



## Treatment-resistant depression and clinical implications of its association with comorbid anxiety disorders

Masahiko Ichiki, M.D., Ph.D.\*, Jiro Masuya, M.D., Ph.D.\*, Takeshi Inoue, M.D., Ph.D.

*Department of Psychiatry, Tokyo Medical University, Tokyo, Japan*

### ABSTRACT

Childhood abuse, trait anxiety, and neuroticism are associated with depression, and activation of the amygdala has been hypothesized as the biological basis of these predisposing factors. Anxiety disorder often coexists with major depressive disorder, and this comorbidity has been postulated to occur owing to the above predisposing factors. However, this possibility has not yet been fully confirmed in clinical studies. A history of childhood abuse, and anxiety disorder or anxiety symptoms have been reported to coexist in patients with treatment-resistant depression. Therefore, the above hypothesis may also apply to treatment-resistant depression. Large-scale studies are needed to test whether childhood abuse, propensity for trait anxiety/neuroticism, amygdala activation, and the coexistence of anxiety disorder/anxiety symptoms are more pronounced in patients with treatment-resistant depression than those with non-treatment-resistant depression. At present, it is clinically clear that treatment-resistant depression more frequently occurs in patients with comorbid anxiety disorders and a history of childhood abuse. The clinical care of patients with treatment-resistant depression keeping this information in mind may lead to a better understanding of these patients, and may also assist in the development of effective treatment strategies.

**Keywords:** *treatment-resistant depression, comorbidity, anxiety disorder, childhood abuse*

Received August 4, 2020 / Accepted August 11, 2020 / Published September 15, 2020.

### Introduction

Misdiagnoses and subsequent inappropriate treatment were pointed out as the main factors causing treatment-resistant depression [1]. Among such cases, the misdiagnosis of bipolar disorder is a good example of a paradigm failure of so-called "treatment-resistant depression" because the treatment guidelines differ between bipolar depression and unipolar depression [2, 3]. Therefore, it is necessary to always reconsider whether a patient truly has treatment-resistant depression. Bipolar disorder often starts with a depressive episode [4], and it takes several years from the onset of the first de-

pressive episode to the final definitive diagnosis of bipolar disorder [5]. As such, a diagnosis of depression in patients with unrecognized bipolar disorder before they manifest manic or hypomanic episodes is not necessarily a misdiagnosis, but is the main cause of treatment-resistant depression [6, 7].

In the previous 10 years, an association between anxiety symptoms / anxiety disorders and treatment-resistant depression was identified [8, 9]; however, the mechanism of this association remains unclear. Reports in the literature suggest that multiple factors, such as childhood abuse, amygdala activation, and bipolar disorder may be involved in this

---

Corresponding author: Takeshi Inoue, M.D., Ph.D., Department of Psychiatry, Tokyo Medical University 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan; Tel: +81-3-3342-6111; Fax: +81-3-3340-4499; E-mail: tinoue@tokyo-med.ac.jp

\*Equally contributed to this paper and will be designated as co-first authors.

association.

In this review, we introduce recent research on treatment-resistant depression and its association with anxiety symptoms and anxiety disorders, which is assumed to be complex. We have defined treatment-resistant depression as “the persistence of moderate depressive symptoms after treatment with two or more antidepressants at a sufficient dose and for a sufficient period” [7, 10].

### **Treatment-resistant depression and comorbidity of anxiety disorder**

According to a multivariate analysis from a large European multicenter study, treatment-resistant depression was characterized by the comorbidity of anxiety disorder, a present risk of suicide, melancholic features, and nonresponse to the first antidepressant treatment in a patient’s lifetime [9]. Although a multivariate analysis was not able to confirm a statistical significance, a univariate analysis indicated that the comorbidity of panic disorder and social anxiety disorder were also significantly associated with treatment resistance. This European multicenter study was the first large epidemiological study on treatment-resistant depression. However, the reason for the association between comorbid anxiety disorder and treatment-resistant depression remains unclear.

