

# Subsyndromal Mood Symptoms: A Useful Concept for Maintenance Studies of Bipolar Disorder?

Michael Bauer<sup>a</sup> Tasha Glenn<sup>c</sup> Paul Grof<sup>e</sup> Rita Schmid<sup>b</sup> Andrea Pfennig<sup>a</sup>  
Peter C. Whybrow<sup>d</sup>

<sup>a</sup>Department of Psychiatry and Psychotherapy, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, and <sup>b</sup>Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany; <sup>c</sup>ChronoRecord Association Inc., Fullerton, Calif., and <sup>d</sup>Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, Calif., USA; <sup>e</sup>Mood Disorders Clinic of Ottawa, Ottawa, Ont., Canada

## Key Words

Bipolar disorder · Subsyndromal symptoms · Patient-reported outcomes

## Abstract

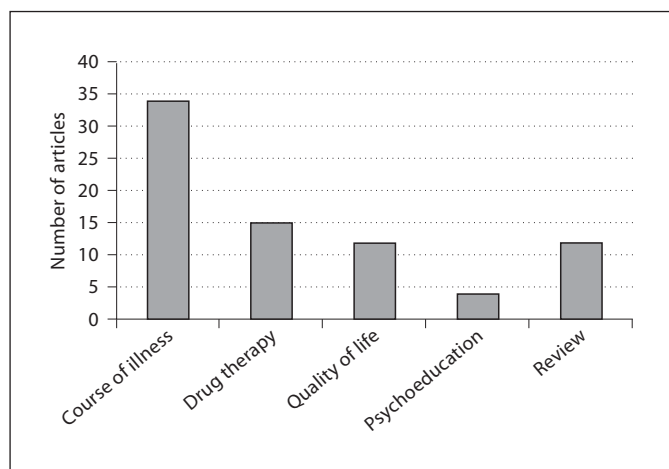
**Objective:** To explore the measurement of subsyndromal mood symptoms in relation to studies of maintenance therapy for bipolar disorder. **Methods:** Literature review of the Medline database using the following selection criteria: (1) 'bipolar disorder' plus 'inter-episode or interepisode or subsyndromal or subclinical or residual or subthreshold' and (2) 'bipolar disorder' plus 'maintenance or prophylaxis or longitudinal'. Studies of children or adolescents and non-English-language reports were excluded. **Results:** Of the studies published between 1987 and October 2007, 77 articles about subsyndromal mood symptoms and 257 studies of maintenance therapy agents were found. Only 11 of the 257 studies of maintenance therapy agents discussed subsyndromal mood symptoms. Of the 77 articles, two thirds were published after 2000. Inconsistent definitions of subsyndromal mood symptoms and different evaluation tools and methodologies were used in the studies. **Conclusions:** There is a need to standardize definitions and validate measuring

approaches for subsyndromal mood symptoms. However, when measured in both naturalistic studies and clinical trials, subsyndromal mood symptoms were frequently reported by patients receiving maintenance therapy and were associated with poor functioning. As with other chronic illnesses, knowledge of the patient's perspective of daily morbidity is important for improving the clinical outcome. Studies of maintenance therapy for bipolar disorder, regardless of the approach, should measure subsyndromal mood symptoms as an additional outcome.

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## Introduction

It has long been observed that patients with bipolar disorder commonly experience symptoms that do not meet the DSM-IV diagnostic criteria for an episode [1–7]. When we investigated the impact of decreasing the minimum episode length requirement to 2 days using daily self-reported data, the number of depressed episodes for all patients quadrupled and the number of hypomanic episodes tripled [8, 9]. The frequent occurrence of subsyndromal symptoms has also been noted in other longi-



**Fig. 1.** Distribution of types of articles on subsyndromal mood symptoms published between 1987 and October 2007.

tudinal studies by either self-report [10] or clinician ratings [11–16] and in 2 randomized, placebo-controlled trials of maintenance therapies by clinician ratings [17]. Furthermore, subsyndromal symptoms were frequently present in a cross-sectional study of patients who were in clinical remission [18]. Subsyndromal symptoms have been associated with significant functional disability [19–28] and with an increased risk of relapse [24, 29–33]. These subsyndromal mood symptoms persist despite the range of pharmacotherapies now available for treating bipolar disorder, and several researchers have noted the need for increased recognition of their clinical significance [5, 6, 15, 28, 34–39]. The purpose of this limited review is to examine the current usage and potential contribution of the measurement of subsyndromal mood symptoms to studies of maintenance therapies for bipolar disorder.

