Brandon Unit, Leicester General Hospital, Leicester LE5 4PW, UK. E-mail: alex.mitchell@leicspart.nhs.uk

Psychotropic complementary medicines

The recent review by Werneke *et al* (2006) contains substantive errors and omissions regarding the *iboga* alkaloid ibogaine and its synthetic congener 18-methoxycoronaridine (18-MC). The review cites a single paper published in 1994 consisting of seven case reports and overlooks two larger studies on the use of ibogaine for the treatment of opioid withdrawal in 32 (Mash *et al*, 2001) and 33 patients (Alper *et al*, 1999). These were retrieved on Medline using the search terms stated by Werneke *et al*. The authors incorrectly state that clinical trials of ibogaine were abandoned because of cerebellar toxicity: this has been limited to the rat at higher doses than those that diminish drug self-administration and opioid withdrawal, and has not been evident in primate or mouse models (Alper, 2001). In 1993 the US Food and Drug Administration authorised Phase I clinical studies in which humans were given ibogaine. These studies were halted only because of a contractual dispute among the study sponsors and not because of safety issues.

Table 6 of Werneke *et al*'s review states that '18-MC binds to the NMDA [*N*-methyl-D-aspartate] receptor' and that this is because of its putative anti-addictive mechanism of action. Mash *et al* (1995) is cited but this paper makes no mention of 18-MC, which lacks significant affinity for the NMDA receptor but is a potent antagonist at the $\alpha_3\beta_4$ nicotinic receptor (Maisonneuve & Glick, 2003). The statement that ibogaine blocks 'the dopamine response in general' is inaccurate, as ibogaine does not have the properties of a dopamine receptor antagonist and does not decrease dopamine release in all brain regions (Maisonneuve *et al*, 1991).

Werneke *et al* stated that 'All recovered papers were reviewed for further relevant references', which would have led, among other sources, to an entire volume devoted to ibogaine of the Medline-indexed serial *The Alkaloids* (Alper & Cordell, 2001) and the additional references cited here. Systematic implementation of the stated search strategy and careful and accurate reading of the papers that were retrieved would have provided a far more credible evidence basis regarding the use of *iboga* alkaloids for the pharmacotherapy of addiction.

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K. R. Alper Departments of Psychiatry and Neurology, New York University School of Medicine, New York, NY 10016, USA. E-mail: kral@nyu.edu

S. D. Glick Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, New York, USA

Author's reply: *Iboga* research remains controversial (Vastag, 2005). Alper & Glick refer to clinical evidence from 'two larger studies'. However, in these papers it is acknowledged that there is no substantial properly conducted trial available. These studies are difficult to interpret and mainly report treatment of acute opiate detoxification – not the topic of our review. It remains unclear how the patients were selected from the sampling frame. The first series includes a subset of 33 patients treated in hotel rooms or apartments in the USA and The Netherlands between 1962 and 1963 and 1989 and 1993 respectively (Alper *et al*, 1999). These are referred to as case reports in our review. The second series of 32 patients was equally difficult to rate. Thirty-two patients were treated in a private facility in 'offshore studies' but substantially more patients may have been treated (Vastag 2005) and information on inclusion and exclusion criteria for the individual patients is not available. In an evidence-based review, this would be difficult to accept. For instance, in meta-analyses of randomised controlled trials, open-label trials would not be included even if they were positive. With regard to longer-term abstinence, Mash *et al* (2001) suggested that 'many' patients were successful but the supporting data were not presented. Notably, in a series of 27 patients, possibly a subset of the 32, reported 1 year earlier, longer-term outcomes were not presented either (Mash *et al*, 2000).

With regard to safety concerns, cerebellar degeneration has been reported in

https://doi.org/10.1192/bjp.188.6.587-b Published online by Cambridge University Press

rat experiments (Xu *et al*, 2000). The absence of similar findings in mouse experiments does not imply that ibogaine is safe in humans. Reports of eight deaths after ibogaine use between 1990 and 2006 have been compiled (http://myeboga.com/fatalities.html). This source notes that more deaths might have occurred but might have not been reported owing to the 'underground nature of ibogaine treatment'. One death occurred at a dose of 4.5 mg/kg orally, a much lower dose than used in the rat experiments. Health problems associated with substance misuse or potentiation of ibogaine toxicity when used with heroin have been implicated. Alper *et al* (1999) when referring to one of the fatalities quoted Vocci, the Director of the Medication Development Division, National Institute on Drug Abuse (MDD–NIDA), that 'this incident was a significant factor in the decision not to pursue a clinical trial of ibogaine following the NIDA review meeting held in March of 1995'.

The antagonism at the $\alpha_3\beta_4$ nicotinic receptor should have been highlighted as a therapeutic target for the modulation of drug seeking but this would not have changed our conclusions since we have not doubted the potential efficacy of ibogaine. However, we maintain that ibogaine and *iboga* extracts may not be safe and thus should not be recommended. Ibogaine derivatives with an improved therapeutic index may prove clinically useful in the future. These are likely to be synthetic, thereby leaving the realm of complementary medicine.

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U. Werneke Department of Psychiatry, Homerton University Hospital, London E9 6SR, UK. E-mail: Ursula.werneke@elcmht.nhs.uk

One hundred years ago

The Medico-Psychological Association of Great Britain and Ireland

THE quarterly general meeting of the Association was held on Thursday, May 31st, at the Medical Society's Rooms, Chandos Street, London, W., under the presidency of Dr. OUTTERSON WOOD.

Epilepsy and changes in the blood and nervous system

Dr. JOHN TURNER read a paper entitled The Relation of Epilepsy to Changes in the Blood and Central Nervous System. He stated that epilepsy was the result of a double cause or tendency, the one an inherently-defective nervous system from a hereditarily-vicious organization, and the other some morbid condition of the blood whereby it shows a special tendency to intravascular clotting, and that the immediate cause of the fits is sudden stasis of the blood stream, resulting from the blocking of cerebral vessels by these intravascular clots. The fits he regarded as only a symptom of the general epileptic condition. Further investigations were related as to the coagulability of the blood in epileptics, which was shown to increase at the times of *petit mal*, *grand mal*, and stasis. Forms of changes in the nerve cells were shown, resembling those described as *réaction à distance*, and persistence of large numbers of subcortical nerve cells was shown. The author also referred to experimental work by ligature of the cerebral arteries in the dog, with acute forms of cell changes. The blood was shown to have a large number of blood plates, and specimens were shown of different forms of intravascular clotting, probably in a large measure derived from amalgamation of the blood plates. Small cortical haemorrhages were also described and shown on the screen, which could be traced to rupture of a vessel blocked up by the clots of coagulated blood referred to.

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Researched by Henry Rollin, Emeritus Consultant Psychiatrist, Horton Hospital, Epsom, Surrey

https://doi.org/10.1192/bjp.188.6.587-b Published online by Cambridge University Press