A group from Harvard University reported that a patient’s nonresponsiveness to selective serotonin reuptake inhibitors (SSRIs) is associated more closely with the presence of anxiety symptoms than the severity of depressive symptoms, although this does not fit the present definition of treatment resistance [8]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) added the specifier “anxious distress” for the diagnosis of depressive disorders, to emphasize the focus on anxiety symptoms [11]. DSM-5 states that high levels of anxiety are associated with higher suicide risk, longer duration of illness, and greater likelihood of nonresponse to treatment. These previous studies by the group from Harvard University may have affected the criteria of DSM-5. Owing to its nature, patients with major depressive disorder often show anxiety symptoms [12]. As DSM-III excluded anxiety symptoms from the diagnostic criteria for major depressive disorder, anxiety symptoms have been regarded as a theoretically different concept from depressive symptoms. Based on this historical back-

ground, anxiety symptoms have now been re-recognized as comorbid symptoms or syndromes of major depressive disorder. This is important information towards conducting further research and deepening our understanding of psychiatry. The conventional German diagnosis method may not have considered the importance of anxiety in major depressive disorder, because it is based on induction rather than deduction, and therefore cannot separate anxiety as a distinct component from depression. Therefore, the philosophy of DSM has made it possible to analyze the coexistence of anxiety and depression.

### **Clinical background of the comorbidities of depressive disorder and anxiety disorder**

Major depressive disorder and anxiety disorder reportedly coexist at high rates [13-16]. Comorbid anxiety disorders are known to negatively affect the outcomes of mood disorders. A prospective study on the long-term course of depression demonstrated that in patients with comorbid anxiety disorders, depression persisted for longer periods, they required more time for remission of the depressive episodes, and were more seriously affected than those without comorbid anxiety disorders [17]. A meta-analysis of several previous studies indicated that comorbid anxiety disorder is a risk factor for suicide and suicide attempts in patients with depressive disorder [18]. Moreover, another meta-analysis indicated the strong associations between illicit drug use and major depressive disorder, between illicit drug use and any anxiety disorder, between alcohol use disorders and major depressive disorder, and between alcohol use disorders and any anxiety disorder [19]. This high rate of comorbidities may reflect the direct or indirect effects of a primary psychiatric disorder on the development of a subsequent disorder, and the existence of a common cause between both disorders through genetic predisposition and socioeconomic factors.

Common characteristics associated with the coexistence of depressive disorders and anxiety disorders have been reported to be a history of childhood trauma, younger disease onset, neuroticism, a longer course of symptoms, and more severe illness [15]. Interestingly, childhood abuse is also a characteristic associated with comorbidity when major depressive disorder is preceded by anxiety disorder, but not when anxiety disorder is preceded by major depressive disorder [13]. In patients with both ma-

major depressive disorder and anxiety disorder, the onset of the anxiety disorder often precedes that of major depressive disorder [15]. A comorbidity of anxiety disorder is significantly more frequent in patients with bipolar disorder than those with major depressive disorder [14, 16]. The results of a large-scale multivariate logistic regression analysis demonstrated that childhood abuse, atypical depression symptoms, and deterioration of health-associated quality of life were commonly associated with comorbid anxiety disorders in patients with bipolar disorder and major depressive disorder; sexual abuse was significantly associated with bipolar disorder and neglect was significantly associated with major depressive disorder [16]. A history of childhood abuse is more frequent in patients with bipolar disorder than in those with major depressive disorder [14]. In addition, a history of childhood abuse is more frequent in patients with treatment-resistant depression than those with non-treatment-resistant depression [20]. Furthermore, one-fourth of patients with treatment-resistant depression are thought to have unrecognized bipolar disorder [6, 7]. Patients with bipolar disorder have more comorbidities of anxiety disorders and a higher rate of history of childhood abuse than patients with major depressive disorder [16]. Taken together, childhood abuse may be the common basis of anxiety disorder and treatment-resistant depression, which may be partly attributable to bipolar disorder. However, there have been no reports to date analyzing the association between anxiety disorder comorbidities and a history of childhood abuse in patients with treatment-resistant depression.

