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• Commentary •

Current problems in the research and development of more effective antidepressants

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Summary: This commentary was stimulated by discussions held at the First China Antidepressants Research and Development Summit held in Beijing in October 2015. Hosted by the Chinese Psychiatrist Psychopharmacology Commission and including leading clinicians, neuroscientists, and representatives of the pharmaceutical industry, the summit focused on the major problems that are limiting the development of more effective antidepressant medications. In the absence of clear biomarkers of depression, clinicians must base treatment decisions on clinical phenomenology; the lack of clear biological targets results in currently available antidepressants that take a long time to be effective, have low rates of full remission, and high rates of relapse. Basic research on depression by neuroscientists in China is internationally recognized, but the vast proportion of candidate chemical compounds Chinese researchers propose as potential treatments for depression fail when tested clinically. This high failure rate of proposed agents has rapidly increased the cost of bringing new drugs to market, so pharmaceutical firms prefer to 'tweak' currently approved medications rather than take the financial risk of supporting the development of novel antidepressants. Thus, the development of new, more effective treatments for depression is at a stalemate. Given the huge impact of depression on the economic development of China and other countries, it is essential to actively solicit the support of governments and communities in the efforts of clinicians, researchers, and the pharmaceutical industry to overcome this stalemate.

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1. Introduction

The discovery of the antidepressant effect of imipramine led to the first biological hypothesis of depression – 'the monoamine hypothesis of depression',[1] which subsequently became the main theoretical justification for the development of a wide range of antidepressant medications. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were the only types of antidepressants commonly used by clinicians for several decades, but in the late 1990s several new agents that had better efficacy and less adverse effects came to market: selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressant (NaSSA), and norepinephrine reuptake inhibitors (NRIs).[2] However, the development and marketing of new psychiatric medications, including new antidepressants, has stalled over the last 15 years (since 2000), primarily because many large multinational pharmaceutical companies have abandoned or downgraded research and development of psychiatric medications. This commentary is based on discussions about current challenges to the research and development of antidepressants in China that were held among clinicians, neuroscientists, and representatives of the pharmaceutical industry who attended the First China Antidepressant Research and Development Summit in Beijing in October 2015.

2. Clinical challenges

Lacking a clear biological pathogenesis of depression, clinicians must base their diagnostic classification and treatment strategies for depression on the highly

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variable clinical phenomenology of the condition. The diagnostic criteria for depressive disorders in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)[3] and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[4] both require that the individual display at least five out of nine symptoms almost daily for at least two weeks, and that these five symptoms must include either a depressive mood or a lack of interest or pleasure. The severity of depressive disorders is usually evaluated by the Hamilton Rating Scale for Depression (HAM-D)[5] or the Montgomery-Åsberg Depression Rating Scale (MADRS).[6] Both of these commonly used scales use the total score of all items in the scale as their measure of the severity of depression, which makes the unsupported assumption that all items in the scale (and, thus, all nine of the symptoms assessed to diagnose depression) are of equal diagnostic weight. However, there are many different clinical variations of depression. For example, three of the nine diagnostic symptoms are considered present if they are more than or less than normal (e.g., insomnia or hypersomnia, psychomotor retardation or psychomotor agitation, and weight loss or weight gain) and other symptoms have varying manifestations (e.g., worthlessness or abnormal self-guilt). Given this diagnostic flexibility, individuals who meet criteria for a 'depressive disorder' can have 1497 different sets of symptoms. Each of these independent symptom sets could, theoretically, have different risk factors, hereditary, biological mechanisms, and – most importantly for the current discussion – responses to medication.[7] Thus similar scores on the HAM-D, MADRS or any other measure of depression among different individuals do not indicate similarity of the clinical profile of the individuals, and changes in the scores of these scales with treatment (typically used to determine effectiveness of medications) probably represent different symptomatic changes in different patients. This heterogeneity makes it difficult to replicate findings and, thus, seriously undermines the interpretation of studies that try to relate clinical changes to the underlying pathological mechanisms of depression and of studies aimed at the development of new antidepressants.[7] Of course, studies about the treatment effectiveness of antidepressants are also often limited by methodological problems including sampling, selection of the control condition, the selection and time of assessment of the outcome measures, and so forth.[8,9]

