Redesigning antidepressant drug discovery

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Abstract

Antidepressant drug discovery and development have been put on hold by many pharmaceutical companies. The main reason for this is the negative efficacy studies with novel specific drugs. Here I argue that the main obstacles are the absence of gene tests and biomarkers as an integral part of a diagnostic process. Further, too much emphasis has been put on validating drug candidates in animal models of psychiatric disorders. A more rapid transfer of drug candidates into human research is necessary to overcome current obstacles that prevent the discovery of next-generation antidepressants.

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Every once in a while, efficiency of treatment with novel antidepressants in daily practice is questioned, by arguing that efficacy in clinical trials has only been shown in severely depressed patients.[1] The fair interpretation of these claims is that the placebo response is lower in severely depressed patients than in mild-to-moderate cases.[2,3] Unfortunately, severe cases are frequently not recruited in efficacy trials, favoring the placebo response that produces negative results. In some publications, negative study results are taken as evidence that antidepressants are nothing but risky placebos.[4] Such reports are hailed in some quarters and the lay press notoriously emphasizes the risk of such medications while neglecting their benefits. The subsequent loss of confidence is sobering, as depressed people, who should be treated with antidepressants might not be because they expect that these drugs may not help.

In fact, depression poses an enormous load on any economy and is a potentially lethal disease, as suicide related to depression is a major cause of death in industrialized countries. The discovery and development of antidepressants in the 1950s markedly reduced this burden, but it is beyond question that better antidepressant drugs are needed. Currently available antidepressants have three major drawbacks: (i) They work in too few people, ie, response rates within 6 to 8 weeks are around 70% while remission rates are sometimes considerably lower; (ii) It takes too long until they work, ie, patients have to wait, sometimes more than 2 months, until they get markedly better; and (iii) despite substantial improvement among new antidepressants, they still have too many side effects that include tiredness, restlessness, sexual dysfunction, weight gain, and in some cases even aggressiveness.[5]

Great strides have been made in improving diagnosis of depressive disorder and its acceptance. As a result of such destigmatization, more cases are diagnosed and treated, but as shown in a recent analysis in Organisation for Economic Cooperation and Development (OECD) countries, there are still more than 50% of cases not receiving any treatment at all.[6]

In the light of this pressing need to improve the situation by treating many more patients with better antidepressants, it is perplexing that despite the enormous market potential almost all pharmaceutical industries in Europe and in the United States have put antidepressant research and development on hold.

The papers in this issue document that the skepticism at the management level of pharmaceutical companies is unjustified, and I will add a few other examples to underscore this. I will also make a few suggestions on how the situation of antidepressant drug discovery and development can be improved.

The diagnostic controversy

Diagnostic classification of psychiatric disorders has been a major problem in drug development in the past, and will be so in the future.[7] While the first edition of the *Diagnostic Statistical Manual of Mental Disorders (DSM-I)* had listed about 100 psychiatric disorders, the fifth edition includes more than 400 disorders, though the clinical condition of patients and their underlying pathologies have certainly not increased four- to fivefold. A diagnostic attribution should tell the clinician how to treat the patient and what the prognostic expectations might be. Both requirements are not fulfilled by current diagnostic schemes, and major

depression has been used as a diagnostic monolith, while in reality it is a catch-all phrase for syndromes with highly variable underlying pathologies.[8] This may work as long as the antidepressant drugs are mechanistically unspecific comparable to broad-spectrum antibiotics, where the disease-causing bacteria are not known. However, once more specific mechanisms are targeted by novel antidepressants, much more information is needed to treat the right patient with the right drug.[9] Thus, the current lack of diagnostic tools that would allow one to stratify patients according to objective signs and symptoms and underlying causal mechanisms is key to the reluctant position of the industry.

