Progress in Neuro-Psychopharmacology & Biological Psychiatry 70 (2016) 103–110

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Refractory bipolar disorder and neuroprogression

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ARTICLE INFO

Article history:
Received 20 June 2015
Received in revised form 28 August 2015
Accepted 8 September 2015
Available online 12 September 2015

Keywords:
Bipolar disorder
Neuroprogression
Sensitization/cross-sensitization
Therapeutic interventions
Treatment refractoriness

ABSTRACT

Immune activation and failure of physiologic compensatory mechanisms over time have been implicated in the pathophysiology of illness progression in bipolar disorder. Recent evidence suggests that such changes are important contributors to neuroprogression and may mediate the cross-sensitization of episode recurrence, trauma exposure and substance use. The present review aims to discuss the potential factors related to bipolar disorder refractoriness and neuroprogression. In addition, we will discuss the possible impacts of early therapeutic interventions as well as the alternative approaches in late stages of the disorder.

1. Introduction

Lifetime prevalence of bipolar disorder (BD) is 2.1% worldwide, with subthreshold forms affecting another 2.4% (Merikangas et al., 2007). According to the World Health Organization (WHO), BD is among the 10 leading causes of disability-adjusted life years (DALY) in young adults (Mathers et al., 2006). It is estimated that, even with treatment, about 37% of patients will relapse into an affective episode within 1 year, and 60% within 2 years (Gitlin et al., 1995). The rates of completed suicide among patients with BD are 7.8% in men and 4.9% in women (Nordentoft et al., 2011). In addition, the life expectancy has been reported to be decreased by 9 years for patients with BD (Crump et al., 2013). It is also known that the diagnosis of BD has an average delay of ten years between the first symptoms and the formal diagnosis (Lish et al., 1994), and that only 20% of the patients who are experiencing a depressive episode are correctly diagnosed with BD (Goldberg et al., 2001).

It has been proposed that early detection and prompt intervention have the potential to decelerate illness progression and the burden associated with BD (Malhi et al., 2013, 2014). Latencies between the first presentation of the disease and the initiation of adequate treatment have been associated with greater morbidity (Post, 2010). Treatment refractoriness – conceptualized as either failure of an acute episode to respond to treatment, persistence of abnormal mood states during treatment, or emergence of mania, mixed states or cycling in the course of optimal treatment (Gitlin, 2001; Poon et al., 2012) – has recently been considered one end-stage phase in illness progression (Berk et al., 2007, 2014). Multiple episodes have been implicated in refractoriness, observed by less responsiveness to lithium (Kessing etal., 2011), cognitive behavioral therapy (Scott et al., 2006), and psychoeducation (Torrent et al., 2013). The delay in recognizing BD and the recurrence of episodes lead to neurobiological disruptions that predispose to subsequent episodes and treatment resistance (Post, 1992).

The progression of BD develops from asymptomatic at-risk individuals, to prodrome, episodicity, and finally chronic illness. Although there are considerable inter-individual differences, with most subjects with BD never progressing to the most debilitating forms of chronic illness, BD should nevertheless be conceptualized as a neuroprogressive disorder (Berk et al., 2011a, b, c). Neuroprogression, defined by the constellation of changes in the nature of the bipolar illness with temporal progression, has been demonstrated by neurobiological and anatomical brain alterations, treatment resistance, reduction in inter-episode interval and chronicity, and functional and cognitive impairment (Post et al., 2012). The dysregulation among physiologic pathways and the failure of endogenous compensatory mechanisms have been considered the biological underpinnings of the cross-sensitization among recurrence of mood episodes, trauma exposure and comorbidity with substance use

Abbreviations: BD, Bipolar Disorder; WHO, World Health Organization; DALY, Disability-Adjusted Life Years; BDNF, Brain-Derived Neurothrophic Factor; O&NS, Oxidative and Nitrosative Stress; CBT, Cognitive Behavioral Therapy; MRI, Magnetic Resonance Imaging; IL, Interleukin; TNF-α, Tumor Necrosis Factor-alpha; sTNF-R1, Soluble TNF-α Receptor-1; sIL-6R, Soluble IL-6 Receptor; sTNF-R1, Soluble TNF-α Receptor-1; IL-1RA, IL-1 Receptor Antagonist; sIL-2R, Soluble IL-2 Receptor; ROS, Reactive Oxygen Species; SOD, Superoxide Dismutase; FAST, Functioning Assessment Short Test; TRBD, Treatment-Resistant Bipolar Disorder; ADR, Adverse Drug Reactions; CR, Cognitive Remediation; ES, Effect Sizes.

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http://dx.doi.org/10.1016/j.pnpbp.2015.09.005
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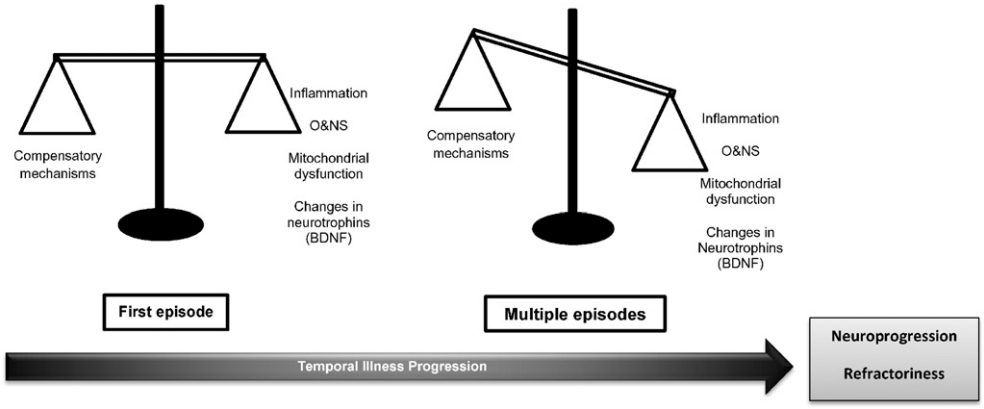

Fig. 1. Differences between early and late stages of bipolar disorder according to illness progression. In the first episode, compensatory mechanisms tend to repair the damage. With chronicity, the damage overweight the repair (allostatic overload) leading to more permanent damage, neuroprogression and refractoriness. BDNF, brain-derived neurotrophic factor; O&NS, oxidative and nitrosative stress.

disorder that lead to neuroprogression of BD (Moreno-Romero and Grimalt, 2014; Rizzo et al., 2014; Schneider et al., 2012) (see Fig. 1).