Given this lack of precision in the targeted symptoms, it is not all that surprising that the outcomes of treatment are less than satisfactory. Major problems with currently available antidepressants include prolonged delays in symptom resolution, low rates of full remissions, substantial residual symptoms after treatment, and high relapse rates.[10] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that after a 14-week course of treatment with citalopram at an effective dosage (average of 41.8 mg/d on average), only 33% of patients recovered; among those who had not recovered, a second course of treatment with a different type of antidepressant at sufficient dosage for a sufficient duration only resulted (at best) in a 30% recovery rate.[11] Given these poor overall outcomes, one recent line of thinking is that multi-target drugs that include both antidepressants and non-monoamine-based agents may be needed to improve the rates of remission for depression. Based on this approach, in the past three years the US Food and Drug Administration (USFDA) approved the marketing of three new combination agents: vilazodone, levomilnacipran, and vortioxetine.[12] These new drugs provide new options for the treatment of depression, and one of them – vortioxetine – may also be effective in reducing the cognitive impairment that often accompanies depression.[13] The most exciting current research focuses on ketamine, which has been shown to provide rapid resolution of depressive symptoms (within two hours); inhaled as a spray in the intranasal cavity three times a week for two-weeks, the therapeutic effects can last for over one month.[14] These new approaches, which require much more extensive evaluation before they can be recommended for all depressed individuals, provide new hope, but they do not resolve the fundamental problem of understanding the relationships between the symptomatology, underlying biological mechanisms, and mechanism of action of the antidepressant.

3. Challenges for neuroscience researchers

International strategies for the research and development of new drugs are aimed at specific clinical conditions and use standardized methods to compare the efficacy and safety of a wide range of agents before recommending a specific drug or drugs for routine clinical care. However, due to the complex clinical presentations and course of illness, unknown pathogenesis, and lack of appropriate animal models for most psychiatric conditions, research and development for psychiatric medications are, for the present, necessarily based on integrating (a) clinical studies that consider the pathological changes in the brain and nervous system which occur when specific clinical syndromes are present and (b) basic science studies that consider the clinical symptoms that are associated with specific pathological changes in the brain and nervous system. The lack of a clear understanding of the pathological changes that lead to the onset of depression and that affect the course of depression makes it impossible to identify biological markers that can be used to assess the effectiveness of interventions aimed at the prevention and treatment of depression.[15] Research aimed at developing new antidepressants is, thus, constrained by existing clinical standards for assessing the effectiveness of antidepressants which probably do not reflect the underlying biological changes associated with depression. Current research can be classified into four main groups: (a) research about prodromal symptoms

of individuals with depression; (b) research about the pathophysiological changes that occur with depression; (c) research about the changes in biological processes induced by the administration of antidepressant medications; and (d) research about interventions aimed at reducing relapse in depression.

The rapid development of neuroscientific techniques in recent years has resulted in several new hypotheses about the pathogenesis of depression, including hypotheses about abnormalities in brain's neurons, abnormalities in neuroplasticity, and abnormalities in the hypothalamic-pituitary-adrenal axis. But the findings supporting these hypotheses are, as yet, insufficient to justify using these models as guidelines for the development of new antidepressant agents.[16] Chinese neuroscientists are active participants in this international effort, but – given the lack of definitive information about the pathogenesis of depression – the potential compounds they have identified in basic research have largely failed when studied clinically.

One of the new hypotheses considers depression the result of abnormalities in neurogenesis.[17] Proponents cite as evidence the finding that adolescents and young adults may have a temporarily increased risk of suicide when initially taking antidepressants, a finding they attribute to the age at which cerebral maturation occurs.[18]

Recent findings about the rapid resolution of depressive symptoms with ketamine (an 'accidental' observation in a study about the effect of ketamine on cognitive impairment) have triggered several new hypotheses about the pathogenesis of depression:[14] some authors suggest that depression is the result of pathological changes in the glutamatergic system (due to abnormal glutamatergic receptors or reduced levels of glutamate) while others consider it the result of abnormalities in the functioning of gliocytes. Studies report that ketamine can elevate the level of extra-cellular glutamine and increase the formation of synapses; the mechanisms underlying its rapid treatment effect may be associated with the brain derived neurotrophic factor (BDNF) and the functioning of the mammalian target of rapamycin (mTOR) signaling pathway.[19]

Investigations about the biological effects of current antidepressants include a study about the effects of fluoxetine on the protein in cell wall membranes.[20] Other neuroscience studies have identified some promising chemical compounds with different mechanisms of action, including drugs related to the glutamatergic system (e.g., lanicemine, riluzole, rapastinel, GLYX-13, and the antagonists for metabotropic glutamate receptor 2 [mGluR2] and metabotropic glutamate receptor 3 [mGluR3][19]) and drugs associated with the cholinergic system that target both affective and cognitive symptoms of depression (e.g., scopolamine, TC-5214, and sabcomeline[21]).

