Part 4. Diagnosing Bipolar Disorder

Treatment and early Intervention in Psychosis Program (TIPP)

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Running Title: Identification of initial mania prodrome

Abstract

While early intervention in psychotic disorders has received much attention over the last few years, early intervention in bipolar disorders is still in its infancy. Such developments are greatly needed in order to reduce the usually very long duration of untreated illness and perhaps to improve outcome that often remains rather poor. Besides promoting earlier diagnosis of first-episode mania and exploring ways to characterize bipolar depression, identification of patients during the prodromal phase to their first manic episode has emerged as a valid domain of investigation. The observation that symptoms developing during this phase are likely to be very non-specific has lead to the recent development of two strategies which may improve the situation. However, to date there is no valid way to identify patients in the prodromal phase to bipolar disorders and more research is warranted in this area.

Key words: early intervention, bipolar disorder, prodrome, mania, first episode.

Introduction

The elaboration of preventive strategies has become a priority in mental health. Early intervention programs for psychotic disorders are examples of such developments which have lead to the emergence of a vast domain of clinical and neuro-scientific research. However, until recently, most of the attention has been directed towards schizophrenia; affective disorders, including the bipolar disorders (BPD), have been neglected (1). Although Fava et al. (2) suggested, thirty years ago, the existence of a prodromal phase preceding the first full manic syndrome by weeks or months and the idea that the identification of such a prodrome would allow the development of earlier and probably more efficient interventions, this domain has received very limited attention. This is rather unfortunate, considering the many elements which suggest that early intervention strategies are needed in BPD. Accumulating data converge to show that outcome of BPD is poorer than formerly thought (3), already after the first manic episode (4,5), suggesting that available treatment strategies are inadequate. In addition, various studies have shown very clearly that a long delay usually occurs between the

onset of the disorder and introduction of adapted treatment, patients spending on average 6 to 10 years before mood-stabilising treatment is introduced (6,7). It is likely that such delays have similar negative consequences to those observed in psychotic disorders (8). Moreover, the high prevalence of co-morbidities observed in patients at first presentation of mania suggests that earlier intervention might prevent their development. Finally, it seems clear to clinicians that patients with first-episode mania have different needs from those who present with a first psychotic episode, suggesting that the development of specific strategies could be very useful for treatment. The identification of patients before the first manic episode, that is during the "initial prodromal phase" (as opposed to the relapse prodromal phase), would not only pave the way to the prevention of a first manic episode, which usually has highly stigmatizing consequences, but it might also allow the prevention of the deterioration occurring before the first manic episode, through the development of specific psychological interventions and the study of the utility of potentially neuroprotective treatments. In addition, a reduction of the delay between onset and appropriate treatment might result in a better treatment response and better engagement of patients.

Which targets for early intervention?

In a recent paper, Berk et al. (9) have retrospectively reconstructed the natural history of the development of the illness in a sample of 207 patients with BPD (see figure 1). On the basis of the various stages through which patients usually go, it is possible to identify various phases where early intervention strategies could be implemented. Indeed, considering the long delay between the time when patients reach treatment threshold and the time where mood-stabilising treatment is started, and based on the observation that more than 50% of patients begin bipolar disorder with a depressive episode, 3 main different targets can be identified for earlier intervention.

The most readily accessible would be to promote a better identification of a first manic episode. Due to frequent co-morbidities and often atypical presentation (high prevalence of psychotic symptoms, irritability and aggressiveness rather than euphoric mood), patients with a first episode of mania are often misdiagnosed and the introduction of proper treatment is therefore delayed (1). Such misdiagnosis can have many consequences, such as prescription of maladapted treatment (antipsychotic or antidepressants), as well as rejection, when mania is misdiagnosed as antisocial behavior. In this context it is important to promote better knowledge of the atypical nature of mania in youth.

A second target may be the identification of bipolar depression, in other words depressive episodes emerging in patients who will later develop BPD. Some recent publications have suggested that some characteristics (such as rapid onset and offset or physical retardation) may be more common in bipolar depression that in unipolar depression, and some authors have recently developed a tool allowing the exploration of such characteristics (10). Such identification could be useful in guiding treatment choice, considering that antidepressant medication which may induce manic episodes in such individuals should be avoided in favor of mood stabilisers.