### Brain region responsible for anxiety

Unlike neurological and neuropsychological symptoms, the brain regions responsible for most psychiatric symptoms remain unknown. However, the brain region responsible for anxiety has been rapidly elucidated since the 1990s, and its detailed neural circuits and molecular biological mechanisms have been clarified [21]. In animals and humans, anxiety and fear symptoms are diminished when the amygdala is damaged on both sides. When a stimulus that causes anxiety or fear, such as gaze, facial expression, pain, or speaking in public occurs, the blood flow to the amygdala increases, which is called amygdala activation [21]. Amygdala activation is more pronounced in patients with anxiety disorder than in healthy subjects. Amygdala activation is reduced by treatments that

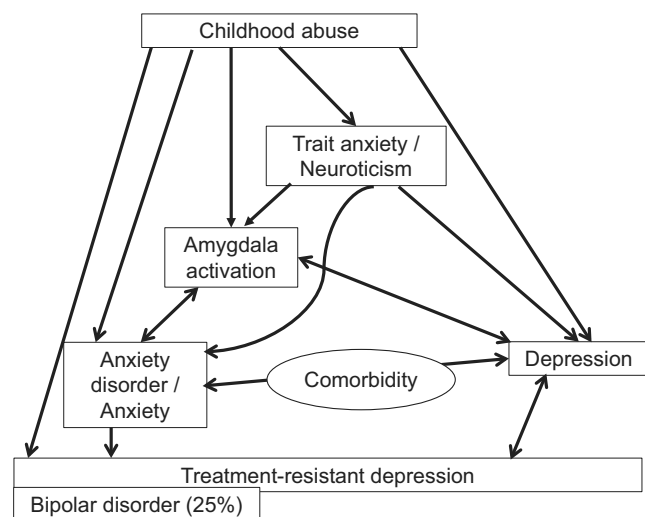
improve symptoms [21]. SSRIs reduce amygdala activation in both anxiety disorder patients and healthy subjects [21]. In animal models of anxiety and fear, the local administration of SSRIs to the amygdala alleviates anxiety and fear by increasing extracellular serotonin concentrations in the amygdala, leading to its inhibition via the serotonin<sub>1A</sub> receptor [21-23]. In addition, the local administration of a serotonin<sub>1A</sub> receptor agonist to the amygdala also showed anxiolytic effects [24]. These findings suggest that the amygdala is the brain region crucial for anxiety, and that an increase in serotonin neurotransmission by treatment with SSRIs or serotonin<sub>1A</sub> receptor agonists reduces anxiety through an inhibitory action via serotonin<sub>1A</sub> receptor stimulation in the amygdala.

A systematic meta-analysis study of functional magnetic resonance imaging data demonstrated that in both major depressive disorder patients and healthy controls, antidepressants decrease activity in the bilateral amygdala in response to negative emotions [25]. However, there has been no study to date comparing amygdala activation in response to negative emotions between patients with treatment-resistant depression and those with non-treatment-resistant depression. A resting functional connectivity study showed that a more distributed decrease in connectivity occurs in the amygdala of patients with non-treatment-resistant depression than those with treatment-resistant depression, whereas patients with treatment-resistant depression showed more disrupted functional connectivity in the prefrontal areas and thalamic areas bilaterally [26]. Therefore, amygdala activity in response to negative emotions in patients with treatment-resistant depression remains inconclusive. Further studies are hence necessary to elucidate the abnormalities and possible heterogeneity of amygdala activation in patients with treatment-resistant depression.

### Childhood abuse and amygdala activation

As described in the previous section, anxiety and fear induces amygdala activation, and this activation is more marked in patients with anxiety disorder than in controls [21, 27-29]. The highly selective SSRIs citalopram and escitalopram reduce amygdala activation in both healthy individuals and social anxiety disorder patients, leading to symptomatic alleviation in the patients [28, 30].

