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Research report

Group-based trajectory modeling: A novel approach to examining symptom trajectories in acute bipolar episodes

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ABSTRACT

Background: Pattern analysis can aid understanding of trajectories of symptom evolution. However, most studies focus on relatively homogeneous disorders with a restricted range of outcomes, prescribed a limited number of classes of medication. We explored the utility of pattern analysis in defining short-term outcomes in a heterogeneous clinical sample with acute bipolar disorders.
Method: In a naturalistic observational study, we used Group-based trajectory modeling (GBTM) to define trajectories of symptom change in 118 bipolar cases recruited during an acute DSM IV episode: major depression (56%), (hypo)mania (26%), and mixed states (18%). Symptoms were assessed weekly for a month using the MATHYS, which measures symptoms independent of episode polarity.
Results: Four trajectories of symptom change were identified: Persistent Inhibition, Transient Inhibition, Transient Activation and Over-activation. However, counter to traditional predictions, we observed that bipolar depression shows a heterogeneous response pattern with cases being distributed approximately equally across trajectories that commenced with inhibition and activation.
Limitations: The observational period focuses on acute outcomes and so we cannot use the findings to predict whether the trajectories lead to stable improvement or whether the clinical course for some clusters is cyclical. As in all GBTM, the terms used for each trajectory are subjective, also the modeling programme we used assumes dropouts are random, which is clearly not always the case.
Conclusion: This paper highlights the potential importance of techniques such as GBTM in distinguishing the different response trajectories for acutely ill bipolar cases. The use of the MATHYS provides further critical insights, demonstrating that clustering of cases with similar response patterns may be independent of episodes defined by mood state.

1. Introduction

The selection of optimum treatments for the management of bipolar disorders (BD) is often undermined by the heterogeneity of clinical presentations. A further level of complexity is the variability in intra-episode BD symptoms and the range and nature of sub-syndromal manifestations of the disorder. For example, depressive episodes may present with retarded, melancholic, agitated or atypical features and manic patients may present as elated, dysphoric, labile, paranoid, etc. (Cassidy et al., 1998). Furthermore, whilst mixed states are defined be the presence of syndromal levels of depressive and manic symptoms, patients not meeting full 'mixed state' criteria frequently present concurrently with sub-syndromal symptoms of one pole of BD alongside syndromal symptoms of the opposite pole (i.e. depressive symptoms during hypomanic episodes and vice versa) (Benazzi, 2007; Henry et al., 2010). In order to better reflect this heterogeneity of BD, DSM V proposes a 'specifier' of mixed symptoms for manic, hypomanic and depressive episodes (http://www.dsm5.org/ProposedRevisions/). Other researchers have suggested that activation rather than mood state may be a more appropriate means of defining different BD presentations (Angst, 2011, Angst et al., 2010).

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Although research has helped to better understand the many and various acute BD presentations, less is known about whether episodes evolve differently according only to episode polarity (depression, hypomania, etc.) or as a function of specific behavioural or vegetative symptom profiles (e.g. level of activation; agitated or retarded, etc.). Until recently, research in this area was hampered by the fact that few rating instruments adequately measured the full range of key symptom dimensions across all polarities. Most assessment scales were developed when more traditional views of depression and mania (as polar opposites) prevailed and so the assessments make assumptions about which symptoms should be measured based on the mood state defining the presenting polarity of the episode, rather than simultaneously measuring the range of mood, cognition and behavioural manifestations of BD regardless of the predominant mood (Johnson et al., 2010).

The above issue is critically important in BD as it invariably confounds the naturalistic assessment of treatment outcomes, whilst studies of comparative effectiveness in BD are more complex than for other disorders. Clinical heterogeneity, as seen e.g. in the range of presentations of acute bipolar episodes, introduces a lack of clarity about which specific classes of drugs are best used for different acute BD symptom profiles. Contemporary research indicates that some treatments, e.g. atypical antipsychotics, are now viewed as efficacious acute treatments of both manic and depressive episodes. However, as randomized controlled trials select homogeneous subgroups who meet traditional episode criteria and trials report aggregate outcomes using conventional ratings scales for assessing change in either manic or depressive symptoms, it is not established whether the benefits of some treatments result from their action on a dimensional characteristic shared by a clusters of patients (e.g. increased activation levels) rather than whether the index BD episode is manic or depressive. Furthermore, we do not know if rate of improvement of symptoms in a depressive episode that is achieved with a specific treatment can be predicted from the rate of improvement of symptoms in a manic episode achieved with the same class of medication. To truly understand the role of medications that can be effective across polarities we need to find novel ways to measure change in symptoms and also new methods to examine response patterns that extend beyond 'good versus bad' outcome categories defined by cutoffs on a mania or a depression rating scale.

