The Current Situation on Major Depressive Disorder in China: Research on Mechanisms and Clinical Practice

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Abstract Depression is the most disabling disorder worldwide that accounts for the highest proportion of global burden attributable to mental disorders. Major depressive disorder (MDD) is characterized by deep sadness, reduced energy, vegetative nervous system dysregulation, cognitive dysfunction, and even a high suicidal tendency. Although other treatment choices are available, antidepressant medication is the front-line treatment option for MDD. Regarding clinical efficacy, only ~50% of patients respond to frontline antidepressants, and <33% obtain remission. Currently, objective indexes to guide clinical decisions are still lacking. Furthermore, knowledge about the neurobiological mechanisms underlying discrepant antidepressant outcomes is still also fragmentary. In the present review, we discuss the current research progress and clinical opinions on MDD in China.

Keywords Major depressive disorder · Epidemiology · Antidepressant · Pathogenesis · Biomarker · China

Introduction

With the promulgation of the “Mental Health Law” in China, mental disorders have attracted increasing attention from society and the government. Major depressive

disorder (MDD) is a severe psychiatric illness characterized by persistent sadness, loss of interest, lack of energy, disturbed sleep, and suicidality. The lifetime prevalence rate for MDD is ~16.2% in most developed countries [1]. Approximately 15%–45% of MDD patients suffer from a chronic, unremitting course of depression despite receiving multiple antidepressant medications [2, 3]. As a consequence, the refractory nature of MDD leads to devastating emotional distress, psychosocial impairment, and a financial toll [4]. Furthermore, MDD is ubiquitous, affecting >350 million people worldwide in their lifetimes [5]. MDD has an adverse impact on comorbid medical illness and cognitive dysfunction, and its overall burden ranks among the highest of all diseases [6].

The purpose of this study was to review the current clinical status and progress of research on the pathogenesis of MDD in China, to integrate evidence-based findings and empirical perspectives on depression treatment from drugs to device-based medications, and to identify how to select the most effective, safe, and rapid therapeutic paradigms for MDD.

Epidemiology of MDD in China

Given the changes in clinical experience and the therapeutic environment since the early 1990s and the evolution of international diagnostic criteria (i.e., from DSM-III to DSM-5) and interview instruments, epidemiological surveys of MDD in China have reported discrepant results. Using meta-analysis, Gu and colleagues revealed that the overall estimation of current, 12-month, and lifetime prevalence rates of MDD is 1.6%, 2.3%, and 3.3%, respectively; the current prevalence is 2.0% in rural areas and 1.7% in urban areas; and female prevalence is 2.1%

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and the male prevalence 1.3% [7]. An epidemiological study also reported that the weighted prevalence estimates for MDD in a southwestern city (Kunming) in China were 1.96% (lifetime), 1.09% (1 year), and 0.93% (1 month) [8]. The lifetime prevalence estimate for Shanghai city is 3.6% [9] and that in Taiwan is 1.2% [10]. Another recent investigation reported that the prevalence rates for MDD among university undergraduates were 3.9% (lifetime), 2.4% (1 year), and 0.4% (1 month) in Mainland Chinese [11]. Importantly, Phillips and colleagues [12] conducted a survey in four provinces of China and found that the adjusted 1-month prevalence of MDD was 2.03% and that of anxiety disorder was 5.63%, and they were more prevalent in females than in males (2.60% *versus* 1.55% and 7.25% *versus* 4.06%, respectively). It has been suggested that the relatively low prevalence of MDD in China (3.02%) might be due to the high presentation rate of somatic problems such as headache or stomach pain in depressed patients, while the current diagnostic criteria focus on sadness, and lack of interest and energy [13]. In addition, because of the prejudice and stigma in Chinese traditional culture, many depressed patients first seek treatment in a general hospital: 4.0% (2.5%–6.1%) of depressed patients are recognized by internists and only 3.0% (1.6%–4.9%) are prescribed antidepressants [14]. Thus, urgent efforts are needed to improve the clinical recognition of MDD among Chinese physicians.

