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REVIEW

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)-1β 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),

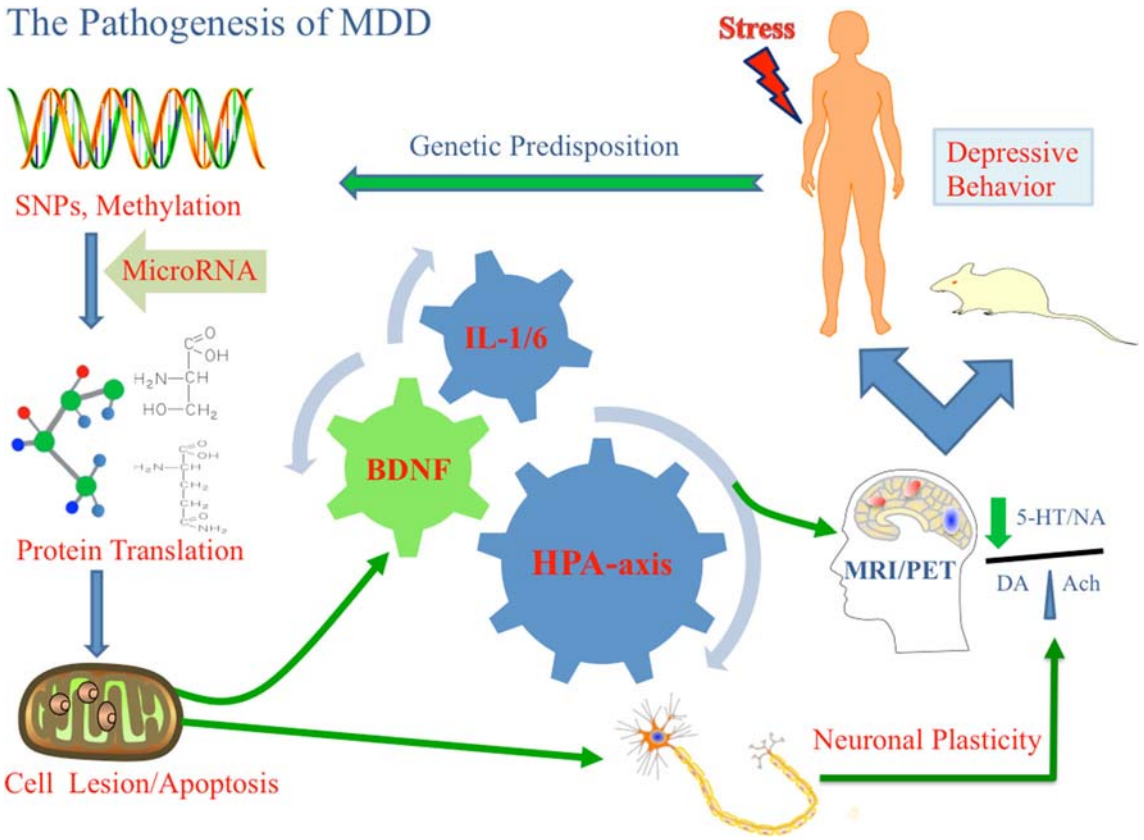

Fig. 1 Key pathophysiological factors involved in the etiology of depression. *MDD* major depressive disorder, *SNPs* single-nucleotide polymorphisms, *IL2/6* interleukin 2/6, *BDNF* brain-derived neurotrophic factor, *HPA-axis* hypothalamic-pituitary-adrenal axis, *5-HT* serotonin, *NA* noradrenalin, *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 GSK3β 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 × 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, antianxietic drugs (e.g., benzodiazepines and buspirone), thyroid hormone, vitamin D, fish oil, ω3 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. Shuganjieyu 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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References

1. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, *et al.* The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003, 289(23): 3095–3105.
2. Lepine BA, Moreno RA, Campos RN, Couttolenc BF. Treatment-resistant depression increases health costs and resource utilization. Rev Bras Psiquiatr 2012, 34: 379–388.
3. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006, 163: 1905–1917.
4. Kessler RC. The costs of depression. Psychiatr Clin North Am 2012, 35: 1–14.
5. World Health Organization. World Health Statistics. Geneva, Switzerland. World Health Organization Press, 2010.
6. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, *et al.* Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013, 382: 1575–1586.