The third early intervention target would be to identify BPD before subjects have reached diagnostic threshold level, in other words to identify the "prodromal phase" to bipolar disorder. While the concept of prodrome to first-episode psychosis is reasonably easy to define as the period preceding the first time when a patient reaches threshold level for psychotic symptoms, it is harder to define a clear target in the context of BPD, due to the many forms its onset can take, ranging from a depressive episode to mania. For this reason, a consensus is currently building to consider that the prodrome to the first manic episode is the most realistic target (11).

Prodrome to first manic episode

Knowledge of the early stages of BPD stems from 2 types of studies (11). A first group of papers is based on prospective follow-up of various samples of subjects, either considered as "at risk for bipolar disorder" (because of a family history of BPD or due to the presence of various psychopathological

manifestations) or belonging to larger prospective follow up of community samples. A second group of publications is based on retrospective studies, reconstructing the early phase of the disorder either in patients who recently presented with a first manic episode or in samples of patients already diagnosed with BPD for some years. Based on these papers, two main conclusions emerge.

The first conclusion is that a prodromal phase to first-episode mania actually does exist. Indeed, the great majority of patients seem to go through a period of noticeable change before the onset of the first manic episode, changes that are clearly detected by those who are in contact with the patient and by patients themselves. This period seems to have a relatively wide range of duration but data on this aspect has only been provided in two studies. Correll et al. (12) found that onset was insidious (>1 year) in 52% of patients, sub-acute (1year-1month) in 45% and that it was acute (<1month) in a very limited number of patients (3%). Conus et al. (13) similarly reported a mean duration of 21 weeks for the prodrome, which lasted less than 10 weeks in 50% of patients and ranged between 24 and 49 weeks for the others. However, the focus of this latter study was on the 12 months preceding mania onset and this may have biased the results.

The second conclusion is that the prodrome to first episode mania is marked by the presence of symptoms which globally fall into 3 categories. First, patients present with mood symptoms, mainly in the form of mood swings, cyclothymic features or depressed mood. Second, they display sleep modification with reduction of sleep or decreased need for sleep. Third, they display behavioral and other types of changes in the form mainly of anger and irritability. While they are present in the vast majority of patients, such symptoms are likely to have rather low specificity in prospective samples. This is, indeed, supported by observation by Correll et al. (12) who found that when comparing samples of patients at high risk for psychosis who developed schizophrenia and those who developed BPD, there was an important overlap in phenomenological manifestations. In addition, the same group reported in a later study (14) that high-risk patients who developed schizophrenia and those who developed bipolar disorder had a very similar cognitive profile during the prodromal phase. In summary, if patients who develop first-episode mania do go through a prodromal phase, its phenomenological characteristics seem too nonspecific to allow reliable identification of patients who are specifically at risk of mania in a prospective approach. In this context, two main initiatives have been proposed, which will be developed in the next section.

Definition of high risk profiles: the BAR criteria

In a strategy derived from the development of Ultra High Risk criteria for psychosis, Bechdolf et al. (15) have reported the conceptualization of at-risk criteria for bipolar disorder (BAR; Bipolar At Risk criteria). Three groups are defined, among subjects who share the characteristics of being aged 15 to 25 and help-seeking for mental health issues : 1) Sub-threshold mania; 2) Depression and cyclothymic features; 3) Depression and genetic risk. The details of these profiles are depicted in table 1.

In order to explore the validity of these profiles, the authors conducted a retrospective file audit study through which they applied BAR criteria to 173 successive help-seeker adolescents who had been admitted to a youth health centre. According to the files, twenty two patients (12.7%) met BAR criteria at admission to the center, while 151 (87.3%) did not. After a mean follow-up duration of 165 days, it was found that only one (0.7%) of the patients who did not meet BAR criteria at baseline had developed a first manic episode during the follow-up period, while 5 (22.7%) of those who met BAR criteria did so. These encouraging results suggested that meeting BAR criteria when presenting as a help-seeking adolescent or young adult was linked with an increased risk of developing mania, and motivated the implementation of a prospective study, currently underway, in a population of help-seeking patients aged 15 to 25, comparing the rate of development of first-episode mania according to BAR status at program entry.

