Treatment-resistant mood disorders

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Treatment-resistant mood disorders pose a great socioeconomic and life-threatening burden on public health system. On one hand, major depressive disorder (MDD) has a lifetime prevalence of 17-21%, and it is a leading cause of disability adjusted life years worldwide accordingly to The Global Burden of Disease study[1]. However, only 30-40% of patients achieve remission following a standard trial with a first-line antidepressant agent[2]. On the other hand, bipolar disorder (BD) affects about 2% of the world's population, with subthreshold forms affecting another 2%[3]. It is known that non-response in bipolar depression is also highly prevalent, and it occurs in 40% of patients[4]. Moreover, the addition of antidepressants to an ongoing treatment with mood stabilizers will be helpful in only a quarter of patients with bipolar depression[5]. It is also known that the rates of completed suicide in patients with BD are 7.8% in men and 4.9% in women[6], which could be partially explained by treatment refractoriness. Therefore, despite the pharmacological and psychological strategies to treat patients with mood disorders, how to treat the large number of patients who are refractory to them is still a major challenge. Lack of such knowledge is an important question since treatment-resistant mood disorder patients are associated with greater morbidity, suicide attempts, as well as with extensive use of mood-related and general medical services[7]. Thus, a book on the subject of treatment resistance is key and of great clinical and public health value.

The book "Treatment-Resistant Mood Disorders"[8] covers the forefront findings in this issue and provides a detailed outline of current therapeutic strategies and future therapeutic targets. It stands out as an essential tool for clinicians and researchers. The first chapters of the book looking for enlighten the reader about the current definitions of refractory mood disorders, as well as aspects related to epidemiology and assessment. Notwithstanding the lack of a clear consensus on a working criteria for treatment resistance mood disorders, several key parameters have been agreed, including the multi-dimensional assessment of the symptoms severity, presence of psychiatric or general medical comorbidity, and the objective determination of previous response to adequate treatments. One interesting point presented by the book is the comorbidity with anxiety disorders, such as posttraumatic stress disorder and panic disorder, which are common among treatment-resistant patients[9,10]. The likelihood of remission in anxious depression was only one third compared with those having pure depression for instance[11]. Besides refractoriness to antidepressants and mood stabilizers, patients with comorbidity anxiety disorders are also associated with functional impairment, poor psychosocial adjustments, more frequent hospitalizations, increase suicidality, and slower recovery from a mood episode[9,10,12].

Both chapters of predictors of treatment response in MDD and BD cover the substantial progress that has been made over the last few years in the search for clinically useful variables. In this vein, a recent work has led to the development of a risk stratification tool for treatment resistance in MDD incorporating both baseline socio-demographic and clinical features[13]. The study was innovative because of the use of machine learning techniques to analyze several variables at the same time leading to a useful predictive tool to assess treatment resistance. However, clinical information alone probably is insufficient for adequate prediction. Genetics and neurobiological markers may help to improve the accuracy of the clinical predictive tools. For instance, a large study including 1761 bipolar type-I patients from the Taiwan Bipolar Consortium showed that two single nucleotide polymorphism located in the introns of GADL1 gene (rs17026688 and rs17026651) were strongly associated with the response to lithium maintenance treatment[14]. Therefore, future studies may combine clinical, genetic, epigenetic, neuroimaging, and/or neurobiological markers to obtain meaningful signatures to predict treatment response and provide a more personalized treatment[15]. Advanced pattern recognition methods, such as machine learning techniques, that could integrate these characteristics may be of great value in this challenge.

The book also supplies updated data about evidence-based pharmacological and psychosocial approaches for treatment-resistant mood disorder, as well as about the use of electroconvulsive therapy, which remains one of the most important tools available. The chapter about evidence-based pharmacological approaches for treatment-resistant depressive disorder is one of the most important for clinical practice, since it provides a detailed and concise overview of the augmentation and switching pharmacological strategies in MDD. Other strategies of non-invasive, such as transcranial magnetic stimulation (TMS), and invasive neurostimulation, such as deep brain stimulation, are also addressed in subsequent chapters. Moreover, the last two chapters provide meaningful information on potential novel therapeutic targets for mood disorders, such as the pathophysiological findings in the glutamatergic and immune system. In this vein, the fast-acting antidepressant Ketamine arises as an option in severe and refractory patients with MDD. Also, the better understand of the latter pathophysiological mechanism could shed some light on how to address cognitive and functional impairment associated to the illness progression that take place in some patients[16].

In summary, the book "Treatment-Resistant Mood Disorders" provides a much-needed overview of all current aspects related to treatment resistance in the mood disorders. It, therefore, will be of great value to clinicians, researchers, and public health officials in helping to fundamentally advance the field of psychiatric refractory treatment.

References

1. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.
2. Carvalho AF, Berk M, Hyphantis TN, McIntyre RS. The integrative management of treatment-resistant depression: a comprehensive review and perspectives. Psychother Psychosom. 2014;83(2):70-88.

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3. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64(5):543-52.

4. De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, et al. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. J Psychopharmacol. 2012;26(5):603-17.

5. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med. 2007;356(17):1711-22.

6. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry. 2011;68(10):1058-64.

7. Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, Rush AJ, et al. The impact of treatment-resistant depression on health care utilization and costs. J Clin Psychiatry. 2002;63(11):963-71.

8. Carvalho AF, McIntyre RS. Treatment-Resistant Mood Disorders. Oxford Psychiatry Library. 2015 March.

9. Lee JH, Dunner DL. The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders. Depress Anxiety. 2008;25(2):91-7.

10. Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2004;161(12):2222-9.

11. Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med. 2004;34(7):1299-308.

12. Pollack MH. Comorbid anxiety and depression. J Clin Psychiatry. 2005;66 Suppl 8:22-9.

13. Perlis RH. A clinical risk stratification tool for predicting treatment resistance in major depressive disorder. Biol Psychiatry. 2013;74(1):7-14.

14. Chen C-H, Lee C-S, Lee M-TM, Ouyang W-C, Chen C-C, Chong M-Y, et al. Variant GADL1 and response to lithium therapy in bipolar I disorder. N Engl J Med. 2014;370(2):119-28.

15. Kapczinski F, Passos IC. Wet minds, dry minds, and the future of psychiatry as a science. Acta Psychiatr Scand. 2015;131(1):7-8.

16. Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. Neuroscience. 2015;300:141-54.