According to the kindling theory (Post, 2010), psychosocial stressors are crucial to first episodes triggering, but, with further relapses, minimal stressors are necessary to ignite new episodes, since recurrence leads to sensitization (Post, 2010). Furthermore, not only were changes observed in the frequency of the episodes, but also in their severity and recovery time (Leverich and Post, 2006; Post, 1992, 2007). Moreover, cross-sensitization to other factors has also been observed with chronicity, especially with traumatic events and substance misuse (Post, 2010). Therefore, the present study aims to review the potential factors related to neuroprogression and treatment refractoriness observed in BD. In addition, we will discuss the impacts of early therapeutic interventions, and alternative approaches in refractory (late) stages of the disorder.

2. Sensitization and cross-sensitization

The sensitization and cross-sensitization processes have been well demonstrated in animals and in humans. It has been observed that not only can each kind of sensitization (to stressors, episodes, and substances of abuse) manifest increasingly pathological endpoints upon their own repetition, but each can potentially convey increased reactivity to the others (Post, 2010; Post and Kalivas, 2013)(see Fig. 2). Recent evidence shows that sensitization and cross-sensitization may lead the illness toward greater behavioral abnormalities, stress responsiveness, and vulnerability to recurrence (Post, 2010; Post and Kalivas, 2013). Consequently, patients will present with cycle acceleration, increased severity and duration of episodes, treatment refractoriness, disability, cognitive impairment, and decrease in life-expectancy (Post, 2010). All of these factors are associated with higher morbidity and mortality throughout the course of BD. (See Fig. 3.)

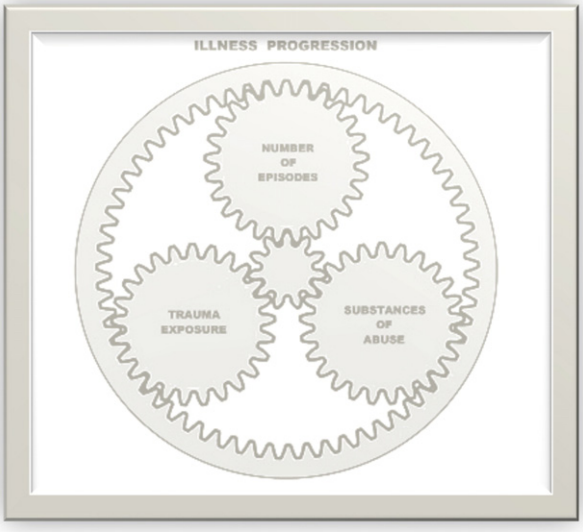

Fig. 2. Sensitization, cross-sensitization and illness progression. Number of mood episodes, substance use, and trauma exposure may show sensitization to themselves and cross-sensitization to the others leading to illness progression and treatment refractoriness.

A naturalistic study from the Danish Case Registry of more than 20,000 individuals is among the strongest evidences for increased vulnerability to relapse as a function of the number of prior episodes (Kessing et al., 2004). According to this dataset, illness progression manifests as faster recurrences. Also, the incidence and latency to a depressive relapse (for either unipolar or bipolar depressive hospitalization) were related to the number of prior hospitalizations for depression, indicating episode sensitization (Kessing and Andersen, 2005; Kessing et al., 1998a,b,c). The same research group has also observed that not only does the number of episodes increase over the course of illness, but also the severity of episodes (Kessing and Andersen, 2005; Kessing et al., 1998a,b,c). In addition to worse clinical outcomes, multiple previous episodes were also implicated in treatment refractoriness, since younger patients with fewer episodes tended to present better response to traditional mood stabilizers and psychoeducation, while patients who suffer from multiple episodes generally responded poorly to lithium and cognitive behavioral therapy (CBT) (Scott et al., 2006; Swann et al., 1999).

In animal studies, it has been suggested that early stressful life events can lead to increased responsivity to stressors in adulthood (stress sensitization). It has also been observed that first episodes generally need psychosocial stressors to be triggered. However, with multiple recurrences, episodes can be precipitated autonomously (Kendler et al., 2001; Kessing and Andersen, 2005; Post, 1992, 2007). Post has demonstrated that, in animal models, the amygdala, when stimulated once a day for one second, generates behavioral responses that lead to full-blown seizures (Post, 1992, 2010; Post and Kalivas, 2013). The amygdala-related kindling, according to his observations, presents three different stages: the initial stage, mid- or completed stage of full-blown seizures, and the late or spontaneous stage (Post, 2010; Post and Kalivas, 2013). The increased response to the same stimulation represents the alterations in neurobiology responsible for stress sensitization (Post, 2010; Post and Kalivas, 2013). There is consistent evidence of similar phenomena in humans (Caspi et al., 2003). In the classic study of Caspi et al, only individuals who had experienced multiple early childhood traumatic events were more vulnerable to the occurrence of affective episodes following stressors in adulthood (Caspi et al., 2003).