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Editorial

Circumspectives: The Promise of Ketamine

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In this issue we reprise a Feature called *Circumspectives*. The general format of a *Circumspectives* article is similar to a debate, with separate sections in which two thought leaders articulate their individual positions on a topic of great importance to our community of researchers. The distinguishing element, however, is that the piece ends with a 'reconciliation' that is co-authored by both and includes ideas or experiments that will move the field forward.

The current *Circumspectives* (Sanacora and Schatzberg, 2015) is entitled 'Ketamine: Promising Path or False Prophecy in the Development of Novel Therapeutics for Mood Disorders?'. It is co-authored by Gerard Sanacora and Alan F Schatzberg, who are leaders in this field. The article is insightfully written and intended to promote a collegial and productive exchange of ideas regarding the impact that ketamine has had in psychiatry within the last decade, as well as recommendations for the future.

Dr Sanacora describes the history of clinical studies of ketamine as an antidepressant, and how the discovery that it produces rapid and robust antidepressant effects in patients with severe (treatment-resistant) depression has changed our thinking. Perhaps the most important legacy of this discovery is that there is now a greater appreciation for the fact that it is possible to design a therapeutic regimen that produces rapid antidepressant effects. At the time of the seminal ketamine report (Zarate *et al*, 2006), the prevailing dogma was that all antidepressant therapies required a time lag of several weeks to become effective. The finding that standard antidepressants stimulate adult hippocampal neurogenesis, a process that requires weeks for new cells to be born and differentiate into neurons, provided a compelling explanation for both the therapeutic effects of the drugs as well as their time lag (Dranovsky and Hen, 2006). The neurogenesis hypothesis has justifiably had a tremendous influence on research and drug development strategies. However, the discovery that ketamine has rapid antidepressant effects in humans—detectable within hours of administration—demonstrated that neurogenesis is not required for an antidepressant response, thereby providing a prominent exception to an influential hypothesis and offering hope that fast-acting but safe antidepressants are possible.

Despite growing enthusiasm for ketamine and its promise, Dr Schatzberg describes some sobering details and gaps in knowledge. Ketamine is a drug of abuse and, despite some exceptionally elegant studies on the mechanism (eg, Li *et al*, 2010; Autry *et al*, 2011), there is no consensus on how it produces therapeutic effects. As one example, Dr Schatzberg points out similarities in some of the molecular actions of ketamine and scopolamine, another familiar and long-standing member of our phamacopea shown to produce rapid antidepressant effects (Furey and Drevets, 2006). It is interesting that the broad classes of agents to which ketamine and scopolamine belong (NMDA antagonists and muscarinic acetylcholine antagonists, respectively) have long been used by behavioral phamacologists to disrupt learning and memory processes in laboratory animals, making it conceivable that, despite common actions on discrete molecules, their key similarity is on more general circuit function, and that a tendency to disrupt memory is what provides relief to patients with treatment-resistant depression.

Perhaps the most provocative aspect of Dr Schatzberg's piece, however, lies in his rhetorical question: is it important to understand ketamine's mechanism of action? This question will be welcomed by some and viewed as heresy by others—which, incidentally, is exactly the intention of *Circumspectives*. The question should provoke thought when considering the history of research on antidepressants and the current state of neuroscience research and development in the pharmaceutical industry. Decades of research and billions of dollars have been invested toward understanding the mechanisms by which drugs such as fluoxetine produce their therapeutic effects. Despite these efforts, there is still no consensus on which of their myriad actions are most crucial, there are currently no major breakthroughs that can trace their heritage to this massive investment, and leading pharmaceutical companies have elected to divest of this type of research. These facts give weight to our rhetorical answer that it may be easier and more fruitful to focus on how the brain works than on how the drugs work.

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Editors welcome suggestions for future *Circumspectives* topics and authors, which can be submitted to journal@acnp.org. Please note that unsolicited articles of this type will not be considered. We envision publishing 1–2 of these Features each year; the next one is already underway.

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