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Treatment-resistant panic disorder: clinical significance, concept and management

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ABSTRACT

Panic disorder is commonly prevalent in the population, but the treatment response for panic disorder in clinical practice is much less effective than that in our imagination. Increasing evidence suggested existence of a chronic or remitting–relapsing clinical course in panic disorder. In this systematic review, we re-examine the definition of treatment-resistant panic disorder, and present the potential risk factors related to the treatment resistance, including the characteristics of panic disorder, other psychiatric and physical comorbidities, and psychosocial stresses. Furthermore, we summarize the potential pathophysiologies, such as genetic susceptibility, altered brain functioning, brain-derived neurotrophic factor, and long-term inflammation, to explain the treatment resistance. Finally, we conclude the current therapeutic strategies for treating treatment-resistant panic disorder from pharmacological and non-pharmacological views.

1. Introduction

Panic disorder, emerging as a diagnostic entity since 1980 with the publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM) III, has gained clinical, scientific, and public health attentions in recent decades (American Psychiatric Association, 1980; Klein, 1999; Roy-Byrne et al., 2006). Panic disorder manifests the recurrent unexpected paroxysmal panic attacks, along with concern for the possibility of future attacks, development of phobic avoidance, or any other change in behavior due to the attacks (Klein, 1999; Roy-Byrne et al., 2006; American Psychiatric Association, 2013; Asmundson et al., 2014). The National Comorbidity Survey-Replication (NCS-R) reports that the prevalence of panic attack estimates 11.2% for 12 months and 28.3% for lifetime, and the prevalence of panic disorder are down to 2.7% for 12 months and 4.7% for lifetime (Kessler et al., 2005a, 2005b, 2006).

The Global Burden of Diseases, Injuries, and Risk Factors Study reported that anxiety disorders, including panic disorder, accounted for approximately 1% of all disability-adjusted life years (DALYs) and 3.5% of all of the years lived with disability (YLDs) worldwide, and among all mental disorders the disease burden caused by anxiety disorders was only second to that by depressive disorders (Lynskey and Strang, 2013; Whiteford et al., 2013). The MacArthur Foundation Midlife Development in the United States survey demonstrated that panic disorder increased an approximately 2-fold risk of 30-day work impairment and caused 1.7 work days missed (Kessler et al., 2001). However, approximately eighty percent and sixty-five percent of patients with panic disorder sought for medical treatment during lifetime and in the recent 1 year (Kessler et al., 2006), but only thirty-six percent of patients make a prompt treatment contact in the first year of onset, with a median duration of 10-year delay in initial treatment contact after onset of panic disorder (Wang et al., 2005, 2007).

Unfortunately, when panic patients underwent an optimal treatment suggested by the current clinical guidelines (American Psychiatric Association, 1998; Baldwin et al., 2005, 2014; Bandelow et al., 2002, 2008), over fifty percent of patients with panic disorder still suffered from threshold or subthreshold panic symptoms and did not achieve a full remission, while only one-third of the patients can maintain a stable panic-free condition during the follow-up (Cowley et al., 1996; Katschnig and Amering, 1998; Swoboda et al., 2003; Wittchen et al., 2008; Batelaan et al., 2010a, 2010b). Furthermore, almost half of the patients with panic disorder relapsed later in life after their remission (Cowley et al., 1996; Hirschfeld, 1996; Swoboda et al., 2003; Yonkers et al., 2003; Bruce et al., 2005; Katon, 2006; Francis et al., 2007). For example, a 5-year naturalistic follow-up study conducted by Cowley et al. showed that thirty percent of the patients were panic-free at 12 months but more than 50% of patients still experienced panic attacks or panic disorder during the follow-up period (Cowley et al., 1996). Swoboda et al. followed patients with panic disorder for 11 years with the evaluation of Panic Attack Scale measuring the frequency of panic attacks, Marks–Sheehan-Scale rating global phobia, and Sheehan Disability Scales assessing three areas of disability, and found that one-third of patients still suffered from panic attacks or panic disorder,

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up to half of patients had the phobic avoidance, and approximately 30% of patients experienced the disability in social life (Swoboda et al., 2003). A growing body of evidence indicated a chronic or a remitting–relapsing clinical course in panic disorder which significantly interfered with the quality of life among the sufferers (Cowley et al., 1996; Hirschfeld, 1996; Katschnig and Amering, 1998; Swoboda et al., 2003; Yonkers et al., 2003; Batelaan et al., 2010a, 2010b). A chronic clinical course was defined as a persistent threshold and sub-threshold panic symptoms, such as panic attacks or phobic avoidance, among patients with panic disorder; a remitting–relapsing clinical course indicated that patients with panic disorder had a period of panic-free interval but developed panic symptoms again later in life (Cowley et al., 1996; Hirschfeld, 1996; Katschnig and Amering, 1998; Swoboda et al., 2003; Yonkers et al., 2003; Batelaan et al., 2010a, 2010b). In this decade, several studies began to discuss and establish the concept of treatment-resistant panic disorder (Stein and Seedat, 2004; Bystritsky, 2006; Menezes et al., 2007; Ammar et al., 2015). In this systematic review article, we will focus on the treatment-resistant panic disorder in the aspects of disease definition, psychopathology, pathophysiology, and treatment.