7. Gu L, Xie J, Long J, Chen Q, Chen Q, Pan R, *et al.* Epidemiology of major depressive disorder in mainland china: a systematic review. PLoS One 2013, 8: e65356.
8. Lu J, Ruan Y, Huang Y, Yao J, Dang W, Gao C. Major depression in Kunming: prevalence, correlates and co-morbidity in a south-western city of China. J Affect Disord 2008, 111: 221–226.
9. Lee S, Tsang A, Huang YQ, He YL, Liu ZR, Zhang MY, *et al.* The epidemiology of depression in metropolitan China. Psychol Med 2009, 39: 735–747.
10. Liao SC, Chen WJ, Lee MB, Lung FW, Lai TJ, Liu CY, *et al.* Low prevalence of major depressive disorder in Taiwanese adults: possible explanations and implications. Psychol Med 2012, 42: 1227–1237.
11. Li W, Meng X, Xu Z, Yu Q, Shi J, Yu Y, *et al.* Prevalence, correlates of major depression: A mental health survey among undergraduates at a mainland Chinese university. Asia Pac Psychiatry 2015. doi: 10.1111/appy.12202.
12. Phillips MR, Zhang J, Shi Q, Song Z, Ding Z, Pang S, *et al.* Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001–05: an epidemiological survey. Lancet 2009, 373: 2041–2053.
13. Smith K. Mental health: a world of depression. Nature 2014, 515: 181.
14. Qin X, Wang W, Jin Q, Ai L, Li Y, Dong G, *et al.* Prevalence and rates of recognition of depressive disorders in internal medicine outpatient departments of 23 general hospitals in Shenyang, China. J Affect Disord 2008, 110: 46–54.
15. Zhu YY, Jing L, Duan TT, Yuan Q, Cao J, Zhou QX, *et al.* Patterned high-frequency stimulation induces a form of long-term depression dependent on GABAA and mACh receptors in the hippocampus. Neuroscience 2013, 250: 658–663.
16. Xu S, Chai H, Hu J, Xu Y, Chen W, Wang W. Passive event-related potentials to a single tone in treatment-resistant depression, generalized anxiety disorder, and borderline personality disorder patients. J Clin Neurophysiol 2014, 31(5): 488–492.
17. Wang D, Mo F, Zhang Y, Yang C, Liu J, Chen Z, *et al.* Auditory evoked potentials in patients with major depressive disorder measured by Emotiv system. Biomed Mater Eng 2015, 26 Suppl 1: S917–S923.
18. Xi G, Zhang X, Zhang L, Sui Y, Hui J, Liu S, *et al.* Fluoxetine attenuates the inhibitory effect of glucocorticoid hormones on neurogenesis in vitro via a two-pore domain potassium channel, TREK-1. Psychopharmacology (Berl) 2011, 214: 747–759.
19. Yi LT, Luo L, Wu YJ, Liu BB, Liu XL, Geng D, *et al.* Circadian variations in behaviors, BDNF and cell proliferation in depressive mice. Metab Brain Dis 2015, 30(6):1–9.

20. Hong W, Fan J, Yuan C, Zhang C, Hu Y, Peng D, *et al.* Significantly decreased mRNA levels of BDNF and MEK1 genes in treatment-resistant depression. Neuroreport 2014, 25: 753–755.
21. Luo J, Min S, Wei K, Cao J, Wang B, Li P, *et al.* Behavioral and molecular responses to electroconvulsive shock differ between genetic and environmental rat models of depression. Psychiatry Res 2015, 226: 451–460.
22. Su M, Hong J, Zhao Y, Liu S, Xue X. MeCP2 controls hippocampal brain-derived neurotrophic factor expression via homeostatic interactions with microRNA132 in rats with depression. Mol Med Rep 2015, 12: 5399–5406.
23. Xi G, Hui J, Zhang Z, Liu S, Zhang X, Teng G, *et al.* Learning and memory alterations are associated with hippocampal N-acetylaspartate in a rat model of depression as measured by 1H-MRS. PLoS One 2011, 6: e28686.
24. Yan HC, Cao X, Das M, Zhu XH, Gao TM. Behavioral animal models of depression. Neurosci Bull 2010, 26: 327–337.
25. Yang C, Hong T, Shen J, Ding J, Dai XW, Zhou ZQ, *et al.* Ketamine exerts antidepressant effects and reduces IL-1beta and IL-6 levels in rat prefrontal cortex and hippocampus. Exp Ther Med 2013, 5: 1093–1096.
26. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, *et al.* mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 2010, 329: 959–964.
27. Wang J, Jing L, Toledo-Salas JC, Xu L. Rapid-onset antidepressant efficacy of glutamatergic system modulators: the neural plasticity hypothesis of depression. Neurosci Bull 2015, 31: 75–86.
28. Chen C, Glatt SJ, Tsuang MT. The tryptophan hydroxylase gene influences risk for bipolar disorder but not major depressive disorder: results of meta-analyses. Bipolar Disord 2008, 10: 816–821.
29. Li Z, Zhang Y, Wang Z, Chen J, Fan J, Guan Y, *et al.* The role of BDNF, NTRK2 gene and their interaction in development of treatment-resistant depression: data from multicenter, prospective, longitudinal clinic practice. J Psychiatr Res 2013, 47: 8–14.
30. Pei Y, Smith AK, Wang Y, Pan Y, Yang J, Chen Q, *et al.* The brain-derived neurotrophic-factor (BDNF) val66met polymorphism is associated with geriatric depression: a meta-analysis. Am J Med Genet B Neuropsychiatr Genet 2012, 159B: 560–566.
31. Xiao Z, Liu W, Gao K, Wan Q, Yang C, Wang H, *et al.* Interaction between CRHR1 and BDNF genes increases the risk of recurrent major depressive disorder in Chinese population. PLoS One 2011, 6: e28733.
32. Shen X, Wu Y, Guan T, Wang X, Qian M, Lin M, *et al.* Association analysis of COMT/MTHFR polymorphisms and major depressive disorder in Chinese Han population. J Affect Disord 2014, 161: 73–78.
33. Xu Z, Zhang Z, Shi Y, Pu M, Yuan Y, Zhang X, *et al.* Influence and interaction of genetic polymorphisms in catecholamine neurotransmitter systems and early life stress on antidepressant drug response. J Affect Disord 2011, 133: 165–173.
34. Wang HC, Yeh TL, Chang HH, Gean PW, Chi MH, Yang YK, *et al.* TPH1 is associated with major depressive disorder but not with SSRI/SNRI response in Taiwanese patients. Psychopharmacology (Berl) 2011, 213: 773–779.
35. Li X, Sun N, Xu Y, Wang Y, Li S, Du Q, *et al.* The norepinephrine transporter gene is associated with the retardation symptoms of major depressive disorder in the Han Chinese population. Neural Regen Res 2012, 7: 1985–1991.
36. Yi Z, Li Z, Yu S, Yuan C, Hong W, Wang Z, *et al.* Blood-based gene expression profiles models for classification of subsyndromal symptomatic depression and major depressive disorder. PLoS One 2012, 7: e31283.
37. Liu Z, Huang L, Luo XJ, Wu L, Li M. MAOA variants and genetic susceptibility to major psychiatric disorders. Mol Neurobiol 2015. doi: 10.1007/s12035-015-9374-0.
38. Cai N, Bigdeli TB, Kretzschmar W, Li Y, Liang J, Song L, *et al.* Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature 2015, 523: 588–591.
39. Wang P, Yang Y, Yang X, Qiu X, Qiao Z, Wang L, *et al.* CREB1 gene polymorphisms combined with environmental risk factors increase susceptibility to major depressive disorder (MDD). Int J Clin Exp Pathol 2015, 8: 906–913.
40. Xu Z, Zhang Z, Shi Y, Pu M, Yuan Y, Zhang X, *et al.* Influence and interaction of genetic polymorphisms in the serotonin system and life stress on antidepressant drug response. J Psychopharmacol 2012, 26: 349–359.
41. Hou Z, Yuan Y, Zhang Z, Hou G, You J, Bai F. The D-allele of ACE insertion/deletion polymorphism is associated with regional white matter volume changes and cognitive impairment in remitted geriatric depression. Neurosci Lett 2010, 479: 262–266.
42. Yang C, Xu Y, Sun N, Ren Y, Liu Z, Cao X, *et al.* The combined effects of the BDNF and GSK3B genes modulate the relationship between negative life events and major depressive disorder. Brain Res 2010, 1355: 1–6.
43. Liu Z, Guo H, Cao X, Cheng C, Yang C, Xu C, *et al.* A combined study of GSK3beta polymorphisms and brain network topological metrics in major depressive disorder. Psychiatry Res 2014, 223: 210–217.
