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Longitudinal course of symptom severity and fluctuation in patients with treatment-resistant unipolar and bipolar depression

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ABSTRACT

Little is currently known about the long-term course of symptom severity and fluctuation in patients with treatment-resistant depression (TRD). We assessed this using the longitudinal interval follow-up evaluation in 115 patients with TRD (84 unipolar, 31 bipolar) with 1–7 years (median 36 months) of follow-up. Of the follow-up months, 39.2% were spent asymptomatic and 21.1% at sub-threshold symptom level, while 15.8% were spent at mild, 13.9% at moderate, and 10.0% at severe depressive episode level. Significantly more unipolar than bipolar patients were continuously symptomatic during follow-up (43% vs. 29%). Patients had a mean of 1.0 (S.D. = 1.2) symptom severity level fluctuations per year. High fluctuating patients had significantly poorer global functioning and quality of life. Although most patients with TRD achieve an asymptomatic state, they continue to fluctuate and experience depressive symptoms in the majority of months, mostly at subclinical or mild severity. However, there are important differences between unipolar and bipolar TRD, with unipolar patients more likely to experience an unremitting depressive state. Additionally, a more fluctuating longitudinal illness course is associated with poorer function and quality of life, and with a bipolar diagnosis. We suggest that the longitudinal illness course is an important outcome to be considered in future TRD research.

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1. Introduction

Depression is a major public health challenge. By 2020 depression is projected to be a leading cause of disability worldwide, second only to cardiovascular disease (World Health Organization, 2011). Most patients treated for a first episode of unipolar or bipolar depression do not achieve full remission with first line pharmacological or psychological treatments (Sackeim, 2001; Fava, 2003). When a narrow definition is used, 20–30% of patients with depression do not show adequate response to antidepressant treatment (Souery et al., 2006; Trivedi et al., 2006), while a broader definition that includes absence of remission – arguably more appropriate – raises this figure to 60% (Greden, 2001; Trivedi et al., 2006).

Compared to those who do not develop treatment resistance, patients with treatment-resistant depression (TRD) experience a more severe and protracted course of illness (Üstün and Kessler, 2002). They

are more likely to experience comorbid physical and mental health problems, to suffer significant short-term (Dunner et al., 2006) and longer-term (Kennedy and Paykel, 2004) social impairment, and are more likely to attempt suicide (Kornstein et al., 2000; Dunner et al., 2006).

TRD includes both unipolar and bipolar depression. However, treatment resistance in bipolar patients has received less attention in the literature, despite being the major cause of disability and mortality in bipolar disorder (BPD) (Kupka et al., 2007). Depressive symptoms and the number of episodes account for the greatest overall reduction in quality of life (Gutierrez-Rohas et al., 2008) and are also associated with significantly increased suicide risk (Colom et al., 2006). Yet, the evidence base for treatment options in bipolar depression remains limited, and even more so for bipolar TRD (Vieta and Colom, 2011).

Relatively few studies have documented the long-term illness course in non-resistant populations with affective disorders (Keller et al., 1992; Judd et al., 1998). Reports indicate that unipolar Major Depressive Disorder (MDD) is characterised primarily by minor and sub-syndromal symptoms – rather than major depressive episodes – and the course is changeable, with major depressive episodes,

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dysthymia, and sub-threshold depressive symptom levels fluctuating over time in the same patient (Judd et al., 1998; Kennedy et al., 2004). Likewise, the longitudinal symptomatic course of BPD (bipolar I and II) is primarily depressive rather than manic, dominated by sub-syndromal and minor depressive symptoms, with fluctuation between symptom severity levels seen within the same patient over time (Judd et al., 2002, 2003a,b). Although these initial studies suggested a 30-fold predominance of depressive symptoms over manic ones in bipolar I compared with a three-fold predominance in bipolar II, a later study (Kupka et al., 2007) suggested a similar three-fold ratio in both sub-types of bipolar disorder. No such studies have yet been reported in the TRD literature, however.

The current study sought to describe the symptomatic course of illness in a cohort with treatment-resistant unipolar and bipolar depression. With the longitudinal follow-up evaluation (LIFE) chart (Keller et al., 1992) used to assess monthly symptom severity in patients followed-up for between 1 and 7 years, the current study aimed to describe patients' illness course in terms of the mean symptom severity, the time spent symptomatic (chronicity), the number of different symptom severity levels per year, and the number of fluctuations between different symptom severity levels. Also of interest was the role of social and clinical factors in predicting patients' symptom severity and symptom fluctuation during follow-up, and whether the longitudinal course of patients with unipolar and bipolar TRD differed.

In light of existing reports on the long-term symptom course of unipolar MDD and bipolar depression (BPD), and what is already known about the clinical characteristics of TRD, we hypothesised that patients would have a generally severe and chronic illness course, but one that fluctuates between multiple levels of symptom severity over time. It was anticipated that a diagnosis of BPD would be associated with a more fluctuating course of illness.

2. Methods

2.1. Design

The study was a retrospective follow-up of patients discharged from a specialist tertiary unit. Follow-up data were collected using both longitudinal and cross-sectional assessments. Data used in this study are based on longitudinal assessment using the Longitudinal Interval Evaluation (LIFE) chart and Psychiatric Status Rating (PSR) (Keller et al., 1992).