Pathogenesis of MDD and Antidepressant Mechanisms

Mainstream Pathophysiology of MDD and Antidepressants

Without doubt, depression is a multifactorial disorder and several plausible and integrative etiological models have been proposed (Fig. 1). This progress offers promising opportunities to improve understanding of the underlying pathogenesis of MDD and generate emerging targets for novel treatment. It is considered that dysfunctions of the hypothalamic–pituitary–adrenal axis and stress-related hormones (such as glucocorticoids), disequilibrium of neurotransmitters, and neuroprogressive and neuroprotective factors are involved in the pathophysiology of depression. Many valuable studies have been carried out in China. Research from an electrophysiological study of neurosis suggested that patterned high-frequency stimulation triggers hippocampal long-term depression *via* gamma-aminobutyric acid receptors and muscarinic acetylcholine receptors [15]. An event-related potential study also detected a significantly attenuated P3 amplitude in treatment-resistant depression (TRD) patients [16].

Importantly, Wang *et al.* [17] demonstrated that MDD patients can be effectively distinguished from healthy individuals by using the analysis of event-related potential features (such as the amplitude of N1, N2, and P3 components). With regard to neurobiochemistry, Xi *et al.* [18] reported that fluoxetine weakens the inhibitory effect of glucocorticoids on neural stem cell proliferation *in vitro via* the TREK-1 channel. Hippocampal cell proliferation and disturbed expression of brain-derived neurotrophic factor (BDNF) have also been associated with chronic mild stress in the development of depression [19]. This viewpoint has been validated by evidence for decreased mRNA expression levels of BDNF and related mitogen-activated protein kinase-1 gene expression in peripheral blood in MDD, especially in TRD [20]. Results from animal experiments have further clarified that electroconvulsive shock can up-regulate hippocampal BDNF in chronic unpredictable mild-stress (CUMS) depressed rats [21]; the underlying mechanism was demonstrated to be associated with homeostatic interactions between methyl-CpG-binding protein 2 and microRNA-132 [22]. Importantly, using the techniques of structural magnetic resonance imaging and magnetic resonance spectroscopy, Xi *et al.* [23] showed that a reduced concentration of the neuronal marker N-acetylaspartate in the hippocampus can be reversed by treatment with antidepressants in CUMS-depressed rats. It has been suggested that N-acetylaspartate might be a more sensitive measure of cognitive function than hippocampal volume in MDD. Prospectively, by equilibrating the major advantages and shortcomings of each model, a novel approach could be beneficial for generating valuable progress in elucidating the pathogenesis of MDD [24].

The important issue in treating depression is to obtain a rapid antidepressant effect. Ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist, has attracted attention from psychiatrists in the process of searching for the elusive “magic bullet” for treating depression. The antidepressant mechanism of ketamine is unclear. Yang *et al.* [25] found that ketamine-induced antidepressant effects are correlated with reduced levels of interleukin (IL)-1 β and IL-6 in the rat prefrontal cortex and hippocampus. Ketamine induces synaptogenesis in the prefrontal cortex of rats by rapidly activating the rapamycin pathway [26]. It has been speculated that aberrant neuronal plasticity in glutamatergic circuits might account for the pathogenesis of depression and thus may serve as a target for rapid antidepressant effects [27].

Genetic Studies

In the past decades, genetic association studies on depression have mainly focused on genes [such as those for the serotonin transporter, monoamine oxidase A (MAOA),

The Pathogenesis of MDD

Fig. 1 Key pathophysiological factors involved in the etiology of depression. *MDD* major depressive disorder, *SNPs* single-nucleotide polymorphisms, *IL2/6* interleukin 2/6, *BDNF* brain-derived

neurotrophic factor, *HPA-axis* hypothalamic-pituitary-adrenal axis, *5-HT* serotonin, *NA* noradrenalin, *DA* dopamine. This figure is based on a template from Sciencesliders® in Microsoft® PowerPoint.

