GABA-A Receptor Modulators: Can they Offer any Improvement over Benzodiazepines in the Treatment of Anxiety Disorders?

Dan V. Iosifescu

Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Linked Comment: Czobor et al. *CNS Neurosci Ther* 2010;16:63–75.

Correspondence

Dan V. Iosifescu, M.D., M.Sc., Massachusetts
General Hospital, 50 Staniford Street, suite 401,
Boston, MA 02114, USA.
Tel: 617-724-7741;
Fax: 617-724-3028;
E-mail: diosifescu@partners.org

doi: 10.1111/j.1755-5949.2009.00127.x

Anxiety disorders are among the most prevalent psychiatric disorders in the general population. Approximately a quarter of the US population experiences pathologic anxiety over the course of their lifetime. Approximately 40 million American adults of age 18 and older, or about 18.1% of people in this age group have an anxiety disorder in a given year [1].

Anxiety disorders are associated with marked impairments in physical and psychosocial function, as well as quality of life. For example, panic disorder is associated with increased rates of alcohol abuse, marital and vocational problems, and suicide attempts (in individuals with comorbid depression and personality disorders). Panic and phobic anxiety are also associated with increased rates of premature cardiovascular mortality in men. Patients with panic disorder lose workdays twice as often as the general population, with 25% of panic patients becoming chronically unemployed, and up to 30% receiving public assistance or disability. Patients with panic disorder are five to seven times more likely to be high utilizers of medical services compared to nonpanic individuals.

Most patients with anxiety disorders improve with pharmacological treatment although the majority do not achieve full and sustained remission with current treatments. High rates of relapse of anxiety symptoms after discontinuation of pharmacotherapy support the need for maintenance therapy for many individuals. There is a clear need for novel, improved treatments with increased efficacy and tolerability.

The association of GABA-A receptor activity with anxiolytic effects has been known for a long time. Benzodiazepines, which act as GABA-A receptor positive allosteric modulators (PAMs), have been used clinically for several decades for the treatment of anxiety. A significant research effort has been devoted to finding novel “anxiolytic” compounds that would be devoid of the side effects of benzodiazepines (such as sedation, memory dysfunction, potential for abuse).

Compounds with activity on serotonin (5-HT) receptors have been successfully used to treat anxiety and selective serotonin reuptake inhibitors (SSRIs) as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) are currently first-line medications for treatment of anxiety. However, clinical efficacy for both SSRIs and SNRIs occurs for most subjects only after 4–8 weeks of treatment. The more selective serotonin 5-HT_{1A} receptor partial agonist buspirone has low efficacy in the treatment of anxiety, while gepirone, another member of this class, has failed to obtain FDA approval.

The option suggested in the current report by Czobor and coworkers in the present issue of *CNS Neuroscience and Therapeutics* is to return to the GABA-A receptor and to investigate other compounds with presumably increased selectivity for anxiolytic effects [2]. Indeed, a review by Sieghart [3] explains that while benzodiazepines interact with all GABA-A receptor subtypes, sedative effects from sedative-hypnotic drugs are primarily associated with α -1 activity, whereas anxiolytic effects are associated with α -2 and α -3 activity. For

example, nonbenzodiazepines hypnotics such as eszopiclone, zolpidem, and zaleplon all have selectivity on the GABA-A α -1 receptor subtypes, while also having activity on other GABA-A subtypes [4].

As highlighted by Czobor and coworkers, ocinaplon (DOV 273,547) is a PAM of GABA-A receptors and it represents a new attempt to find the "nonbenzodiazepine selective anxiolytic." The current report also illustrates the difficulty of extrapolating animal data to efficacy and tolerability in humans.

Previous animal data [5] had suggested that ocinaplon may have significant anxiolytic activity at doses with minimal effects related to sedation or muscle relaxation. The short-term (4 weeks) clinical study presented here was to test these effects in subjects with generalized anxiety disorder. The results of the study appear encouraging; ocinaplon did separate from placebo in the primary analysis. It is likely that ocinaplon or another similar GABA-A allosteric modulator might prove to be a nonsedating anxiolytic with benzodiazepine-like efficacy.

However, accepting the results of the current study requires a big caveat. The study was terminated early after one subject experienced very significant liver transaminase elevation. The early termination triggered a very high rate of noncompletion (more than 50% of the ocinaplon group and 60% of the placebo group did not complete the 4 weeks of treatment). Therefore, the main study results represent an inference in a group where more than half of the subjects did not complete the study.

Overall, this study supports a clear promise of anxiolytic efficacy for ocinaplon, at doses apparently associated with low rates of sedation or cognitive dysfunction (e.g., attention difficulties). This is very positive and justifies further development of either ocinaplon or other GABA-A allosteric modulators. However, the significant liver transaminase elevation and the limitations of the current study described earlier also justify some skepticism until more clinical data will be available on this or other similar compounds.

References

1. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Arch Gen Psychiatry* 2005;**62**:617–627.
2. Czobor P, Skolnick P, Beer B, Lippa A. A multicenter, placebo-controlled, double-blind, randomized study of efficacy, and safety of ocinaplon (DOV 273,547) in generalized anxiety disorder. *CNS Neurosci Ther* 2010;**16**:63–75.
3. Sieghart W. Structure, pharmacology, and function of GABA-A receptor subtypes. *Adv Pharmacol* 2006;**54**:231–263.
4. Sanna E, Busonero F, Talani G, et al. Comparison of the effects of zaleplon, zolpidem, and triazolam at various GABA(A) receptor subtypes. *Eur J Pharmacol* 2002;**451**:103–110.
5. Lippa A, Czobor P, Stark J, et al. Selective anxiolysis produced by ocinaplon, a GABA(A) receptor modulator. *Proc Natl Acad Sci USA* 2005;**102**:7380–7385.