In healthy individuals, the degree of amygdala acti-



**Figure 1.** A schema of the hypothesis of the associations of treatment-resistant depression with childhood abuse, trait anxiety, amygdala activation, and comorbidity of anxiety disorder and anxiety symptoms

vation increases with a history of childhood abuse [31]. Amygdala activation is also reported to occur during facial recognition tasks in patients with depression, and activation is reduced by treatment with SSRIs [32]. It has been suggested that the amygdala activation observed in patients with depression is not caused by the depression itself, but is rather a result of a history of childhood abuse, which is common in patients with depression [31]. Interestingly, a history of childhood abuse increases depressive symptoms in general adult volunteers via an increase in trait anxiety [33], and trait anxiety is associated with amygdala activation [34]. Thus, the association between amygdala activation and childhood abuse explains the biological basis of anxiety symptoms in patients with anxiety disorder and depression. The comorbidity of depression and anxiety disorder may be explained by amygdala activation, but the underlying mechanism has not been clarified to date. A history of childhood abuse has been pointed out as a cause of treatment-resistant depression [20, 35]. Amygdala activation is hence hypothesized to be more marked in patients with treatment-resistant depression, leading to the increased comorbidity of anxiety disorder, but this point requires further analysis in the future.

### Clinical mechanism of the comorbidity of anxiety disorder/anxiety symptoms in treatment-resistant depression

Summarizing the above-mentioned studies leads to

the associations shown in Figure 1. Associations among individual factors have been reported to date, but whether any of these factors are closely associated with treatment-resistant depression requires future clarification. As mentioned in the Introduction section, clinical studies to date indicate that about 25% of patients diagnosed as having treatment-resistant depression actually have “unrecognized bipolar disorder” [7, 24]. Although anxiety disorders are more common in patients with bipolar disorder than in those with major depressive disorder [14, 16], and childhood abuse affects the symptoms and course of bipolar disorder [36, 37], factors other than childhood abuse and comorbid anxiety in Figure 1 are likely to be associated with the involvement of bipolar disorder in treatment-resistant depression. We hence propose the hypothesis that childhood abuse increases trait anxiety/neuroticism and amygdala activation, and these factors then induce comorbid anxiety disorders/anxiety symptoms, and this complex interaction finally results in the treatment-resistance of major depressive disorder. Patients with unrecognized bipolar disorder are often diagnosed as having treatment-resistant depression, and may hence increase the occurrence of these complex interactions.

### Clinical implications of our hypotheses

Because SSRIs attenuate amygdala activation and neuroticism, SSRIs may be effective for the treatment of major depressive disorder with comorbid anxiety disorder [21,38]. Treatment guidelines recommend SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs) for the treatment of major depressive disorder with comorbid anxiety disorder or anxiety symptoms, although there are no clear lines of evidence regarding their efficacy [2, 39]. However, SSRIs are not expected to have any further therapeutic effects on patients with treatment-resistant depression, most of whom have already been treated by SSRIs. Furthermore, other classes of antidepressants (SNRIs, bupropion, and the addition of serotonin<sub>1A</sub> receptor agonists) are reportedly not effective for patients with anxious major depressive disorder, including inadequate responders to SSRIs [40]. On the other hand, the addition of typical and atypical antipsychotic drugs was reported to be effective for comorbid anxiety disorders and symptoms of major depressive disorder [41]. Adjunctive aripiprazole, which is a first-line drug for treatment-resistant depression, is effective for treatment-resistant anxious depression [42].

In treatment-resistant depression, dopamine receptor D<sub>2</sub> stimulation may be required in addition to serotonin reuptake inhibition for increased treatment efficacy against anxiety, which also indicates the involvement of multiple neurotransmitters in anxiety [43]. It may hence be necessary to use other drugs that act on other anxiety-associated neurotransmitters (i.e., dopamine, noradrenaline, and glutamate) for the treatment of comorbid anxiety in treatment-resistant depression [43]. In addition, psychotherapy interventions that focus on personality traits, such as trait anxiety and neuroticism, may also be effective therapeutic interventions, as these personality traits underlie the comorbidity of anxiety disorders.

### Conclusion

The clinical relevance of only a history of childhood abuse and comorbid anxiety disorder has been clarified for treatment-resistant depression. Therefore, it is uncertain whether the hypothesis shown in Figure 1 applies as a mechanism for the comorbidity of anxiety disorder in treatment-resistant depression. At present, we can hence only say that providing clinical care to patients considering their history of childhood abuse and comorbid anxiety disorder will deepen our understanding of patients with treatment-resistant depression, and lead to an accurate medical diagnosis.