## Methods

The published literature was searched using the Medline database with selection criteria of ‘bipolar disorder’ plus ‘inter-episode or interepisode or subsyndromal or subclinical or residual or subthreshold’. This was supplemented by manual searches of relevant cross-referenced articles. To find all the maintenance drug studies conducted during the same time period, a second search using ‘bipolar disorder’ plus ‘maintenance or prophylaxis or longitudinal’ was completed. Both open and controlled trials of maintenance therapies were included. Articles about children or adolescents were excluded. Only English-language publications were included.

## Results

### *Type and Number of Articles Found*

Seventy-seven articles on subsyndromal mood symptoms that were published between 1987 and October 2007 were identified. Of the 77 articles, 24 (31%) were published before the year 2000 and 53 (69%) after the year 2000. The distribution of article type for these 77 articles is shown in figure 1, with the greatest number of articles (34; 44%) being about the course of illness. For the same time period, between 1987 and October 2007, 257 studies of maintenance therapy agents were found. Only 11 of the 257 discussed subsyndromal symptoms, and 8 of these 11 studies involved lithium.

### *Definition and Measurement of Subsyndromal Mood Symptoms*

In the 77 articles, no common definition of subsyndromal mood symptoms was used. Examples of these definitions include mood symptoms of minor severity [15], symptoms that meet some but not all the DSM-IV criteria and last for the standard episode length [27], symptoms that meet the DSM-IV criteria for severity but not for episode length [8, 9, 24] and symptoms less severe than hypomania or minor depression [3, 5, 6, 11, 12]. Furthermore, each study used a unique methodological approach to measuring subsyndromal mood symptoms, involving diverse instruments and time intervals between measurements (table 1). All studies were included in the analysis regardless of definition or methodology.

## Review and Discussion

### *Frequent Subsyndromal Symptoms*

Although there is no standard definition of subsyndromal mood symptoms and evaluation approaches differ, subsyndromal mood symptoms were detected in every longitudinal study that measured them [1, 4, 8–17, 19, 23, 26, 27, 29, 30, 34, 38, 40, 41]. Several recent longitudinal studies lasting over a year have reported that patients with bipolar disorder spent about half the time ill, predominantly with subsyndromal symptoms [12, 13, 15, 38]. Subsyndromal depressive symptoms predominate over subsyndromal manic symptoms [7, 9, 11–13, 16, 17, 42, 43], and the frequency of subsyndromal depressive symptoms does not differ between bipolar I and bipolar II disorders [9, 16]. Furthermore, symptoms of depression that occur outside of an episode may at times be severe in intensity [9]. Up to 70% of patients with bipolar disorder

**Table 1.** Examples of instruments used to measure subsyndromal mood symptoms

Study	Number of patients	Study length	Instrument	Measurement frequency	Rater
Altshuler et al. [27]	759	several years	Inventory of Depressive Symptomatology-Clinician Rated [80]	2 weeks	clinician
Frye et al. [17]	575 originally	2 pooled 18-month trials	Hamilton Rating Scale for Depression-17 and Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia-Change Version [81]	weekly, biweekly, monthly, per protocol	clinician
Paykel et al. [15]	204	18 months	Longitudinal Interval Follow-up Evaluation [82]	weekly	clinician
MacQueen et al. [24]	138	1 year	modified NIMH Life Chart method	daily	clinician
Judd et al. [11]	146	13 years	Longitudinal Interval Follow-up Evaluation	weekly	clinician
Angst et al. [1]	591	15 years	Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology [83]	yearly questionnaire; 4 interviews in total	clinician
Bauer et al. [8, 9]	203	5 months	ChronoRecord software [75, 76]	daily	self-report
Kupka et al. [14, 16]	539	1 year	NIMH Life Chart methodology	daily	self-report; clinician adjusted
Calabrese et al. [43]	593	1 year	Mood Disorder Questionnaire [84]	survey of prior 4 weeks and prior year	self-report
Denicoff et al. [10]	30	2 years	NIMH Life Chart Methodology-p	twice daily	self-report

NIMH = National Institute of Mental Health.

experience interepisode symptoms [30, 44], and these are not a phenomenon only of the sickest patients, when defined as those experiencing an episode that meets the DSM-IV criteria at some point during the study period. Subsyndromal symptoms of both depression and hypomania also occurred frequently in patients who did not meet the criteria for a DSM-IV episode during the study period [8, 9]. In the post hoc analysis of 2 placebo-controlled maintenance trials, the median time to the onset of subsyndromal symptoms in patients stabilized on lithium or lamotrigine was just 15 days [17].