In unipolar depression research, pattern analysis validly differentiates initial rate of change in symptoms in response to treatment and can predict (to a certain extent) the outcomes achievable in the continuation and maintenance phases (Quitkin et al., 1984). More recently, Marques et al. (2010) have applied this approach to treatment outcomes in schizophrenia, concluding that trajectory models of response, rather than the simple responder/non-responder dichotomy, provide a better statistical account of how antipsychotics may work. However, these studies largely address samples with relatively homogeneous presentations (e.g. acute psychosis) and observe the response pattern attained with a limited number of classes of medications (e.g. atypical antipsychotics). Before applying response pattern analysis models in BD, we need to establish the nature of symptom change in routine clinical settings and examine whether the trajectories generated lead to the identification of meaningful clusters of individuals with similar response characteristics. Studies need to include not only an appropriate statistical approach to pattern analysis but also a symptom measure that can potentially differentiate if changes in symptoms represent a beneficial shift towards euthymia or 'overshoots' euthymia and marks a 'switch' into (hypo)mania or depression.

This paper describes a 'exploratory study' study aimed

a) To clarify trajectories of change in acute BD episodes over time. To do this, we used group-based trajectory modeling (GBTM), which is a statistical method designed to explore heterogeneity in clinical groups by identifying distinct trajectories of change (Nagin, 2005).
b) To assess more subtle changes in symptoms and reduce the risk of false positive classifications of acute outcome (e.g. an individual who meets good outcome criteria for improvement in depression using standard rating scales, but has actually developed hypomanic symptoms). To do this, we employed the MATHYS (Multidimensional Assessment of Thymic States) which is an assessment tool that measures BD symptom dimensions and severeity irrespective of the polarity of the acute BD episode (Henry et al., 2008).

2. Experimental procedures

2.1. Sample

With ethical approval, we recruited a convenience sample of acutely ill BD inpatients and outpatients who were willing and able to give written informed consent to participate in the study. Those exhibiting comorbidity, suicidality or psychotic symptoms were included (unless consent was an issue). As this was an observational study, treatment remained under the control of the responsible clinical team and any changes were made independently from the investigators.

2.2. Clinical assessment

All participants were assessed using the mood section of the French version of the DIGS, a structured clinical interview incorporating DSM-IV diagnostic criteria (Nurnberger et al.,1994) during an acute episode. The severity of the mood episode was quantified with both the (Montgomery and Asberg, 1979) Montgomery and Asberg Depression Rating Scale (MADRS) and the Bech and Rafaelsen Manic scale (MAS) (Bech et al., 1978) and then patients were asked to complete the MATHYS, rating how they felt during the preceding week (week 1); the MATHYS was repeated on three further occasions (end of weeks 2, 3, 4).

There are few clinical tools to assess bipolar episodes independently of polarity, but this was of critical importance in trying to make a more sophisticated interpretation of trajectories of change over time. We therefore employed the MATHYS (Multidimensional Assessment of Thymic States), a self-report scale that can be used especially to assess activation levels and emotional reactivity regardless of current BD episode status (Henry et al., 2008). This scale, designed *a priori*, includes five relevant quantitative dimensions (an English version can be accessed at: http://www.biomedcentral.com/content/supplementary/1471-244X-8-82-S1.doc). Thus, classic features, such as cognition, motivation, psychomotor agitation or retardation and sensory perception, are assessed quantitatively (i.e., racing thoughts or subjectively feeling that their thoughts are slower, physical agitation or retardation, and increase or decrease in sense perception). Examples of items include: 'My brain never stops'; 'My brain seems to be functioning in slow motion'. Similar concepts are applied to the evaluation of emotion (i.e. focusing on whether the patient felt emotion with normal intensity, greater intensity, or less intensity). Examples of these items include: 'My emotions are very intense'; 'My emotions are not very strong'.

Analysis of the psychometric properties of the scale reveal that is has good validity and internal consistency (Cronbach's alpha coefficient = 0.95), and that scores are moderately correlated with both the Montgomery Asberg Depression Rating Scale (depression score; $r = -0.45$) and the Bech-Rafaelson Mania Scale (mania