•Forum•

Why is diagnosing MDD challenging?

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Summary: Depression is highly prevalent and one of the major contributors to disability worldwide. However, one of the findings from the DSM-5 field trials was that inter-rater reliability for diagnosing major depressive disorder was very poor. Why is diagnosing MDD so challenging? This article attempts to explain why undefined pathogenesis and complicated phenotypes complicate the diagnosis of MDD. However, further biomarker and translational research is still necessary to help clinicians screen and diagnose depression in the future rather than relying solely on current subjective diagnostic criteria.

Key words: depression; diagnosis; pathogenesis; phenotype; biomarker

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Depression is one of the most common mental disorders and a leading cause of years of life lost due to disability and disease burden worldwide. The global burden of disease (GBD) study in 2010 ranked depression as the second leading cause of burden. Disability-adjusted life years (DALYs) calculated by adding years lived with a disability (YLDs) and years lost because of disease-specific premature death (YLLs) was used to quantify the global burden attributable to depressive disorders. The 2010 GBD presented that MDD was one of the leading causes of DALYs, accounting for 2.5% of global DALYs. Also, the burden of depression was higher in women than men, and the largest proportion of YLDs from depressive disorder occurred among adults of working age. Moreover, depressive disorder was confirmed as a leading direct cause of the global disease burden and MDD also contributed to the burden allocated to suicide and ischemic heart disease.[1,2] Yet depression is widely undiagnosed. The prevalence of depression was estimated to be only 3.02% in China, which was significantly lower than that in Afghanistan (22.5%) as well as the United States (4.45%).[3] One of the reasons for this inconsistent epidemiological data might be inaccurate assessment and diagnosis.

One of the findings from the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) field trials was frustrating due to the very poor inter-rater reliability of clinicians when diagnosing major depressive disorder (MDD). The DSM-5 field trials were performed by using a test-retest reliability design with a stratified sampling method across six adult and four pediatric sites in the United States and one adult site in Canada over a 7- to 10- month period. Diagnostic interviews according to DSM-5 criteria were conducted by 279 clinicians from various mental health disciplines who received special training. Overall, 2,246 patients with various diagnoses and levels of comorbidity were recruited, and interclass kappa coefficients were calculated. The standards for the reliability coefficients for DSM-5 categorical diagnoses were set as follows: intraclass kappa of 0.8 and above were “excellent”; from 0.60 to 0.79 were “very good”; from 0.40 to 0.59 were “good”; from 0.20 to 0.39 were “questionable”; and those below 0.20 were “unacceptable”.[4] The results showed that clinician agreement about the MDD diagnosis was in the questionable range (Kappa = 0.20-0.39), and the pooled intraclass Kappa was 0.28 (95%CI 0.20-0.35) at the adult field trial sites and 0.28 (95%CI 0.15-0.41) at the pediatric field trial sites, respectively.[5]

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How is it that difficult to recognize MDD?

The most fundamental and challenging factor may be that depression is a highly heterogeneous disease and its real pathogenesis has not been clearly elucidated. Genome-wide association studies on depression have typically failed to identify the specific genetic variants involved [6], although depression has a well-established genetic loading.[7,8] Gene-environment interactions whereby a person inherits sensitivity to environmental factors could also play a key role in MDD.[9] Again, several plausible etiological hypotheses that might be helpful for understanding the pathophysiological and therapeutic mechanisms of MDD have been proposed. Undoubtedly, depression is a multifactorial disorder and knowledge about the underlying neurobiological mechanisms is still fragmentary.[10]

As well, depression is a complex disease with many various phenotypes. Depressive symptoms could occur due to or comorbid with substance use, other psychiatric diseases or other medical conditions. Most of all, depressive symptoms are the core presentations of both unipolar depression (that is major depressive disorder) and bipolar depression. In particular, a series of important articles from the National Institute of Mental Health Collaborative Depression Study have suggested that patients with bipolar disorder are depressed for a much longer period than hypomanic or manic throughout the course of the illness.[11-13] The symptoms of hypomania tend to be more difficult to recognize, partly because the patients often consider their manic symptoms to be normal and symptoms are highly variable.[14] Therefore, these factors may potentially contribute to misdiagnosing patients with unipolar depression when in fact they have bipolar disorder. Moreover, the DSM-5 expands the scope of MDD by adding some depressive subtypes (such as disruptive mood dysregulation disorder) and specifiers (such as “with mixed features”, “with anxious distress”, “with melancholic features”, “with atypical features”, “with peripartum onset”, “with seasonal pattern”, etc.), which may further increase the difficulty of improving the inter-rater reliability of clinicians diagnosing MDD.[15]

Embarrassingly, the diagnosis of MDD still relies on the clinical judgment of individual clinicians with high levels of subjectivity and potential variability. As a result, there is an urgent need for diagnostic tools or modalities with greater objectivity that could improve on current psychiatric practice that relies mainly on self-reporting of symptoms and clinical interviews.[16] Over the past two decades, a growing amount of research on putative biomarkers for MDD have increasingly suggested that MDD patients have significantly different biological profiles compared to healthy controls. However, difficulty in elucidating their exact relationships within depression pathophysiology makes individual markers inconsistent diagnostic tools.[17]

Finally, this is partly because of a lack of patient advocates, the stigma surrounding the condition, and inadequate mental health resources.[10]

Altogether, diagnosing MDD is challenging. Further biomarker research is still needed and may potentially improve our understanding of pathophysiology as well as antidepressant mechanisms, narrow differential diagnoses, and help to refine current diagnostic criteria. For now, the promising biomarker candidates are mainly involved in the hypothalamic-pituitary-adrenal axis system, thyroid function and antoimmunity, cytokines and inflammatory response, oxidative stress, neurotrophins, genetics and epigenetics, proteomics, metabolomics, and multiplex-based assays. [17] Hopefully, more sophisticated and integrated biomarkers can be discovered and applied for screening and diagnosing depression in the future as an advance over relying solely on current subjective diagnostic criteria.

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Conflict of interest statement

All authors declare that they have no conflicts of interest.

Authors’ contribution

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为什么诊断抑郁症是一个挑战?

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概述：抑郁症非常普遍，也是全球范围导致残疾的主要原因之一。然而，DSM-5 现场测试发现诊断抑郁症（major depressive disorder, MDD）的评估者间信度是很差的。为什么诊断 MDD 如此具有挑战性？本文尝试阐明为什么抑郁症发病机制的不确定性和表现形式的复杂性会使诊断变得困难。然而，将来仍然需要其他的生物标志物和转化医学研究来帮助临床医生筛选和诊断抑郁症，而不是单纯依靠目前的主观性诊断标准。

关键词：抑郁症、诊断、发病机制、表型、生物标志物

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