44. Hou ZH, Yuan YG. The progress of imaging genetics in depression. Chinese J Psychiat 2009, 42: 185–187.
45. Fang Z, Zhu S, Gillihan SJ, Korczykowski M, Detre JA, Rao H. Serotonin transporter genotype modulates functional connectivity between amygdala and PCC/PCu during mood recovery. Front Hum Neurosci 2013, 7: 704.
46. Wang Z, Yuan Y, Bai F, You J, Li L, Zhang Z. Abnormal default-mode network in angiotensin converting enzyme D allele carriers with remitted geriatric depression. Behav Brain Res 2012, 230: 325–332.
47. Yin Y, Hou Z, Wang X, Sui Y, Yuan Y. The BDNF Val66Met polymorphism, resting-state hippocampal functional connectivity and cognitive deficits in acute late-onset depression. J Affect Disord 2015, 183: 22–30.
48. Chen J, Xu Y, Zhang J, Liu Z, Xu C, Zhang K, *et al.* Genotypic association of the DAOA gene with resting-state brain activity in major depression. Mol Neurobiol 2012, 46: 361–373.
49. Liu CH, Ma X, Song LP, Tang LR, Jing B, Zhang Y, *et al.* Alteration of spontaneous neuronal activity within the salience network in partially remitted depression. Brain Res 2015, 1599: 93–102.
50. Chen Y, Wang C, Zhu X, Tan Y, Zhong Y. Aberrant connectivity within the default mode network in first-episode, treatment-naive major depressive disorder. J Affect Disord 2015, 183: 49–56.
51. Peng D, Liddle EB, Iwabuchi SJ, Zhang C, Wu Z, Liu J, *et al.* Dissociated large-scale functional connectivity networks of the precuneus in medication-naive first-episode depression. Psychiatry Res 2015, 232: 250–256.
52. Guo W, Liu F, Yu M, Zhang J, Zhang Z, Liu J, *et al.* Decreased regional activity and network homogeneity of the fronto-limbic network at rest in drug-naive major depressive disorder. Aust N Z J Psychiatry 2015, 49: 550–556.
53. Guo W, Liu F, Xiao C, Zhang Z, Liu J, Yu M, *et al.* Decreased insular connectivity in drug-naive major depressive disorder at rest. J Affect Disord 2015, 179: 31–37.
54. Guo W, Liu F, Liu J, Yu M, Zhang Z, Liu G, *et al.* Increased cerebellar-default-mode-network connectivity in drug-naive major depressive disorder at rest. Medicine (Baltimore) 2015, 94: e560.

55. Zheng H, Xu L, Xie F, Guo X, Zhang J, Yao L, *et al.* The Altered Triple Networks Interaction in Depression under Resting State Based on Graph Theory. Biomed Res Int 2015, 2015: 386326.
56. Su L, Cai Y, Xu Y, Dutt A, Shi S, Bramon E. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. BMC Psychiatry 2014, 14: 321.
57. Luo H, Tang JY, Wong GH, Chen CC, Lum TY, Chi I, *et al.* The Effect of Depressive Symptoms and Antidepressant Use on Subsequent Physical Decline and Number of Hospitalizations in Nursing Home Residents: A 9-Year Longitudinal Study. J Am Med Dir Assoc 2015, 16:1048–1054.
58. Kuo CL, Chien IC, Lin CH, Cheng SW. Trends, correlates, and disease patterns of antidepressant use among elderly persons in Taiwan. Soc Psychiatry Psychiatr Epidemiol 2015, 50: 1407–1415.
59. Zhang Y, Becker T, Ma Y, Koesters M. A systematic review of Chinese randomized clinical trials of SSRI treatment of depression. BMC Psychiatry 2014, 14: 245.
60. Wang D, Li Z, Li L, Hao W. Real-world, open-label study to evaluate the effectiveness of mirtazapine on sleep quality in outpatients with major depressive disorder. Asia Pac Psychiatry 2014, 6: 152–160.
61. Ma D, Zhang Z, Zhang X, Li L. Comparative efficacy, acceptability, and safety of medicinal, cognitive-behavioral therapy, and placebo treatments for acute major depressive disorder in children and adolescents: a multiple-treatments meta-analysis. Curr Med Res Opin 2014, 30: 971–995.