One example of a 'new' antidepressant under development is anti- interleukin-6 (IL-6) antibody, an agent that is currently used for treating rheumatoid arthritis (RA). As is true for the identification of many novel antidepressant agents, the antidepressant properties of anti-IL-6 antibody were not identified due to its biological functions but, rather, by observant clinicians focused on another problem. Researchers observed that the depressive symptoms of individuals with comorbid depression and RA improved when the RA was treated with anti-IL-6 antibody and, importantly, that the improvement in depression was unrelated to the improvement in RA. Subsequent studies found that blood serum levels of IL-6 are elevated in individuals with depression and return to normal after effective treatment of the depression.[22] Other studies with animal models of depression also reported elevated levels of IL-6 and found that treatment with anti-IL-6 antibody (which reduced serum IL-6) was associated with improved social interactions and sugar and water consumption of the animals (i.e., less 'depressive' symptoms). Further work is need, but this translational research may lead to novel, more effective antidepressants that are grounded in new hypotheses about the mechanism of action of antidepressants and, possibly, about the pathogenesis of depression itself.

4. The challenge for the pharmaceutical industry

Over the last three decades, the cost of developing new drugs has skyrocketed and the time required to bring new medications to market has almost doubled. The estimated research and development cost of fluoxetine (marketed since 1987) was about 230 million dollars ($US) and that of duloxetine (marketed in 2004) was over 900 million dollars; by 2010 the average cost of marketing a new drug was already more than 2 billion dollars. There are no mechanisms for sharing losses within the pharmaceutical industry when a promising agent fails to reach the market, so large multi-national pharmaceutical firms have understandably become increasingly conservative as the costs of drug development have escalated. These conservative strategies involve cutting the size of their own research departments; buying patents of chemical compounds from universities, research centers, or small-size pharmaceutical research centers; and making small changes to currently approved medications (e.g., changing the dosage, method of administration, or indicated conditions; slightly altering the chemical structure; or combining two medications into a single pill) and promoting them as new drugs. These financially driven changes seriously limit the research, development and marketing of novel antidepressants.

One factor that contributes to the rapidly rising cost and protracted time for developing and marketing new drugs is the increasing number of laws and regulations on new drug development imposed by governmental agencies.[23] In response to consumers' demands for safer,

more effective medications, official drug administration agencies in many countries have become increasingly strict in their scrutiny of new drugs. This problem is further magnified by major differences in the regulations governing drug approval between different countries.[23]

Despite the rapidly decreasing investment of multi-national pharmaceutical firms in the development of antidepressants, the potential huge size of the market for antidepressants that could improve on the less-than-satisfactory effectiveness of current antidepressants would stimulate a rapid redirection of research resources towards antidepressants if a truly 'breakthrough' drug was a possibility. Given its very rapid action and its perceived effectiveness in treating treatment-resistant depression and depression in bipolar disorder,[24,25] ketamine is such a drug. Research about ketamine is surging and will, hopefully, lead to a better understanding of the pathogenesis of depression and to the development of a new class of more effective antidepressants.

5. The need to combine forces

Global burden of disease studies have consistently reported that depression is the leading cause of health burden among the neuropsychiatric disorders, and one of the leading overall causes of years lived with disability in both high-income countries and low- and middle-income countries (including China).[26] Depression seriously affects the economic development of all countries around the world, so it has recently been recognized as a high-priority health condition by the World Health Organization, the United Nations, and the World Bank. Improving the prevention, recognition, and effective treatment of depression is an essential component in the global efforts to improve the standard of living and quality of life of the world's population.

