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Review article

Personalized management of bipolar disorder

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ABSTRACT

Bipolar disorder (BD) is one of the most serious psychiatric disorders. The rates of disability, the risk of suicide attempts and their high lethality, as well as frequent and severe psychiatric and medical comorbidities, put it among the major causes of mortality and disability worldwide. At the same time, many patients can do well when treated properly. In this review, we focus on those aspects of the clinical care that offer the potential of individualized approach, in the context of the recent technology driven advances in the comprehension of the neurobiological underpinnings of BD. We first review those clinical and biological factors that can help identifying individuals at high risk of developing BD. Among these are a family history of BD and/or completed suicide, prodromal symptoms (in childhood and/or adolescence) such as anxiety and mood lability, early onset, and poor response to antidepressants. Panels of genetic markers are also being studied to identify subjects at risk for BD. Further, neuroimaging studies have found an increased gray matter density in the right Inferior Frontal Gyrus (rIFG) as a possible risk marker of BD. We then examine clinical factors that influence the initiation, selection and possibly discontinuation of long-term treatment. Lastly, we discuss the risk of side effects in BD, and their relevance for treatment adherence and for treatment monitoring. In summary, we discuss how a personalized approach in BD can be implemented through the identification of specific clinical and molecular predictors. We show that the realization of a personalized management of BD is not only of a theoretical value, but has substantial clinical repercussions, resulting in a significant reduction of the long-term morbidity and mortality associated to BD.

1. Introduction

Bipolar disorder (BD) is one of the most serious psychiatric disorders. The rates of disability, the risk of suicide attempts and their high lethality, as well as frequent and severe psychiatric and medical comorbidities, put it among the major causes of mortality and disability worldwide [1]. At the same time, many patients can do well when treated properly [2]. The clinical management of BD has been the subject of comprehensive treatment guidelines [3–8]; it is not our purpose to reiterate their recommendations, but rather focus on those aspects of the clinical care and of recent genetic and neurobiological research that offer the potential of individualized approach. Personalized medicine aims to stratify patients according to specific clinical and/or biological characteristics and develop tailored (personalized) interventions. Such subgroups of patients, sharing distinct clinical and biological characteristics, have been identified in BD: lithium-responsive [9], early onset [10], and mood-incongruent psychosis [11]. Research studies performed on these subpopulations have led to a better comprehension of the neurobiological underpinnings of BD. However, this progress has not yet translated into a full clinical implementation of personalized approaches in psychiatry. This delay is at least in part explained by the absence of a diagnostic test for BD and for psychiatric disorders in general. The accuracy and precision of BD diagnosis still rely on clinical assessment. However, it is conceivable that the integration of accurate clinical information with data coming from consolidated (genomics, transcriptomics, proteomics, epigenomics, metabolomics) and more innovative (microbiomics, lipidomics, metallomics, foodomics) “omics” approaches, will lead to development of a reliable personalized approach in BD. Indeed, these technologies allow the large-scale analysis of biological variation using a holistic, hypothesis-free approach. It is conceivable that the information obtained with “omics” analyses might provide a more in-depth and unbiased coverage of the biological pathways underlying complex psychiatric disorders. In this context, we offer an overview of clinical and neurobiological data supporting personalized management of various aspects of BD. First, we review clinical and neurobiological markers,

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which may help differentiating individuals at risk for the development of BD from those with diverse psychopathological trajectories. Then, we discuss the factors that can guide clinicians in deciding when to initiate and/or discontinue a long-term treatment and how to select it for an individual patient. We also review treatment-related safety concerns and how to prevent side effects through an implementation of accurate clinical monitoring, which might take advantage of electronic technologies and innovative data mining approaches.

2. Who becomes ill? From at-risk to prodrome to bipolar disorder

A critical issue in setting up personalized approaches in psychiatry is an accurate diagnosis. Differently from other areas of medicine, where a diagnosis can often be corroborated by results of a blood test, psychiatry relies on clinical criteria, and the reliability of diagnostic assessment is strongly dependent on the accuracy of the information gathered. This is particularly true for BD, which is a relatively heterogeneous disorder. In most cases, it is usually not difficult to diagnose a typical *manic episode*, but many patients present with atypical or mixed features. Differentiating hypomania from other conditions (for instance, personality disorders) can be challenging, though, especially in the absence of reliable collateral information. But the main − and clinically most relevant − concerns relate to differential diagnosis of early stages of BD. The illness usually manifests first with depressive rather than manic episodes or even with non-specific prodromes. As pointed out in several prospective studies of offspring of parents with BD, the illness tends to develop in certain stages and their recognition combined with reliable family history information can be particularly helpful [12–23]. Children of BD patients might present diverse symptoms preceding the illness onset. Among these clinical manifestations are sub-threshold mood symptoms, affective lability [12,15,22,24–26], anxiety [22,24,27], impairment in specific areas of cognitive functioning, including attention [21,28,29], or altered sleep regulation [13,19,22]. Individuals at genetic risk of BD showed consistently affective morbidity of predominant depressive polarity in the prodromal stage of the illness, with the index episode almost always depressive [17,19,20]. The manifestation of an early depressive morbidity in high-risk cohorts appears to be a robust predictor of bipolarity [12,15]. High-risk studies have also shown that there might be a latency of several years from a depressive onset to the first hypo/manic episode and the consequent diagnosis of a BD [17,22]. These observations are clinically relevant and have substantial implications for the implementation of a robust personalized approach in BD. During the “pre-bipolar” stage, young people may receive antidepressant treatment with the risk of iatrogenic worsening of the clinical picture. This has been demonstrated by O’Donovan and colleagues who found that a poor response to antidepressants prescribed in acute depressive phases was a significant predictor of later bipolarity [30].