2.2. Participants

The analysis sample consisted of 115 patients discharged from the Affective Disorders Unit (ADU), a specialist inpatient unit for complex and difficult-to-treat mood disorders. The ADU is a tertiary service that accepts patients referred from across the United Kingdom. Multimodal treatment incorporating the major evidence-based therapies for affective disorders is offered, including pharmacotherapy (typically medication combinations and high dose therapy, where indicated), individual and couple psychological therapy, occupational therapy, and other physical therapies (e.g. ECT) as indicated. All patients were referred with a depressive episode that was resistant to treatment. Diagnosis was established using the International Classification of Disease, 10th revision (ICD-10), after a full, longitudinal clinical assessment including access to old case notes and the use of appropriate standardised interviews (Mini International Neurosychiatric Interview (MINI+) or Structured Clinical Interview for DSM (SCID), Structured Assessment of Personality (SAP), Clinician Rated Inventory of Depressive Symptomatology and Young Mania Rating Scale); only patients with a primary diagnosis of unipolar MDD or BPD were included in the study. Treatment resistance (defined as the failure to respond to at least one adequate antidepressant trial) was generally severe: on discharge from the ADU, all patients had received at least one prior antidepressant trial (median=6, IQR=6) and 96 (83.5%) had received at least one mood stabiliser (median=2, IQR=3) including 26 (83.9%) of BPD patients. Sixty-nine percent of patients had already received ECT with no sustained response. Follow-up assessments were undertaken at least 1 year after discharge from hospital, except in three cases where for practical reasons patients were followed-up between 10 and 11 months post-discharge. All study procedures were approved by the Joint South London and Maudsley and the

Institute of Psychiatry National Health Service Research Ethics Committee, and all patients gave informed written consent prior to participation in the study.

2.3. Outcomes

The study had three main outcomes. The first outcome sought to determine the severity of patients' illness in terms of the percentage of follow-up months spent at five symptom severity levels (level 1=asymptomatic, level 2=sub-threshold, level 3=mild depressive episode, level 4=moderate depressive episode, level 5=severe depressive episode), and the chronicity of illness in terms of the number of follow-up months spent symptomatic, and whether or not patients achieved asymptomatic status at any point during follow-up. The second outcome assessed fluctuations between symptom severity levels, including the total number of different levels, the number of shifts between severity levels per year, and the magnitude of fluctuations between levels. The third outcome investigated predictors of symptom fluctuation (number of shifts between symptom severity levels per year) and mean symptom severity during follow-up. Five variables were identified *a priori* (social support, number of prior depressive episodes, duration of ADU admission, life events in 12 months to follow-up, and diagnosis: unipolar vs. bipolar) as possible predictors of symptom fluctuation and mean symptom severity. A further analysis using the same predictor variables sought to distinguish patients with a high number of yearly symptom severity level fluctuations from those with a low number of fluctuations. In order to determine the impact of symptom fluctuations, we examined differences in global level of functioning and quality of life in high- and low-fluctuating groups.

2.4. Assessment instruments

The LIFE chart was the primary measure used to assess long-term symptom severity (Keller et al., 1992). The LIFE chart is a widely used follow-up scale that allows the weekly or monthly symptomatic status of patients to be assessed retrospectively at follow-up intervals of 6 months or longer. Symptoms are ordinarily rated on a 6-point scale using the Psychiatric Rating Scales (PSR) (Keller et al., 1992). A score of 1 represents an asymptomatic state, while a score of 6 indicates a major depressive episode including psychotic symptoms or other severe impairment. Although operationally linked to the Research Diagnostic Criteria (Spitzer et al., 1978) in the original design, the PSR has been subsequently adapted for use with the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 1994). In the current study, a modified PSR rating adapted for the follow-up of depression in the UK was used (Kennedy et al., 2003; Kennedy and Paykel, 2004). The modified version expands the PSR ratings from a 6-point to a 7-point scale, representing five symptom severity levels. A score of 1 or 2 indicates remission/return to usual self, a score of 3 or 4 indicates partial remission/response or persisting sub-syndromal symptomatology, and a score of 5, 6, or 7 indicates a depressive episode (5=mild, 6=moderate, 7=severe). Any time spent in mania was recorded using an equivalent 7-point scale. The PSR scores in the current study represented the monthly clinical status of patients for the time between discharge from hospital to the follow-up date.

The LIFE chart was administered by two research psychiatrists. The raters had satisfactory inter-rater agreement, based on 13 ratings (Fekadu et al., 2011). The inter-rater reliability for syndrome level categorisation of relevant outcomes was good ($\kappa=0.9$; $p<0.001$); the correlation for the overall agreement between the raters was also good (Spearman's $\rho=0.912$; $p<0.001$).

The Oslo 3 Support scale (OSS) was used to assess general social support (Dalgard et al., 2006) and the List of Threatening Experiences (LTE) scale was used to assess recent life events. The Global Assessment of Functioning (GAF) scale (Hall, 1995) and the Quality of Life Enjoyment & Satisfaction Questionnaire (QLESQ) (Endicott et al., 1993) were used to investigate an association between patients with high (>1) and low (<1) number of symptom severity level fluctuations per year and functional outcome and quality of life.

2.5. Data management and statistical analyses

Total months spent at the five depressive symptom severity levels were summed and expressed as a percentage of the total number of months available for each patient, but did not include months spent in hypomania/mania. Thus, months spent in mania in remission (level 1 or 2) were scored as 'asymptomatic' and included in the above analysis while months spent in hypomania (score of 3 or 4) or mania (score ≥ 5) were excluded. The total and mean number of shifts, magnitude of shifts, and number of shifts per year were calculated for each patient by including all follow-up months in the analysis, including any months spent in mania. Shifts between levels were calculated in terms of any month-to-month change between depressive symptom severity levels or change in polarity (change in polarity defined as change from some level of depression to some level of mania or vice versa). Any shifts within mania/hypomania were not included. The magnitude of shifts was calculated based on the size of shift between the five depressive symptom severity levels, scored from 0 (no shift) to 4 (a shift across four symptom severity levels, that is, level 1 to level 5, or vice versa). Shifts within mania were not included.

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