Dealing with a problem of this magnitude requires the concerted effort of clinicians, researchers, and pharmaceutical firms and substantial regulatory and financial support of national governments. Affected individuals with depression, their family members, the general public, and the media must also become active participants in the effort to mobilize the necessary resources and the long-term political commitment needed to address this complex problem. Given the different priorities, timelines, and responsibilities of these different stakeholders, this will not be an easy task.

Improving our ability to rapidly develop, test, and market novel antidepressants that can improve on the limited effectiveness of currently available medications is an important step in this wider effort. In China there needs to be a non-government platform where clinicians, neuroscience researchers, industry representatives, and government administrators can collectively discuss related issues and subsequently release authoritative recommendations to all relevant stakeholders in the country about the best way to coordinate and support the innovative, multi-disciplinary research needed. Academic associations such as the Chinese Psychiatrist Psychopharmacology Commission (CPPC) would be a good 'home' for such an endeavor. This multi-stakeholder platform could regularly release different types of recommendations aimed at promoting the development of new antidepressants (and, potentially, other new psychiatric medications):

a) compile annual reports about the priority research topics needed to support the ongoing effort to develop novel antidepressants;
b) promote government policies that make it easier to bring new agents to market rapidly;
c) recommend substantial increases in government support for basic research about depression so that the financial burden for pharmaceutical firms to bring a novel medication to market would be substantially reduced;
d) recommend revision of the current governmental system for supporting mental health research, placing a greater emphasis on collaborative studies between clinicians and basic scientists with the goal of ensuring that basic science findings are rapidly translated into clinical projects;
e) recommend that funding agencies selectively support long-term panel studies and the development of registries of patients (with less emphasis on cross-sectional studies and short term studies) that monitor clinical and biological parameters throughout the full course of depressive episodes and throughout the lifetime of individuals who experience multiple episodes of depression;
f) support efforts to develop better animal models of depression;
g) emphasize work on biochemical, anatomical, and genetic biomarkers to help identify biologically distinct subtypes of depression that may be selectively responsive to different medications;
h) continue efforts to identify clinically homogeneous subtypes of depression and better, more specific measures of the outcome of antidepressant treatment;
i) consider the potential utility of traditional Chinese medications in the treatment of depression;
j) promote the training and early-career support of a cadre of young researchers in related fields.

Cross-disciplinary efforts in China are quite difficult to establish and maintain, so the creation of an effective platform of stakeholders dedicated to the development of more effective antidepressants – an effort that could take many years to realize – will not be easy. But it is long past time that we take up this challenge. The health and long-term economic development of China depends on our success.

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Dr. Guang Chen is employed by the Johnson & Johnson Innovation Center and Dr. Zheng Li is employed by the Lundbeck Global Medical Research and Development Center. The discussions at the summit that led to this commentary did not pertain to any specific commercial products. Drs. Chen and Li participated in these discussions, but they did not participate in the preparation, revision, or decision to submit this manuscript.

目前研究和开发更有效的抗抑郁药过程中存在的问题

司天梅，于欣

概述：受 2015 十月在北京举行的第一届中国抗抑郁药研究与发展峰会上的讨论的启发，我们撰写了这篇述评。该峰会由中国医师协会精神科医师分会精神药理学和药物治疗工作委员会 (Chinese Psychiatrist Psychopharmacology Commission, CPPC) 发起，参与人员包括一流的精神科临床医生、神经科学研究者和国内外大型制药企业研发人员，会议重点讨论了那些限制了更有效的抗抑郁药物发展的主要问题。在没有明确的抑郁症生物标志物的情况下，临床医生必须在临床现象的基础上做出治疗决策；缺乏明确的生物靶点导致目前可用的抗抑郁药需要很长一段时间才有效，完全缓解率低，并且复发率高。中国神经科学家对抑郁症的基础研究是国际公认的，但他们提出的。 作为治疗抑郁症潜在的候选化学成分大部分在临床试验时失败了。这种试剂的高失败率和大部分可用药物的不令人满意的结果迅速增加了新药进入市场的成本，所以制药公司更喜欢“调整”目前的药物而不是冒资金风险来支持新的抗抑郁药的发展。因此，发展新的、更有效的抑郁症治疗成为一个僵局。鉴于抑郁症对中国和其他国家的经济发展的巨大影响，在临床医生、研究人员和制药行业的共同努力下积极争取政府和社区的支持来克服这种僵局是必不可少的。

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