American College of Neuropsychopharmacology

RESEARCH HIGHLIGHT

The GABA-B receptor agonist baclofen helps patients with alcohol use disorder: why these findings matter

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The efficacy of the Food and Drug Administration (FDA)-approved medications for alcohol use disorder (AUD) is evidence-based and indisputable [1, 2]. Although not all medications always work for all patients, skepticism often contributes to the lack of their wider use in clinical practice. Therefore, a critical goal is expanding their use in clinical practice, so that more and more patients with AUD may benefit from these treatments.

The identification of new pharmacological targets and the development of new medications for AUD are also critical goals. Inspired by initial rodent work [3], researchers started testing the GABA-B receptor agonist baclofen in patients with AUD. However, human studies have generated inconsistent results, which have led to conflicting opinions and have left the question on the potential role of baclofen in AUD treatment unanswered. This uncertainly has been amplified by some skepticism because the baclofen studies were mainly positive in Europe but negative in the U.S. For example, baclofen 30 mg/day was effective in a trial, the first of its kind, in patients with AUD and cirrhosis in Europe [4], while another trial conducted by Garbutt and colleagues in the U.S. did not show differences between baclofen 30 mg/day and placebo [5]. The main authors of these two studies jointly pointed out the need for precision medicine approaches, as there were clear differences in patient characteristics between the U.S. and European studies, the latter reporting higher severity of dependence and drinking levels and receiving shorter behavioral interventions [6].

Meanwhile, the attention on the baclofen/AUD story was captured by a best-selling book authored by a French physician claiming that his own AUD was cured by self-prescribing high doses of baclofen (up to 270 mg/day). International mass media featured this book. Some donors and pharma provided funds to conduct clinical studies in AUD testing high doses of baclofen with, again, conflicting findings. Equally concerning, in recent years, opinions on the baclofen/AUD story have become even more polarized, with those who were skeptical about its efficacy and concerned about safety on the one hand, and those who erroneously saw baclofen as a miracle drug on the other. Lessons may be learned from the French baclofen events. A physician spoke up about his addiction without shame or fear, donors and pharma decided to invest in medication development for AUD and a national drug regulation agency paid attention to the evaluation of a medication for AUD. Unfortunately, this story also raises important issues in the field. First, while we all love seeing dose–response curves in rodent experiments and even better in clinical studies, it is more complicated to make a drug more effective by simply increasing its dose. Second, the French story increased the polarizing opinions on baclofen and AUD, and further distracted from a fundamental principle in science; let the data decide and drive the next step(s). Notably, this is exactly what Dr. Garbutt and colleagues proceeded to do.

Based on their first clinical trial [5], and from the work done by other scientists in the baclofen/AUD field [7], Garbutt and colleagues focused their research to two main points. First, baclofen should work better in patients with higher AUD severity and drinking, hence they increased the alcohol drinking cut-off in their inclusion/exclusion criteria. Second, while doses like 270 mg/day are obviously concerning from a safety standpoint, testing a potential dose–response of baclofen within a clinically sound range was important. As described in their paper in *Neuropsychopharmacology* [8], their latest clinical study led to positive and exciting results. Baclofen was superior to placebo in reducing heavy drinking days and increasing abstinent days in individuals with AUD. Baclofen 90 mg/day had greater efficacy overall than the 30 mg/day dose, although tolerability was lower in women. Gender was a moderator of response, with men benefiting from 90 mg of baclofen/day but not from 30 mg/day, whereas women showed benefit from baclofen 30 mg/day, marginal benefit from 90 mg/day, and worsened tolerability at 90 mg/day. This new clinical study by Garbutt and colleagues should be regarded as a critically important study with findings that matter to the baclofen/AUD field, the GABA-B/addiction field, and the medication development addiction field at-large.

This new study matters because it confirms that baclofen itself may be a promising medication for AUD [7]. Statistically speaking, the effect sizes were respectful [8]. However, it is essential to remember again that no medication will work for all patients [1] and baclofen is no exception. Baclofen may help some patients with AUD, most likely those with higher severity of alcohol addiction, experiencing higher levels of drinking and/or with alcohol-associated liver disease [7]. Furthermore, other factors play

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a role in baclofen response (or lack of) in patients with AUD, including—but not limited to—dose and gender, as Garbutt and colleagues have shown [8]. Furthermore, the worsened tolerability in women taking baclofen 90 mg/day is very important to consider because it shows that its potential use should be limited to patients who tolerate it and that clinical monitoring is critical.

But chiefly this new study matters because, beyond baclofen, it supports that the GABA-B receptor is an important target for further investigation for AUD and substance use disorders in general. Indeed, the next recommended step is not to conduct additional work on baclofen but rather to investigate and invest in GABA-B positive allosteric modulators, which hold a wider therapeutic index and a lower potential for tolerance development and dose escalation compared to baclofen, based on preclinical studies [3].

Finally, this new study matters because it is an excellent reminder that medication development for a complex disorder, like AUD, with a heterogenous population is challenging, often producing mixed results across studies. During the next decade, advances are needed in precision medicine to better understand who responds favorably to a medicine to allow clinicians to deliver medications in a more efficient, effective, and safer manner. This approach may require an algorithm of combining individual characteristics and novel biomarkers to new computational analytical approaches. As a colleague once stated, "*medication development is like playing golf. You watch on TV and it seems easy. Then, you try to actually play and realize that it's not easy at all.*"

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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