Another antecedent of BD, which is not mood-specific, is anxiety. High-risk studies have shown consistently that: 1) rates of anxiety disorders are higher in children of affected parents compared to those of unaffected parents [12,14,19,22–25,31], and 2) the early manifestation of anxiety disorders predicts the manifestation of major affective disorders, including BD [19,22,23,26].

Alteration of sleep patterns appears also to predict the development of BD in high-risk offspring [13,19,22]. Levenson et al. [13] observed that specific sleep problems such as frequent nighttime awakenings (rated by both parents and offspring), inadequate sleep (parent reported), and increased difficulty falling asleep on weekends (offspring reported) predicted conversion to BD among non-BD offspring of BD parents, whereas being an evening type was associated with lower likelihood of conversion. Further, sleep disorders were antecedent of BD in high-risk offspring [19,22].

These data demonstrate the importance of setting-up accurate clinical monitoring of high-risk offspring of BD probands, which should include, beside mood, measures of sleep and anxiety, and possibly cognition. It should be noted, however, that although these prodromal symptoms are associated with an increased likelihood of developing BD or a mood disorder in general, in a proportion of high-risk individuals these symptoms are not followed by affective disorders or even by any Axis I condition. The increase of specificity of predictive models incorporating these variables could be obtained by adding biological data such as those identified through “omics” technologies.

In general, the evaluation of the clinical predictors points to the relevance of family history as the major risk factor [32,33]. It needs to be noted that family history as collected in routine clinical services is often not accurate enough to be used reliably [34,35]. We recommend obtaining family history details not only from the proband, but also from other informants where possible and using a systematic approach rather than blanket questions of “who else in the family had a similar condition?”. Going through the histories of family members one-by-one not only improves the validity of collected data, but may provide further insights about the family dynamics. This type of systematic assessment of family history, as well as of all other relevant clinical features may appear time consuming, but improves the accuracy of diagnosis and facilitates correct treatment, thus saving considerable amount of time and suffering in the long term.

As mentioned, establishing the risk of BD so far relies on clinical features. Ultimately, personalized approaches should be able to combine clinical data with genetic or biological information. One such option is quantifying the genetic risk, using polygenic risk scores [36–42]. Specifically, polygenic risk scores have been used to validate the existence of BD subgroups (for instance BD type 1 versus type 2, presence/absence of psychosis, age at onset subgroups, polarity of onset) [37–39], but also to predict the development of BD in major depressive disorder (MDD) patients or in high-risk offspring [36,41].

For instance, Hamshere et al. [38] tested whether schizophrenia (SCZ) polygenic risk alleles were able to discriminate between individuals with and without psychotic features. Although the schizophrenia-derived polygenic risk score discriminated between those with schizoaffective BD (Research Diagnostic Criteria) and BD patients, it did not significantly discriminate between those with BD with and without psychosis [38]. Another study found that polygenic risk score not only significantly discriminated between BD and healthy controls, but also differentiated psychotic and non-psychotic BD patients [37]. Finally, Ruderfer et al. [39] found a polygenic signature, derived from a genome-wide association study (GWAS) of BD and SCZ cases compared with healthy controls, which effectively discriminated BD and SCZ cases. Further, the BD polygenic risk score predicted the manic dimension of SCZ patients [39].

Of great interest is the suggestion that polygenic signatures can predict conversion to BD. Wiste et al. [41] found that a polygenic risk score for BD, derived from a large GWAS meta-analysis, was associated with bipolar-like phenotypic features such as early onset, suicide attempt, recurrent depression, atypical depression, subclinical mania, subclinical psychosis, and severity in MDD patients. Although not replicated in two independent cohorts, these findings indicate that BD-based polygenic signatures might help detecting MDD patients who will later convert to BD. Another plausible strategy for a risk assessment is the use of biomarkers as illustrated by Haenisch et al. [42] who found that a panel of 20 markers differentiated between first onset MDD patients and patients who later developed (hypo)manic symptoms, with a good predictive performance.

An alternative approach has been based on brain imaging data. Several studies suggested that increased gray matter density in the right Inferior Frontal Gyrus (rIFG) may be a marker of risk [43–45]. Additionally, the same region shows an altered pattern of brain connectivity bilaterally [46]. While these data are intriguing and may ultimately help clarify some of the pathophysiological mechanisms of the illness, their predictive power in clinical practice needs to be tested in prospective longitudinal observations.

In summary, there are promising clinical and genetic/neuroimaging

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