LETTER TO THE EDITOR
Response to Ameisen
Giovanni Addolorato1,*, Lorenzo Leggio1,2 and on behalf of all authors

1Institute of Internal Medicine, Catholic University of Rome, Largo A. Gemelli 8, I-00168 Rome, Italy and 2Center for Alcohol and Addiction Studies, Brown University Medical School, Providence, RI, USA
*Corresponding author. Tel: +39-06-30155650; Fax: +39-06-35502775; E-mail: g.addolorato@rm.unicatt.it

We thank Dr Ameisen for his interest on our manuscript (Addolorato et al., 2011) and appreciate the opportunity to respond to his comments. As noted by Dr Ameisen (Ameisen, 2011), in our manuscript, we refer not only to his case report (Ameisen, 2005), but also to the case report by Bucknam (2007). We appreciate Dr Ameisen’s clarification that in his own case report high-dose baclofen suppressed (as opposed to reduced) alcohol craving and consumption. Dr Ameisen correctly states that Bucknam’s title and abstract report the word ‘suppression’; however, the full-length text of Bucknam (2007) leads to the surprising discovery that the patient described a dramatic reduction (but not suppression) in alcohol craving and consumption.

We did not mean to misinterpret Dr Ameisen’s opinion. Rather, we provided an overall ‘take home’ message based on both case reports (Ameisen, 2005; Bucknam, 2007) given that high-dose baclofen did not have an identical effect in these two patients.

(We would point out too, that in Agabio’s case report (Agabio et al., 2007), mentioned by Dr Ameisen where the patient’s alcohol craving and drinking were suppressed, this happened from the beginning of the treatment with baclofen 30 mg/day, the same dose used in our previous trials.)

Dr Ameisen uses the word ‘suppression’ to indicate that alcohol craving and consumption were completely stopped. Beyond the anecdotal reports mentioned above, we have already reported in our double-blind, placebo-controlled, randomized clinical trials (DBPCRCTs) that baclofen 30 mg/day stopped (i.e. suppressed) completely alcohol consumption in a high percentage of the study patients (Addolorato et al., 2002, 2007). Similarly, while we reported the statistically significant effect of baclofen, as compared with placebo, in reducing alcohol craving in the whole samples of our controlled trials (e.g. Addolorato et al., 2002, 2007), on the other hand we note that in some patients treated with baclofen, alcohol craving was ‘suppressed’ (i.e. psychometric craving scores of zero).

In other words, we agree with Dr Ameisen that baclofen can ‘suppress’ alcohol dependence in some individuals, but at this stage we cannot say if this effect (i.e. suppression, as opposed to reduction) is merely a dose-dependent effect, given that this has been described even with 30 mg/day. Given the heterogeneity of the alcohol-dependent population (Leggio et al., 2009), it is likely the several factors might explain why the response to baclofen can be different across different patients and range from a robust effect (Addolorato et al., 2002, 2007) to the lack of differences between baclofen and placebo (Garbutt et al., 2010). We have hypothesized, for example, that differences in the severity of alcohol dependence (i.e. severity of alcohol withdrawal, amount of alcohol drinking, anxiety) can explain, at least partially, the differences in the response to baclofen (Leggio et al., 2010).

We share with Dr Ameisen the importance of testing doses of baclofen >30 mg/day in order to see if higher doses could lead to a higher efficacy of baclofen in treating alcohol dependence. This is the reason why, for example, we developed a protocol and performed a dose-ranging (60 vs. 30 mg/day) DBPCRCT recently described (Addolorato et al., 2011). While anecdotal reports (Ameisen, 2005; Bucknam, 2007) and open-label observations (Ameisen and De Beaurepaire, 2010) represent important early-stage steps, on the other hand, no conclusions can be drawn until DBPCRCTs under well-controlled and rigorous conditions are performed with the high doses proposed by Dr Ameisen. This is especially important if we keep in mind that the doses proposed by Dr Ameisen highly exceed the doses for which baclofen is approved for its current clinical indication (muscular spasticity) in several countries (e.g. 75 mg/day in Italy, 100 mg/day in the UK and 80 mg/day in the US). Dr Ameisen mentions ‘well established safety of baclofen at up to 300 mg/day for a benign condition (muscular spasticity)’. Although the use of high-dose baclofen in neurological settings has been reported (Smith et al., 1991), and was also supported by a personal communication in his original report (Ameisen, 2005), sedative side-effects are typically dose-dependent and may represent a reason limiting the use of baclofen in neurological settings (Dario and Tomei, 2004; Montane et al., 2004). It is possible that tolerance to baclofen is different in patients with neurological disorders vs. alcoholic patients. For example, we have described a cross-tolerance to the sedative effects of baclofen and alcohol in our alcohol-dependent patients (Addolorato et al., 2005). This is consistent with the very safe profile of our DBPCRCTs with baclofen 30 mg/day (Addolorato et al., 2002, 2007) and 60 mg/day (Addolorato et al., 2011), where sedation has never been a major safety concern. However, the doses proposed by Dr Ameisen greatly exceed those used in clinical practice for neurological diseases and in our DBPCRCTs. Indeed, while in his comment to our manuscript Dr Ameisen focuses on the dose of 270 mg/day described in his own case report, we note that Dr Ameisen himself reported there that at the dose of 270 mg/day somnolence became an inconvenient side-effect, and therefore the dose was progressively reduced to 120 mg/day (Ameisen, 2005).

In summary, no conclusions can be drawn on the use of very high doses of baclofen for alcohol dependence until
trials with rigorous safety monitoring and using controlled designs (i.e. DBPCRCTs) fully address not only the efficacy but also the safety of high-dose baclofen to treat alcoholic patients.

REFERENCES