2. Remission of panic disorder and the definition of treatment resistance

At first we have to define the treatment resistance of panic disorder. Relative to that the treatment resistance of depression has been commonly investigated despite the fact that many clinical and diagnostic debates still existed (Souery et al., 2006; Gaynes, 2009; Papakostas and Ionescu, 2015), the treatment resistance of panic disorder was much less explored and still unclear. Before we discuss the treatment resistance of panic disorder, we should first understand the definition of remission of panic disorder because, as observed by Bystritsky, treatment resistance was reversely associated with the treatment remission (Bystritsky, 2006). The diagnosis of panic disorder was constructed in two domains: unexpected panic attacks presented by various autonomic and somatic symptoms, such as palpitation, sweating, dizziness, paresthesias, chills, and derealization, and persistent cognitive anxiety and worries for additional attacks and the implications of the attack or its consequences, such as losing control, going crazy, and having a heart attack (Craske et al., 2010; Asmundson et al., 2014). Actually, the absence of autonomic and somatic symptoms of panic disorder did not mean a real recovery from panic disorder. For example, a panic patient did not suffer from panic attacks again but he or she still ruminated about the catastrophic experiences that he or she experienced at previous panic attacks all the time. This example suggested that symptomatic remission (panic-free condition) was not equal to, and even far away from, the functional remission (recovery) in panic disorder. On the other hand, the presence of panic attacks may not always indicate pathology and could be a normal response to an ongoing stress (Bystritsky, 2006). The assessment of remission and recovery in panic disorder should be multidimensional, and should always include not only the autonomic and somatic symptoms but also the functional parameters.

Two potential remission criteria for panic disorder were proposed (Ballenger et al., 1998; Ballenger, 1999, 2001; Doyle and Pollack, 2003) (Table 1). Criteria option 1 definition was based on the basis of almost complete resolution in 5 principal domains: panic attacks (the core feature of panic disorder), anticipatory anxiety, panic-related phobias, well-being/severity of illness, and functional and social impairment caused by the panic disorder (Ballenger, 1999). No or minimal anxiety was defined as a Hamilton Rating Scale for Anxiety (HAM-A) score less than or equal to 7 to 10; no or mild functional and social impairment was defined as a Sheehan Disability Scale score less than or equal to 1 on each item (Ballenger, 1999, 2001). In addition, resolution of depression, defined as a Hamilton Rating Scale for Depression (HAM-D) score less than or equal to 7, was included in the remission criteria of panic disorder (Ballenger, 1999, 2001). Criteria option 2 was only defined as a Panic Disorder Severity Scale score (PDSS) less than or equal to 3 with one individual item more than 1 and HAM-D score less than or equal to 7 (Ballenger, 2001). PDSS incorporated panic attack frequency, agoraphobic avoidance, generalized/free floating and anticipatory anxiety, as well as functional impairment, into a single measure. Briefly speaking, the more appropriate approach for defining the remission of panic disorder should be to integrate the symptomatic criteria, such as HAM-A or Panic Disorder Severity Scale, and the functional criteria, such as Clinical Global Impressions scale (CGI) or Sheehan Disability Scale score (Bandelow, 2006; Bandelow et al., 2006). The symptom severity defined by the symptomatic criteria and the functional impairment defined by the functional criteria are significantly inter-related, indicating that the less symptom severity is correlated with the less functional impairment (Bandelow, 2006; Bandelow et al., 2006). For example, based on the CGI scale, it was calculated, which HAM-A score ≦ 10 corresponds to a CGI-severity score of "not at all ill" or "borderline mentally" (as natural definition of "remission" by clinicians) (Bandelow, 2006; Bandelow et al., 2006).

Table 1
Proposed remission criteria of panic disorder[a].

Criteria option 1	Criteria option 2
Essentially free of panic attacks No or mild agoraphobic avoidance No or minimal anxiety: HAM-A score ≤ 7–10 No functional impairment: Sheehan Disability Scale score ≤ 1 on each item No or minimal symptoms of depression: HAM-D score ≤ 7	PDSS total score ≤ 3, and no individual item score > 1 HAM-D score ≤ 7

HAM-A: Hamilton Rating Scale for Anxiety; HAM-D: Hamilton Rating Scale for Depression; PDSS: Panic Disorder Severity Scale.
[a] Based on Ballenger et al. and Doyle et al.

Treatment resistance of panic disorder should be defined as the failure to achieve remission criteria mentioned in the above (options 1 and 2) after at least 6 months of optimal treatment (Ballenger, 1999, 2001; Roy-Byrne et al., 2005; Bandelow, 2006; Bystritsky, 2006). The longitudinal studies investigating the long-term outcome of panic disorder determined that approximately one-third of panic patients would be considered fully recovered from the standard treatments, the other one third would be considered improved, and the last one-third would be classified as the treatment-resistant group by the contemporary treatments (Brown et al., 1996; Cowley et al., 1996; Katschnig and Amering, 1998; Swoboda et al., 2003; Yonkers et al., 2003; Bystritsky, 2006).

3. Factors related to the treatment resistance

Factors related to treatment resistance of panic disorder could also be defined as factors related to the failure to achieve the remission of panic disorder. We delineated five major risk domains, including characteristics of panic disorder, personal demographic characteristic, medical comorbidities, psychiatric comorbidities, and psychosocial factors, with the treatment resistance of panic disorder in the following text (Table 2).

3.1. Characteristics of panic disorder

The greater severity of panic symptoms, the higher frequency of panic attacks, the previous history of panic attack and disorder, the longer course of panic disorder, the persistent existence of anticipatory anxiety and panic-related phobias, the younger age of panic attack onset, and the lower level of individual functioning have been proven to be related to the susceptibility to the treatment resistance of panic disorder (Hirschfeld, 1996; Katschnig and Amering, 1998; Yonkers et al., 2003; Francis et al., 2007; Batelaan et al., 2010a, 2010b; Ginsburg et al., 2011; Ramsawh et al., 2011; Sibrava et al., 2013). Furthermore, a growing number of evidence suggested the persistent