#### *Subsyndromal Symptoms and Outcome*

Ongoing subsyndromal symptoms may have a strongly negative impact on every aspect of life for patients with bipolar disorder. Multiple researchers have reported that subsyndromal symptoms are associated with a poor func-

tional outcome, including high levels of unemployment, underemployment or inability to complete home duties [19, 21, 23, 24, 27, 28], impairment of social adjustment that impacts on family life, interpersonal relationships and social activities [20, 26–28], and low self-esteem [22]. The presence of subsyndromal symptoms also increases the risk of relapse into episodes of mania or depression [29–32].

#### *Other Subsyndromal Symptoms*

Other morbidity that is associated with bipolar disorder may contribute to the daily level of subsyndromal mood symptoms, especially of depression [39]. Cognitive impairments that persist after the resolution of episodic mood symptoms have been detected across a range of tasks of attention, memory and executive function [45–47] and are associated with low psychosocial functioning

[33, 48] and subsyndromal mood symptoms [49]. Sleep disturbances including insomnia are frequently reported in patients in remission from acute episodes [50]. Side effects of medications routinely used to treat bipolar disorder may negatively impact cognitive functioning [51] and cause sedation or fatigue. Furthermore, the high rates of comorbidities associated with bipolar disorder, including substance abuse, anxiety disorders and eating disorders, may intensify the subsyndromal symptoms [24, 37, 52]. Patient nonadherence with treatments may also contribute to subsyndromal symptoms.

#### *Clinical Trials of Maintenance Agents for Bipolar Disorder*

Diverse factors may contribute to the unexpected subsyndromal load present in many patients receiving maintenance treatment for bipolar disorder. Although recognition of their importance is increasing, subsyndromal mood symptoms are not routinely measured during studies of maintenance therapy for bipolar disorder. The principal method used to determine drug efficacy is randomized clinical trials in which a predetermined primary outcome parameter is measured in all study participants to detect the response to treatment. In clinical trials of agents for either acute or maintenance treatment of bipolar disorder, the primary outcome is defined clinically, using physician-observed events such as the time until an intervention [53] or episode recurrence [54]. These events are intermediate end points, defined as a measure that is of genuine clinical benefit, but is not the ultimate end point of the disease such as survival [55]. Intermediate end points are regularly used as the basis for Food and Drug Administration (FDA) marketing approval, although improvement in an intermediate end point may not result in reduced morbidity or mortality [55]. While the value of the events used to determine efficacy for maintenance treatment of bipolar disorder is unquestionable, it appears that these intermediate end points may not translate directly into improvements in daily morbidity as defined by subsyndromal mood symptom levels. Furthermore, the sample size during clinical trials of efficacy is designed to measure and detect a significant difference in the primary outcome and not the daily symptom load.

The relationship between subsyndromal symptoms and the time to relapse may not be the same for all medications [17]. Bipolar disorder is a complex, heterogeneous disease with a significant genetic component. The variability in effectiveness and suppression of subsyndromal symptoms may define subtypes of the disorder or reflect genetic polymorphisms in disease pathways or drug me-

tabolism [56]. As proposed for nonpsychiatric illnesses with unclear pathophysiology, some maintenance agents may only influence a portion of a complex disease process or may act through an unintended, independent mechanism of action [57, 58]. Lastly, the issues relating to efficacy studies and the apparent overestimation of the effectiveness of medications in clinical practice have been well documented [59, 60].

#### *Specific Treatment of Subsyndromal Mood Symptoms*

There are few articles regarding the specific treatment of subsyndromal mood symptoms, and measures generally follow the established practice guidelines for the treatment of a major relapse, although there is limited evidence that increasing the dosage of lithium [30, 61] or an anticonvulsant [62] may be useful. In clinical practice, multiple psychotropic drugs are routinely prescribed, in part as an attempt to improve control over subsyndromal symptoms. Psychoeducation techniques, when used as adjuvants to pharmacological treatments, may help to reduce interepisode symptoms [63–66]. In the future, biomarkers may be used to measure residual disease.