Development of a high-risk scale for first-episode mania

Considering the limited specificity of symptoms observed during the prodrome to first episode mania, Conus et al. (13) followed another strategy, based on the principle that the predictive value of

these symptoms might increase if they were to occur in a patient who also has certain characteristics that are common in patients with bipolar disorders. For example, the presence of mood swings and irritability in a young person whose father has BPD would seem more likely to announce an impending first episode of mania than if it occurred in a patient without such a family background. On the basis of a literature review (11), these authors identified various factors that could be classified within 2 groups.

First, they found mention in the literature of a certain number of risk factors, such as family history of BPD or exposure to trauma during childhood. Risk factors are not early manifestations of the disorder per se; they are demographic attributes, family characteristics or life events that either retrospectively have been observed to be more frequent in the life history of subjects who later present with BPD, or that prospectively have proven to confer a higher risk to develop the disorder.

Second, they identified, in the literature, biological characteristics as well as certain early developmental, behavioral or personality patterns that are more frequently reported in the life history of BPD subjects. Although they may be early manifestations of the disorder itself, they do not clearly present as attenuated manifestations of BPD and could therefore be considered as "markers of potential vulnerability to BPD" until further research provides sufficient evidence to identify them either as elements of the bipolar spectrum of disorders or as a defined stage in the development of BPD.

In a sample of 22 patients with first-episode mania, these authors conducted detailed retrospective interviews both with patients and their relatives, and explored which of the factors described above were reported in the majority of cases (13). This selection of items has been combined with the most common phenomenological characteristics of first-episode mania prodrome to build a scale (the First Episode Mania At Risk Questionnaire, FEMARQ), validity of which is currently being studied.

Conclusions

On the basis of the very few studies available to date, it seems that the identification of a prodromal phase to first-episode mania could be identified. This phase is marked by the presence of mood swings, depressed mood, cyclothymic features and sleep disruption as well as irritability or anger dyscontrol. However, such symptoms have very limited specificity, and strategies based on their sole presence are very unlikely to allow the identification of at-risk patients. Two main strategies have been recently developed in order to shed some additional light on this domain, and are currently under investigation in order to see if they have any validity in the prospective identification of patients who will develop first-episode mania.

Until these tools, or others to be developed, have proven their validity, the identification of patients at ultra-high risk to develop BPD during the prodromal phase to the first manic episode, is not possible. At present, the best clinical strategy to promote early intervention in BPD is therefore to improve identification of first-episode mania in young people in order to decrease the duration of untreated illness, during which many of the secondary complications develop which, in turn, seriously impede the recovery potential of such young patients.

GP Comment

What have I learned from this paper?

This article introduces the idea of a prodromal phase before the first manic episode during which patients undergo noticeable changes in mood, sleep and behaviour. However, such symptoms have limited specificity and further research is needed before this prodromal phase can be used to identify at-risk patients reliably. At present, we must identify the first episode of mania quickly and implement early intervention with mood stabilisers to improve long-term outcome.

Dr Jenny Hopwood, GP Trainee.

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Table 1:
BAR Criteria (adapted from Bechdolf et al. (15))

I. Age 15-25 years

II. Fulfill criteria of at least one of three groups within the last 12 months:

Group 1: Sub-threshold mania
Mania-like symptoms for at least two consecutive days but less than 4 days: period of abnormally and persistently elevated, expansive or irritable mood + at least 2 criteria from the list: (1) inflated self-esteem or grandiosity, (2) decreased need for sleep (e.g. feels rested after only three hours sleep), (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or subjective experience that thought are racing, (5) distractibility, (6) increase goal-directed activity (either socially, at work, or sexually) or psychomotor agitation.

Group 2: Depression + Cyclothymic features:
Depression for at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation

+ Cyclothymic features: Numerous episodes with sub-threshold manic symptoms not meeting group I criteria. e.g. sub-threshold mania as defined in group I only for 4 hours within a 24-hour period and at least 4 cumulative lifetime days meeting the criteria

Group 3: Depression + Genetic Risk:
Depression for at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation

+ Genetic Risk: First degree relative with bipolar disorder.

Figure 1:

Natural history of the development of BPD and potential early intervention targets. (Adapted from Berk et al. (9))