### CONFLICT OF INTEREST

Takeshi Inoue has received personal fees from Otsuka Pharmaceutical, Tanabe Mitsubishi Pharma, Pfizer, Takeda Pharmaceutical, Kyowa Pharmaceutical Industry, MSD, and Dainippon Sumitomo Pharma. The authors report no other conflicts of interest in this work.

### ACKNOWLEDGEMENT

We thank Dr. Helena Popiel of the Department of International Medical Communications, Tokyo Medical University for editorial review of the manuscript.

### REFERENCES

[1] Parker GB, Malhi GS, Crawford JG, Thase ME. Identifying “paradigm failures” contributing to treatment-resistant depression. *J Affect Disord* 2005; 87: 185-191.  
 [2] Kennedy SH, Lam RW, McIntyre RS, et al.

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry* 2016; 61: 540-560.  
 [3] Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018; 20: 97-170.  
 [4] Daban C, Colom F, Sanchez-Moreno J, García-Amador M, Vieta E. Clinical correlates of first-episode polarity in bipolar disorder. *Compr Psychiatry* 2006; 47: 433-437.  
 [5] Akiskal HS, Maser JD, Zeller PJ, et al. Switching from ‘unipolar’ to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry* 1995; 52: 114-123.  
 [6] Li CT, Bai YM, Huang YL, et al. Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study. *Br J Psychiatry* 2012; 200: 45-51.  
 [7] Inoue T, Nakagawa S, Kitaichi Y, et al. Long-term outcome of antidepressant-refractory depression: the relevance of unrecognized bipolarity. *J Affect Disord* 2006; 95: 61-67.  
 [8] Papakostas GI, Fan H, Tedeschini E. Severe and anxious depression: combining definitions of clinical sub-types to identify patients differentially responsive to selective serotonin reuptake inhibitors. *Eur Neuropsychopharmacol* 2012; 22: 347-355.  
 [9] Souery D, Oswald P, Massat I, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry* 2007; 68: 1062-1070.  
 [10] Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press, 1995: 1081-1097.  
 [11] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders : DSM-5*. Washington, D.C.: American Psychiatric Publication Inc., 2013.  
 [12] Radford M, Nakane Y, Ohta Y, Mann L, Kalucy R. A study of depression in two cul-