62. Guo T, Xiang YT, Xiao L, Hu CQ, Chiu HF, Ungvari GS, *et al.* Measurement-Based Care Versus Standard Care for Major Depression: A Randomized Controlled Trial With Blind Raters. Am J Psychiatry 2015, 172: 1004–1013.
63. Wang YX, Xiang YT, Su YA, Li Q, Shu L, Ng CH, *et al.* Antipsychotic Medications in Major Depression and the Association with Treatment Satisfaction and Quality of Life: Findings of Three National Surveys on Use of Psychotropics in China Between 2002 and 2012. Chin Med J (Engl) 2015, 128: 1847–1852.
64. Fang Y, Yuan C, Xu Y, Chen J, Wu Z, Cao L, *et al.* A pilot study of the efficacy and safety of paroxetine augmented with risperidone, valproate, buspirone, trazodone, or thyroid hormone in adult Chinese patients with treatment-resistant major depression. J Clin Psychopharmacol 2011, 31: 638–642.
65. Du J, Zhu M, Bao H, Li B, Dong Y, Xiao C, *et al.* The Role of Nutrients in Protecting Mitochondrial Function and Neurotransmitter Signaling: Implications for the Treatment of Depression, PTSD, and Suicidal Behaviors. Crit Rev Food Sci Nutr 2014. doi: 10.1080/10408398.2013.876960.
66. Li L, Ma X. The guideline of depression prevention and treatment in China, 2nd edition. Beijing: Chinese medical multimedia press 2015.
67. Li X, Xing B, Yu E, Chen W, Wu H. The combined treatment of venlafaxine and quetiapine for treatment-resistant depression: a clinical study. J Neuropsych Clin N 2013, 25(2): 157–160.
68. Chang CM, Sato S, Han C. Evidence for the benefits of nonantipsychotic pharmacological augmentation in the treatment of depression. CNS Drugs 2013, 27 Suppl 1: S21–27.
69. Hou Y, Hu P, Zhang Y, Lu Q, Wang D, Yin L, *et al.* Cognitive behavioral therapy in combination with systemic family therapy improves mild to moderate postpartum depression. Rev Bras Psiquiatr 2014, 36: 47–52.
70. Huang TT, Liu CB, Tsai YH, Chin YF, Wong CH. Physical fitness exercise versus cognitive behavior therapy on reducing the depressive symptoms among community-dwelling elderly adults: A randomized controlled trial. Int J Nurs Stud 2015, 52: 1542–1552.
71. Zu S, Xiang YT, Liu J, Zhang L, Wang G, Ma X, *et al.* A comparison of cognitive-behavioral therapy, antidepressants, their combination and standard treatment for Chinese patients with moderate-severe major depressive disorders. J Affect Disord 2014, 152–154: 262–267.
72. Chen F, Lv X, Fang J, Yu S, Sui J, Fan L, *et al.* The effect of body-mind relaxation meditation induction on major depressive disorder: A resting-state fMRI study. J Affect Disord 2015, 183: 75–82.
73. Liu B, Zhang Y, Zhang L, Li L. Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study. BMC Psychiatry 2014, 14: 342.
74. Jin Y, Phillips B. A pilot study of the use of EEG-based synchronized Transcranial Magnetic Stimulation (sTMS) for treatment of Major Depression. BMC Psychiatry 2014, 14: 13.
75. Xie J, Chen J, Wei Q. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a meta-analysis of stimulus parameter effects. Neurol Res 2013, 35: 1084–1091.
76. Feng SF, Shi TY, Fan Y, Wang WN, Chen YC, Tan QR. Long-lasting effects of chronic rTMS to treat chronic rodent model of depression. Behav Brain Res 2012, 232: 245–251.
77. Du L, Qiu H, Liu H, Zhao W, Tang Y, Fu Y, *et al.* Changes in Problem-Solving Capacity and Association With Spontaneous Brain Activity After a Single Electroconvulsive Treatment in Major Depressive Disorder. J ECT 2016, 32: 49–54.
78. Song GM, Tian X, Shuai T, Yi LJ, Zeng Z, Liu S, *et al.* Treatment of Adults With Treatment-Resistant Depression: Electroconvulsive Therapy Plus Antidepressant or Electroconvulsive Therapy Alone? Evidence From an Indirect Comparison Meta-Analysis. Medicine (Baltimore) 2015, 94: e1052.