Targeting the stress hormone system

The past experiences of the pharmaceutical industry with CRHR1-antagonists illustrate this dilemma: in the 1980s the long sought-after corticotropin releasing hormone (CRH) was isolated and characterized by the late Wylie Vale. Among other important findings it was shown, in transgenic mice either overexpressing CRH or carrying deletions of the relevant type 1 receptor (CRHR1) through which CRH acts in the brain, that enhanced CRH signaling via CRHR1 is most likely one important mechanism that may cause depression. This view is particularly plausible, as many patients with depression have overactive stress hormone secretions as evidenced by elevated plasma cortisol and corticotropin concentrations, prior or after dexamethasone administration and exaggerated responses of these hormones to the combined dexamethasone/CRH test. Importantly, CRH was found to be elevated also in the cerebrospinal fluid in about 30% of patients with major depression. These and many other findings encouraged pharmaceutical companies to develop non-peptidergic CRHR1 antagonists that are orally available and can penetrate into the brain where they are believed to reduce CRH/CRHR1 signaling.[10] After the first promising explorative study, all these newly developed CRHR1 antagonists showed negative results in controlled efficacy trials. Indeed, the jury is out as to whether these trials were really negative or rather failed, because a drug that specifically binds to nothing else but CRHR1 can only work among those patients where enhanced CRH signaling is causing the disease. Thus, without knowing in which patients this is the case and assuming that only 20% to 30% of depressives have CRH overactivity, we might treat a vast majority of patients with the wrong drug, if we give it to all of them. But how could one figure out who is having a "CRH problem"? In the light of this, the negative study results were unsurprising. Another disappointment was that against expectation the usual stress hormone assessments were not informative, as central CRH overactivity showed to be dissociated from peripheral stress hormone activity despite CRH being one of the "master hormones" also regulating peripheral response to stress.[11] This issue was resolved with the help of a conditional mouse mutant, where the CRHR1 was deleted in specific brain areas.[12] These studies made it clear that CRH produces depression-like symptoms independently of its pituitary action. What is badly needed is a set of gene tests and biomarkers identifying patients who are likely to respond to CRHR1 antagonists. In search of such information, CRH overexpressing mice were studied in a specialized sleep laboratory, and it was found that these mice have REM-sleep disinhibition, ie, increased activity of paradoxical sleep where enhanced eye movements occur. This abnormality disappears once these transgenic mice are treated with CRHR1 antagonists.[13] Likewise, patients that fulfilled the criteria for major depression but had different sleep EEG signatures responded much better to a CRHR1 antagonist if they had increased REM density. That prompts quite unexpectedly the question of whether a sleep EEG analysis might help to identify patients that would benefit from a CRHR1 antagonist.[11] Such a mechanism-based approach is required to make progress in the field, which will see a departure from blockbusters and the generation of individualized treatments based on gene tests and biomarkers.

This proposition is further exemplified for mifepristone, which blocks the progesterone and glucocorticoid receptors (GR). Research led by Alan Schatzberg postulated that the hypercortisolemia observed in many patients with psychotic depression is enhancing dopaminergic neurotransmission.[14] Therefore, blocking GR in dopaminoceptive neurons could be beneficial for these patients. In fact, mifepristone, by blocking GR, is a successful treatment for many, but not all patients with psychotic depression. Here again, the need for biomarkers allowing to identify GR antagonist responders is obvious. Similar to the results from CRH overexpressing mice, an animal model that generates biomarkers helping the clinician to identify responders to GR antagonists is much more helpful than struggling endlessly with the generation of a mouse model for psychotic depression.[15]

The lesson we have learned in the past is that there is no chance of developing a mouse model that fits closely to a set of diagnostic criteria for human psychiatric disorders.[16] The forced swim test, for example, is not telling us anything about depression, and is even counterproductive for discovery of antidepressants beyond monoaminergic mechanisms of action. It is unlikely that complex human diseases such as schizophrenia, depression, obsessive-compulsive disorder, anorexia, or panic disorder can be modeled in a mouse, fish, or fly. Such efforts are not even needed as long as animal models give us a hint about the relevance of a DNA sequence variation emerging from human genetic studies, or of epigenetic modifications induced by gene x environment interactions that are pertinent for our understanding of the pathogenesis of psychiatric disorders.

The logical consequence of these developments is that we need human clinical data, eventually reinforced by animal experiments, to develop gene tests and biomarkers that inform the clinician about the underlying mechanism and guide more targeted treatments.[9]

After decades of "murinization" of antidepressant research and discovery efforts with sobering results, it is time to remember Protagoras *(490 BC - 411 BC)*: "Man is the measure of all things." To translate this wisdom into a redesigned drug discovery and development of next-generation antidepressants, we need to catch the signals for novel targets at the bedside. The "bench to bedside" strategy has not delivered. Once novel potential drug candidates are discovered, they need to be validated in humans, not in animals, immediately after toxicity issues are resolved. ❑

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