- tures: a transcultural study with Japanese and Australian clinically depressed patients. *Jpn J Psychiatry Neurol* 1989; 43: 119-132.
- [13] de Graaf R, Bijl RV, Ten Have M, Beekman AT, Vollebergh WA. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *J Affect Disord* 2004; 82: 461-467.
- [14] Inoue T, Inagaki Y, Kimura T, Shirakawa O. Prevalence and predictors of bipolar disorders in patients with a major depressive episode: the Japanese epidemiological trial with latest measure of bipolar disorder (JET-LMBP). *J Affect Disord* 2015; 174: 535-541.
- [15] Lamers F, van Oppen P, Comijs HC, et al. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry* 2011; 72: 341-348.
- [16] Inoue T, Kimura T, Inagaki Y, Shirakawa O. Prevalence of comorbid anxiety disorders and their associated factors in patients with bipolar disorder or major depressive disorder. *Neuropsychiatr Dis Treat* 2020; 16:1695-1704.
- [17] Gaynes BN, Magruder KM, Burns BJ, Wagner HR, Yarnall KS, Broadhead WE. Does a coexisting anxiety disorder predict persistence of depressive illness in primary care patients with major depression? *Gen Hosp Psychiatry* 1999; 21: 158-167.
- [18] Hawton K, Casanas ICC, Haw C, Saunders K. Risk factors for suicide in individuals with depression: a systematic review. *J Affect Disord* 2013; 147: 17-28.
- [19] Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: A systematic review and meta-analysis. *Drug Alcohol Depend* 2015; 154: 1-13.
- [20] Toda H, Inoue T, Tsunoda T, et al. The structural equation analysis of childhood abuse, adult stressful life events, and temperaments in major depressive disorders and their influence on refractoriness. *Neuropsychiatr Dis Treat* 2015; 11: 2079-2090.
- [21] Inoue T. Neuroscientific understanding of the mechanism of action of SSRI in the treatment of anxiety disorders. *Anxiety Disord Res* 2018; 10: 20-28 (in Japanese).
- [22] Izumi T, Kitaichi Y, An Y, Inoue T, Yoshioka M. The amygdala is the target brain site of anxiolytic effects of SSRIs. In: Pinna G, Izumi T, eds. *Facilitating Resilience after PTSD: A Translational Approach*. New York: Nova Science Publishers, 2018: 19-89.
- [23] Inoue T, Li XB, Abekawa T, et al. Selective serotonin reuptake inhibitor reduces conditioned fear through its effect in the amygdala. *Eur J Pharmacol* 2004; 497: 311-316.
- [24] Li X, Inoue T, Abekawa T, et al. 5-HT1A receptor agonist affects fear conditioning through stimulations of the postsynaptic 5-HT1A receptors in the hippocampus and amygdala. *Eur J Pharmacol* 2006; 532: 74-80.
- [25] Ma Y. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. *Mol Psychiatry* 2015; 20: 311-319.
- [26] Lui S, Wu Q, Qiu L, et al. Resting-state functional connectivity in treatment-resistant depression. *Am J Psychiatry* 2011; 168: 642-648.
- [27] Furmark T, Tillfors M, Marteinsdottir I, et al. Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Arch Gen Psychiatry* 2002;59:425-433.
- [28] Gingnell M, Frick A, Engman J, et al. Combining escitalopram and cognitive-behavioural therapy for social anxiety disorder: randomised controlled fMRI trial. *Br J Psychiatry* 2016; 209: 229-235.
- [29] Stein MB, Goldin PR, Sareen J, Zorrilla LT, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry* 2002; 59: 1027-1034.
- [30] Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biol Psychiatry* 2006; 59: 816-820.
- [31] van Harmelen AL, van Tol MJ, Demenescu LR, et al. Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Soc Cogn Affect Neurosci* 2013; 8: 362-369.
- [32] Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* 2001; 50: 651-658.
- [33] Uchida Y, Takahashi T, Katayama S, et al. Influence of trait anxiety, child maltreatment,

- and adulthood life events on depressive symptoms. *Neuropsychiatr Dis Treat* 2018; 14: 3279-3287.
- [34] Indovina I, Robbins TW, Nunez-Elizalde AO, Dunn BD, Bishop SJ. Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans. *Neuron* 2011; 69: 563-571.
- [35] Nelson J, Klumpp A, Doebler P, Ehring T. Childhood maltreatment and characteristics of adult depression: meta-analysis. *Br J Psychiatry* 2017; 210: 96-104.
- [36] Toda H, Inoue T, Tanichi M, et al. Affective temperaments play an important role in the relationship between child abuse and the diagnosis of bipolar disorder. *Psychiatry Res* 2018; 262: 13-19.
- [37] Daruy-Filho L, Brietzke E, Lafer B, Grassi-Oliveira R. Childhood maltreatment and clinical outcomes of bipolar disorder. *Acta Psychiatrica Scandinavica* 2011; 124: 427-434.
- [38] Quilty LC, Meusel LA, Bagby RM. Neuroticism as a mediator of treatment response to SSRIs in major depressive disorder. *J Affect Disord* 2008; 111: 67-73.
- [39] Sakurai H, Uchida H, Kato M, et al. Pharmacological management of depression: Japanese expert consensus. *J Affect Disord* 2020; 266: 626-632.
- [40] Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR\*D report. *Am J Psychiatry* 2008; 165: 342-351.
- [41] Gao K, Muzina D, Gajwani P, Calabrese JR. Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: a review. *J Clin Psychiatry* 2006; 67: 1327-1340.
- [42] Trivedi MH, Thase ME, Fava M, et al. Adjunctive aripiprazole in major depressive disorder: analysis of efficacy and safety in patients with anxious and atypical features. *J Clin Psychiatry* 2008; 69: 1928-1936.
- [43] Inoue T, Nishikawa H, Koyama T. Progress in the neuroscience regarding fear conditioning: new development of cerebral localizationist theory. *Jpn J Clin Psychiatry* 2006; 35: 639-649.