79. Moritz S, Cludius B, Hottenrott B, Schneider BC, Saathoff K, Kuelz AK, *et al.* Mindfulness and relaxation treatment reduce depressive symptoms in individuals with psychosis. Eur Psychiatry 2015, 30: 709–714.
80. Wang T, Wang L, Tao W, Chen L. Acupuncture combined with an antidepressant for patients with depression in hospital: a pragmatic randomised controlled trial. Acupunct Med 2014, 32: 308–312.
81. Gong H, Ni C, Shen X, Wu T, Jiang C. Yoga for prenatal depression: a systematic review and meta-analysis. BMC Psychiatry 2015, 15: 14.
82. Qu M, Tang Q, Li X, Zhao R, Li J, Xu H, *et al.* Shen-Qi-Jie-Yu-Fang has antidepressant effects in a rodent model of postpartum depression by regulating the immune organs and subsets of T lymphocytes. Neuropsychiatr Dis Treat 2015, 11: 1523–1540.
83. Ang W, Chen G, Xiong L, Chang Y, Pi W, Liu Y, *et al.* Synthesis and biological evaluation of novel naphthalene compounds as potential antidepressant agents. Eur J Med Chem 2014, 82: 263–273.
84. Fan L, Gong J, Fu W, Chen Z, Xu N, Liu J, *et al.* Gender-Related Differences in Outcomes on Acupuncture and Moxibustion Treatment Among Depression Patients. J Altern Complement Med 2015, 21: 673–680.
85. Yeung WF, Chung KF, Ng KY, Yu YM, Zhang SP, Ng BF, *et al.* Prescription of Chinese Herbal Medicine in Pattern-Based Traditional Chinese Medicine Treatment for Depression: A Systematic Review. Evid Based Complement Alternat Med 2015, 2015: 160189.
86. Li G, Ruan L, Chen R, Wang R, Xie X, Zhang M, *et al.* Synergistic antidepressant-like effect of ferulic acid in combination with piperine: involvement of monoaminergic system. Metab Brain Dis 2015, 30: 1505–1514.

87. Zhai XJ, Chen F, Chen C, Zhu CR, Lu YN. LC-MS/MS based studies on the anti-depressant effect of hypericin in the chronic unpredictable mild stress rat model. J Ethnopharmacol 2015, 169: 363–369.
88. Wang X, Zeng C, Lin J, Chen T, Zhao T, Jia Z*, et al.* Metabonomics approach to assessing the modulatory effects of St John's wort, ginsenosides, and clomipramine in experimental depression. J Proteome Res 2012, 11: 6223–6230.
89. Zhang X, Kang D, Zhang L, Peng L. Shuganjieyu capsule for major depressive disorder (MDD) in adults: a systematic review. Aging Ment Health 2014, 18: 941–953.
90. Zhang ZQ, Yuan L, Yang M, Luo ZP, Zhao YM. The effect of Morinda officinalis How, a Chinese traditional medicinal plant, on the DRL 72-s schedule in rats and the forced swimming test in mice. Pharmacol Biochem Be 2002, 72(1–2): 39–43.
91. Liu CC, Wu YF, Feng GM, Gao XX, Zhou YZ, Hou WJ*, et al.* Plasma-metabolite-biomarkers for the therapeutic response in depressed patients by the traditional Chinese medicine formula Xiaoyaosan: A (1)H NMR-based metabolomics approach. J Affect Disord 2015, 185: 156–163.
92. Fan HM, Sun XY, Guo W, Zhong AF, Niu W, Zhao L*, et al.* Differential expression of microRNA in peripheral blood mononuclear cells as specific biomarker for major depressive disorder patients. J Psychiatr Res 2014, 59: 45–52.
93. Li M, Metzger CD, Li W, Safron A, van Tol MJ, Lord A*, et al.* Dissociation of glutamate and cortical thickness is restricted to regions subserving trait but not state markers in major depressive disorder. J Affect Disord 2014, 169: 91–100.
94. Guo W, Liu F, Xue Z, Gao K, Liu Z, Xiao C*, et al.* Decreased interhemispheric coordination in treatment-resistant depression: a resting-state fMRI study. PLoS One 2013, 8: e71368.
95. Chi KF, Korgaonkar M, Grieve SM. Imaging predictors of remission to anti-depressant medications in major depressive disorder. J Affect Disord 2015, 186: 134–144.
96. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015, 372: 793–795.
97. Ledford H. Medical research: if depression were cancer. Nature 2014, 515: 182–184.