tryptophan hydroxylase 1/2 (TPH-1/2), serotonin receptor 1A, catechol-O-methyl transferase, and BDNF] [28–33] that are correlated with the activity of monoaminergic agents (i.e., serotonin, norepinephrine, and dopamine). Unfortunately, no robustly validated genetic risk loci have been identified to date. Researchers in China have made their own unique contribution to this field. Evidence from allele frequency analysis suggests that the TPH1 218A allele has a higher prevalence in Taiwanese MDD patients [34]. Recently, in the Han Chinese population, Li *et al.* [35] found that the rs2242446 and rs5569 single-nucleotide polymorphisms (SNPs) in the norepinephrine transporter gene are associated with the retardation symptoms of depression. Furthermore, Yi and colleagues [36] have described a signature of 48 expressed genes and proposed that these genes might have diagnostic effects and differentiate subsyndromal symptomatic depression, MDD, and healthy subjects. Another study also confirmed that the SNP rs1137070 of the MAOA gene has significant associations with MDD [37]. Importantly, using sparse whole-genome sequencing in Chinese women, researchers have

identified two loci for MDD on chromosome 10: one near the sirtuin1 gene, and the other in an intron of the phospholysine phosphohistidine inorganic pyrophosphate phosphatase gene [38]. These results indicate that the categorical MDD-related gene remains elusive and the inherited factors may be affected by acquired elements, such the effects of development.

The research field in MDD has changed trajectories to multimodal approaches, such as multi-gene synergistic effects [29], gene-environment interactions [39, 40], and genetic imaging [41]. Yang *et al.* [42] reported that the BDNF-glycogen synthase kinase (GSK) 3B gene-environment interaction can modify the effect of negative stress on the risk of developing MDD in a Chinese population. Moreover, another finding from this group showed a significant interaction among GSK3 β genotypes, disease status, and the altered topological organization of resting-state functional brain networks in MDD patients [43]. These findings indicate that gene polymorphisms might affect genetic susceptibility by mediating neuronal activity and neuroplasticity in the development of MDD.

Brain Mapping Studies

Many key brain structures are involved in emotion processing, such as the hippocampus, amygdala, anterior cingulate cortex, insula, and orbitofrontal cortex [44]. Accumulating evidence from imaging genetics has indicated that multimodal functional brain networks in MDD are associated with the activation of dozens of genes linked to ion channel activity and synaptic function [41, 45, 46]. One of the important genes is BDNF, of which the Met allele of rs6265 is involved in decreased functional connectivity between the bilateral hippocampus and cerebellum in depression [47]. Another study [48] focused on the D-amino-acid oxidase activator gene that mediates glutamatergic function, and found that rs2391191 of this gene showed a genotype $\times$ disease status interaction in the left uvula and middle temporal gyrus of MDD patients.

In China, there has been an increasing focus on the aberrant coupling of intrinsic activity in MDD within two key neuro-cognitive networks: the salience network [49] and the default-mode network (DMN) [50, 51]. Guo and colleagues [52] proposed a group of changes including decreased regional activity and network homogeneity of the fronto-limbic network, decreased insular connectivity [53], increased cerebellar-DMN connectivity, and disrupted white-matter integrity in MDD patients [54]. Recently, a study using graph theory determined that the degree of connectivity between the DMN and the central executive network is significantly decreased in MDD patients compared with healthy controls [55]. Evidence from positron emission tomography also revealed reduced insular, limbic, basal ganglia, thalamic, and cerebellar glucose metabolism in MDD [56]. These reports further support the hypothesis that abnormal activity in emotion-related networks underlies the onset of MDD. However, given the heterogeneity of imaging studies, the underlying neuropathogenesis of MDD still needs to be further elucidated.

Clinical Treatment of MDD

Antidepressants

The prevalence of antidepressant use increases yearly both in Mainland China [57] and in Taiwan [58]. A systematic review [59] of 71 double-blind, randomized, controlled trials (RCTs) compared selective serotonin reuptake inhibitors (SSRIs: fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline) with other antidepressants such as selective noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), traditional Chinese medicine (TCM), and/or placebo. The

