Development of New Psychopharmacological Agents for Depression and Anxiety

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KEYWORDS

• Antidepressants • Anxiolytics • Ketamine • NMDA antagonists
• Glutamatergic agents • Glucocorticoid antagonists • Obotulinum toxin
• Mu-opioid agents

KEY POINTS

- Antidepressant and anxiolytic drug development has largely stalled.
- There are several so-called start-up companies and small to mid-sized pharmaceutical companies that are still developing novel agents, and these are offering promise for the field.
- Most of our currently available agents for depression and anxiety are based on neurotransmitter models (norepinephrine or serotonin) of the disorders.
- A great deal of effort has gone into developing new agents that have alternative mechanisms of action that may provide relief for patients' symptoms via alternative neurobiological circuits or systems.
- Several failures in antidepressant development have occurred over the past 10 years. These failures may provide clues for future development, and it is reasonable to review several of them.
- Efforts have been expended at developing pharmacogenetic and other biological markers that can not only improve matching available drugs to patients but can stimulate new drug development for specific subtypes of disorders. Another approach has been to improve imaging tools that can be used to better screen compounds for pharmacological effects.

Conflicts of Interest: Dr A.F. Schatzberg has served as a consultant to Clintara, Forum (EnVivo), Genentech, Lundbeck/Takeda, McKinsey, Merck, Naurex, Neuronetics, One Carbon, Pfizer, and Sunovion. He has had equity in Amnestix, Cervel, Corcept (cofounder), Delpor, Merck, Neurocrine, Pfizer, Titan, and Xhale. He is a named inventor on pharmacogenetic use patents on glucocorticoid antagonists and on prediction of antidepressant response.

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Psychiatr Clin N Am 38 (2015) 379–393
http://dx.doi.org/10.1016/j.psc.2015.05.009 **psych.theclinics.com**
0193-953X/15/$ – see front matter

There has been much written in recent years regarding the somewhat sorry state of affairs in the development of new psychotropic agents.[1,2] In the past decade, we have seen fewer new clinical entities in development, in part because of the relatively high failure rates in separating drugs from placebo. Various reasons for these failures have been provided, including the poor validity of diagnostic categories, inflation of baseline measures to ensure patients will meet entry criteria, and poor consistency or reliability of ratings both within and across sites (see later discussion). Many large-scale pharmaceutical companies have become frustrated and have publicly announced their decision to stop active drug development in psychiatry. There are, however, several so-called start-up companies and small to mid-size pharmaceutical companies that are still developing novel agents, and these are offering promise for the field. Several of these have also resulted in partnerships between so-called Big Pharma and smaller companies. This review discusses several agents and strategies that are currently in development which highlight numerous issues commonly confronted in drug development in psychiatry.

Most of the currently available agents for depression and anxiety are based on neurotransmitter models (norepinephrine or serotonin) of the disorders. The original tricyclic antidepressants block the reuptake of norepinephrine and, to a lesser extent, serotonin, and often had anticholinergic and antihistaminic properties. The latter 2 accounted for much of the side effects seen with these agents, particularly the risk of death in overdose. Monoamine oxidase inhibitors also regulate the catabolism of the biogenic amines intracellularly, and provided another avenue to regulate these systems. Here, untoward interaction with various foods and other drugs could provoke hypertensive crises that were potentially lethal. The second-generation selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have become the drugs of choice for depression and anxiety disorders, and these agents by and large block the reuptake of norepinephrine and serotonin while producing little in the way of anticholinergic or antihistaminic effects. Thus, they are much safer.

Unfortunately, large-scale clinical trials such as STAR*D and I-SPOT report relatively large percentages of subjects not responding to monotherapy with SSRIs and SNRIs, such that other methods to treat these nonresponding patients are required.[3,4] To this end, a great deal of effort has gone into developing new agents that have alternative mechanisms of action (MoAs) that may provide relief for patients' symptoms via alternative neurobiological circuits or systems. However, we are still at the point of not understanding which circuit or system is awry in an individual patient, and this lack of biological specificity makes difficult the development and practice of personalized medicine and even nonpersonalized medicine for the psychiatric patient. This article reviews 4 strategies that take different routes (**Box 1**). The first focuses on agents that affect the excitatory neurotransmitter glutamate and its circuits in the brain. The second explores glucocorticoid receptor antagonists in delusional depression. Glucocorticoids are steroid hormones that are found throughout the body. In the brain, they bind to both a high-affinity mineralocorticoid receptor and low-affinity glucocorticoid receptors and responsive elements on various neurotransmitter regulatory genes. The third examines botulinum toxin and its ability to modulate a potential brain circuit that involves outputs to facial muscles and includes the prefrontal cortex and the amygdala. The last approach involves the opioid system in the brain, and explores the use of partial μ agonists administered either alone or with an opioid antagonist. These 4 strategies represent varied approaches and offer some promise for future drug development. In addition several recent, failed development efforts with drugs that have a variety of alternative MoAs, and the lessons that can be gleaned from these efforts, are discussed.