#### *Subsyndromal Mood Symptoms and Chronicity*

The importance of subsyndromal mood symptoms increases after the high symptom load present during an acute episode is stabilized and the disease becomes chronic. However, since the efficacy of most maintenance therapies has been established for acute mania or depression, patients who meet the DSM-IV criteria for an episode may derive more benefit than those whose current problems are due to subsyndromal mood symptoms. Moreover, the common occurrence of subsyndromal symptoms suggests that the response to an agent during the acute episode may not always predict the patients with the best functional outcome or the success of maintenance therapy with the same agent. Unless subsyndromal symptoms can be reduced to a level tolerable to the patient, the same agent that seemed invaluable when treating the dramatic symptoms of the acute episode may seem to be ineffective over time. Furthermore, since symptoms fluctuate rapidly in the natural course of bipolar disorder [67, 68], if the commonly used maintenance agents have only a modest impact on the daily symptom load, it may be difficult to distinguish the effects of chronic treatment from the natural fluctuations in the disease.

#### *Measuring Patient Perception of Disease*

The high frequency of subsyndromal mood symptoms and associated functional impairment implies that pa-

tient well-being is not solely determined by the presence or absence of episodes that meet the DSM-IV criteria. Indeed, it is not unusual for patient perception of disease burden to be at variance with clinician ratings, since there is only a weak correlation between objective or clinician measures and patient reports of functional limitations in a variety of chronic conditions such as chronic obstructive pulmonary disease, low-back pain, rheumatoid arthritis and stroke [69]. Therefore, as in other chronic illnesses where prevention and control rather than cure is the aim of therapy, it is important to obtain the patient's perspective on their daily functioning and well-being [69]. The need for the patient perspective has been recognized by the regulators with the recent FDA release of a draft guidance regarding the use of patient-reported outcomes (PRO) as a new outcomes classification [70]. Validated PRO instruments can provide unique measures that are complementary to traditional clinician measures of efficacy [70]. Of the 215 prescription-only new drugs approved by the FDA between 1997 and 2002, 23 drugs, primarily antimigraine drugs and antiepileptics, relied solely on PRO end points for approval, while another 41 drugs for a range of chronic conditions such as Parkinson's disease, rheumatoid arthritis, asthma and allergies included PRO along with traditional end points [71].

There is a need to incorporate measurement of subsyndromal symptoms and the patient perspective of life quality into future maintenance studies of bipolar disorder, regardless of whether the study has an efficacy, effectiveness or hybrid design. However, since patients with hypomania may lack insight, self-reported data must be interpreted with care and should supplement but not replace clinician findings. In the future, as with other chronic conditions, achieving an acceptably low daily burden of symptoms in bipolar disorder may become as important a goal for long-term stability as is the recovery from an acute episode [72].

Several validated tools are available to measure daily mood symptom load in bipolar disorder, including the National Institute of Mental Health Life Chart using paper [10] or a palmtop computer [73], the ChronoSheet using paper [74] or the ChronoRecord software for a personal computer [75, 76]. There are also several instruments to measure quality of life in patients with bipolar disorder, as reviewed elsewhere [77]. Detailed investigations are also required to understand the frequency, duration and severity of subsyndromal symptoms that are tolerable to most patients with bipolar disorder and the impact of treatment of subsyndromal symptoms on long-term outcome. A useful approach to the study of new

medications may be to determine if they reduce the burden of subsyndromal symptoms when used as adjunctive agents, similar to the methodology used for anticonvulsants in epilepsy [78].

#### *Limitations*

Only the Medline database was searched. The number of studies of subsyndromal mood symptoms was small, and these contained inconsistencies in definitions, measurements and study design. Subsyndromal symptoms other than mood-related symptoms were included in some studies. Furthermore, the frequency and pattern of subsyndromal symptoms experienced by normal controls, unmedicated patients with bipolar disorder or patients with other mood disorders is not known. Finally, understanding the pattern of subsyndromal mood symptoms is not intended to blur the critical diagnostic concept of bipolarity [79].

#### **Conclusion**

There is a need to standardize the definition of subsyndromal mood symptoms in bipolar disorder and to validate approaches for measuring them. Future studies of maintenance agents in bipolar disorder should consider the daily symptom load, regardless of the study design. For some patients, subsyndromal mood symptoms that do not respond to treatment may be as deleterious as an acute episode that responds to treatment. The goal of maintenance therapy for bipolar disorder is not just to increase the time to the next episode, but also to improve daily symptom burden and allow patients to return to everyday functioning. Measures of subsyndromal symptom load should become important adjunctive measures to traditional measures, as future approaches shift away from the prevention of episodes towards achieving a level of daily disease activity that allows the patient an acceptable quality of life. With the availability of newer agents for maintenance treatment, the degree of relief provided from subsyndromal symptoms may distinguish between therapies and help to individualize treatments. As study designs for maintenance therapies for bipolar disorder continue to evolve, it is time to include the daily symptom burden as an additional measurable outcome.

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