results suggested that SSRIs have a significant advantage over TCAs in terms of the response rate and remission rate. Frequently, MDD patients use benzodiazepines to improve sleep quality, but this may have many adverse effects, such as drug abuse. Wang *et al.* [60] reported that mirtazapine improves sleep quality and reduces the accompanying use of sleep medications in MDD. Compared to adult patients, the antidepressant is a double-edged sword when considering the safety and efficacy of prescribing drugs for children and adolescents. Evidence-based research has suggested that sertraline and mirtazapine show optimally-balanced safety, efficacy, and acceptability for children and adolescents with MDD [61]. Specifically, to date, no effective and safe antidepressant has been approved by the China Food and Drug Administration (CFDA) for treating MDD in children/adolescents. The method of care is also an important factor impacting the outcome of antidepressant treatment. A recent RCT [62] demonstrated that measurement-based care is more feasible and effective than standard treatment (clinicians' choices) for outpatients with moderate to severe MDD. However, evidence from high-quality, randomized, double-blinded, placebo-controlled trials in the Chinese population is still lacking.

The potentiating medications for MDD treatment include antipsychotics, mood stabilizers, anxiolytic drugs (e.g., benzodiazepines and buspirone), thyroid hormone, vitamin D, fish oil, ω 3 fatty acids, and folate [63–65]. For TRD patients, the guidelines for depression prevention and treatment in China (2nd edition) suggest that cautiously combined therapies would be effective, such as SSRIs and TCAs, or SSRIs and mirtazapine [66]. Atypical antipsychotic augmentation (such as risperidone, olanzapine, ziprasidone, and aripiprazole) is considered efficacious in improving depressive symptoms. Evidence from combination therapy indicates that quetiapine [67] is efficacious and safe in the combined treatment of TRD. However, due to side-effects, the prescription of antipsychotics should be prudent. Chang *et al.* [68] reported that lithium and thyroid hormone augmentation might improve the response to TCAs but not that to SSRIs. Further trials are warranted to provide robust evidence-based options for synergistic treatment in MDD, especially for the treatment of TRD.

Psychological Therapies

In addition to treatment with antidepressant drugs, practice guidelines have recommended cognitive behavioral therapy (CBT) and psychodynamic therapy as treatments of choice for depression. Hou *et al.* [69] reported that CBT in combination with systematic family therapy can improve mild to moderate postpartum depression. A randomized controlled trial [70] compared the effectiveness of a

physical fitness exercise program and CBT in elderly depressed patients, and the results revealed that the CBT group gained more perceived social support and alleviation of depressive symptoms, whereas better improvement in energy and quality of life was reported in the fitness exercise group. With regard to the remission rate, monotherapy with antidepressant or with CBT has similar efficacy to the treatment of combined CBT and antidepressant in MDD [71]. In addition, body-mind relaxation might modulate activity in the prefrontal cortex in multiple emotion-processing systems and construct reappraisal strategies in treating MDD [72]. These significant endeavors as psychological therapies have gained support from psychologists and patients because of their efficacy and safety.

Novel Device-Based Therapeutics

Many clinical practices use device-based therapeutics for MDD, especially for TRD patients [73]. However, concerning efficacy, the results remain controversial. A randomized, controlled, double-blinded treatment study [74] suggested that individuals with EEG-based synchronized repetitive transcranial magnetic stimulation (rTMS) exhibit a significantly greater reduction in depression severity compared to controls. The antidepressant efficacy of rTMS depends on its parameters; varying the stimulus parameters can have different antidepressant effects [75, 76]. Du *et al.* [77] reported that modified electric convulsive therapy (MECT) can improve problem-solving by affecting the spontaneous activity in several regions, including the frontal cortex, thalamus, and cerebellum. Combination therapies of MECT plus antidepressants are considered to be effective for TRD but increase the risk of memory impairment [78].

Traditional Chinese medicine

Alternative medical approaches [79–82] include TCM, acupuncture, meditation, yoga, and some novel compounds [83] (e.g., naphthalene compounds). According to the theory of TCM, MDD is related to blocked substance-qi in the liver. In line with this theory, researchers in China have proposed that acupuncture and moxibustion can improve the symptoms of depression by soothing the liver and regulating the mind [84]. Many herbal formulae have been used to treat depression, such as the Xiaoyao decoction and the Chaihu Shugan decoction [85]. The Chinese herb *Radix Angelicae Sinensis* is also considered to have antidepressant-like effects. Recently, researchers showed that ferulic acid, the main polyphenolic component of *Radix Angelicae Sinensis*, can regulate serotonergic and noradrenergic functions in mice with depression-like behaviors [86].

Another important Uygur drug in China, St John's Wort (*Hypericum perforatum*, SJW), is also widely used in Western countries. The main component in SJW extracts is hypericin, which can alleviate CUMS-induced depression symptoms and stabilize the excitatory amino-acids and monoamine neurotransmitter metabolites [87]. Another study [88] further reported that, like SJW, the ginsenosides can attenuate the symptoms of depression. Shuganjiyeu capsules (main components are SJW and *acanthopanax*) are also an effective herbal product for treating mild and moderate depression in China [89]. Importantly, another extracted drug from TCM, *Morinda officinalis* oligose [90], has been approved by the CFDA to treat MDD with safety and tolerability. Regarding which herbal formulas have higher efficacy in the treatment of MDD, evidence is still not conclusive.

Biomarkers for Diagnosis or Treatment Responses

Currently, the diagnosis and therapy of MDD depends on the subjective reporting of symptoms, clinical behavioral monitoring, and mental assessment, with a risk of misdiagnosis, inappropriate treatment and adverse outcomes. Despite the considerable amount of exploratory research on MDD, there is little knowledge about reliable and robust biomarkers for diagnosis, treatment choice, and outcome predictions. Promising approaches include gene tests, proteomics and metabolomic markers, neuroendocrine profiles, electrophysiology, and imaging techniques. In China, Liu and colleagues suggested that increased levels of plasma trimethylamine oxide, glutamine, and lactate could serve as efficacy markers of the TCM formula Xiaoyaosan [91]. Other substantial efforts have focused on specific markers of diagnosis and clinical prognosis in MDD. A recent study [92] concluded that increased expression of microRNAs (such as miRNA-26b, miRNA-1972, and miRNA-4485) in peripheral blood mononuclear cells might qualify as diagnostic biomarkers for MDD. Li and colleagues [93] reported that decreased glutamate and cortical thickness in the pregenual anterior cingulate cortex can serve as a regional trait marker in MDD. Importantly, decreased interhemispheric coordination in the calcarine cortex qualifies as an imaging biomarker to differentiate patients with TRD [94]. However, a robust biomarker with high sensitivity and specificity for identifying the disease and best course of treatment still needs to be identified. Promising studies designed to find characteristic brain network changes in MDD, which could be treated as a hallmark to predict early antidepressant responses or clarify diagnosis, would be useful to guide clinical practice.

Conclusions and Future Perspectives

Considered collectively, the overall efficacy of antidepressant treatment is not yet satisfactory. The current two outstanding and pending issues are as follows.

Elucidating the Pathogenesis of MDD

Research on the mechanisms underlying MDD and the efficacy of newly-developed antidepressants remains unpredictable, with frequent failures. Future studies of depression mechanisms with a robust biomarker for diagnosis may reliably identify which of the hypotheses is most pertinent to MDD. Subsequently, novel therapies, such as new herbs and modified psychotherapies (e.g., balancing psychotherapy) could be widely used in China. Robust imaging biomarkers that predict treatment responses could generate a personalized pattern of treatment in which depressed patients receive optimal therapy according to their individual neuroimaging features, instead of applying the current empirical therapeutic approach [95].

Improving the Accuracy of Diagnosis and the Effectiveness of Treatment

Considering clinical applications, the overall efficacy of antidepressants remains at a low level, and the current focus on individual research groups in China restricts the development of neuroimaging or genetic research. The practice of sharing ‘big data’ holds great promise for yielding robust, specific, and sensitive biomarkers for the accurate diagnosis of MDD. With respect to the treatment philosophy of “Precision Medicine” [96], we must make more efforts to develop genetically-targeted therapies. In future, the ideal medical framework is that MDD patients would receive appropriate drugs based on their gene tests. However, even though MDD involves gene-environment interactions, a risk gene mutation has not yet been identified. One of the biggest challenges for the field is to instill confidence and attract more visionary scientists to tackle the problems of depression, but the task appears to pose a dilemma [97]. We should not give up thinking that the issue is intractable. With the creative efforts of psychiatrists and society from clinics and labs, an even brighter future will emerge soon.

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