Journal of Affective Disorders 136 (2012) 1059–1061

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Mixed depression: A study of its phenomenology and relation to treatment response

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ARTICLE INFO

Article history:
Received 11 October 2011
Accepted 14 November 2011
Available online 14 December 2011

Keywords:
Mixed depression
Phenomenology
Major depressive disorder
Bipolar disorder
Neuroleptic treatment

ABSTRACT

Background: Mixed depression reflects the occurrence of a major depressive episode with subsyndromal manic symptoms. Not recognized in DSM-IV, it is included in the proposed changes for DSM-5. Observational and cross-sectional studies have suggested that mixed depression is present in up to one-half of major depressive episodes, whether in MDD or bipolar disorder. Based on observational studies, antidepressants appear to be less effective, and neuroleptics more effective, in mixed than pure depression (major depressive episodes with no manic symptoms). In this report, we examine the specific manic symptoms that are most present in mixed depression, especially as they correlate with prospectively assessed treatment response.
Methods: In 72 patients treated in a randomized clinical trial (ziprasidone versus placebo), we assessed the phenomenology of manic symptom type at study entry and their influence as predictors of treatment response.
Results: The most common symptom presentation was a clinical triad of flight of ideas (60%), distractibility (58%), and irritable mood (55%). Irritable mood was the major predictor of treatment response. DSM-based diagnostic distinctions between MDD and bipolar disorder (type II) did not predict treatment response.
Conclusion: In this prospective study, mixed depression seems to be most commonly associated with irritable mood, flight of ideas, and distractibility, with irritability being an important predictor of treatment outcome with neuroleptic agents. If these data are correct, in the presence of mixed depression, the DSM-based dichotomy between MDD and bipolar disorder does not appear to influence treatment response.

1. Introduction

Mixed episodes are currently defined in the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as requiring fully syndromes of acute mania and the acute major depressive episode (MDE). Recent studies have found that many patients with MDEs have subsydnromal manic symptoms, and that this condition occurs both in major depressive disorder (MDD) and in bipolar disorder (Akiskal and Benazzi, 2004; Benazzi, 2001; Judd et al., 2002). This condition, termed mixed depression (Benazzi, 2002, 2008), is included in the draft proposal for DSM-IV, to be called MDD with manic features, or bipolar depression with manic features.

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doi:10.1016/j.jad.2011.11.024

Studies have found that such patients with mixed depression appear to have different clinical course and treatment outcomes, compared to MDEs without manic symptoms (pure depression) (Dilsaver and Benazzi, 2008; Dodd et al., 2010; Keller et al., 1986). Some observational studies in mixed depression have suggested poor antidepressant response (Goldberg et al., 2009) and enhanced neuroleptic response (Koukopoulos et al., 2007).

The purpose of this analysis was to acquire phenomenological data to help identify the key symptomatic features of mixed depression in patients with MDD or bipolar disorder during an acute major depressive episode.

2. Methods

Seventy two (72) adult patients (age 18–65) with DSM-IV bipolar disorder type II or major depressive disorder were recruited if they currently had a DSM-IV major depressive episode, while also presenting with 2 or 3 DSM-IV manic criteria (not more or less). Interviews and rating scales included the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (First et al., 1995), the Montgomery Asberg Depression Rating Scale (MADRS) (Galinowski and Lehert, 1995), the Mania Rating Scale for the SADS-C (MRS), the Hamilton Anxiety Scale (HAM-A), the Clinical Global Impression for Bipolar Disorder (Spearing et al., 1997), and the Global Assessment of Functioning (Jones et al., 1995). Patients received ziprasidone versus placebo in randomized fashion as part of a larger clinical trial, with change in MADRS scores as the main outcome measure (Patkar et al., in press).

Euphoric mood was defined as a score of 2 or greater on the MRS Item 1: Elevated Mood; Irritability was defined as a score of 2 or greater on the MRS Item 9 ("Overt Anger") with a score of 1 or greater on the SAFTEE Item 6 ("Irritability").

Regression modeling was conducted to identify predictors of mixed depression diagnosis. All analyses were done in JMP (SAS Institute Inc., Cary, NC).

3. Results

Frequency of individual manic symptoms is presented in Table 1. Flight of ideas and distractibility were present in 55% of the sample. 17% of patients presented both flight of ideas and decreased need for sleep. The three most frequently presented manic symptoms (flight of ideas, distractibility, and insomnia) presented together in 17% of patients. When analyzing change in MADRS using all three of these manic symptoms separately as predictors, effect estimates (mean differences) along with their 95% confidence intervals (CI) were: flights of ideas −1.85 (95% CI −5.76, 4.45); distractibility −2.88 (95% CI −4.20, 5.96); insomnia 1.92 (95% CI −8.52, 6.72).

Table 1
The frequency and correlation between manic symptoms presented at baseline and change in MADRS scores.

Manic symptom	Effect estimate (mean difference)	95% confidence interval	Frequency
Increased activities	−1.51	−4.09, 10.12	22%
Distractibility	−3.21	−5.61, 8.04	58%
Decreased need for sleep	1.92	−8.52, 6.72	44%
Grandiosity	−1.06	−7.12, 10.25	14%
Pressured speech	0.10	−7.94, 7.74	24%
Thoughtlessness	0.56	−7.57, 7.70	28%
Flight of ideas	−2.54	−5.73, 4.64	60%

MADRS = Montgomery Asberg Depression Rating Scale.
Effect estimate reflects mean difference in MADRS scores.

Subjects tended to express more irritability than euphoric quality of mood at baseline, with 59% reporting irritability, either subjectively felt or expressed overtly to others, and 15% reporting euphoric mood. Using MADRS Item 3 ("Inner Tension"), 77% of patients reported feeling anxious or on edge at least occasionally, and 18% reported continuous feelings of inner tension. The mean HAM-A score was 14 ± 6.39. Scores under 17 denote a mild severity of anxiety, suggesting that our sample was not particularly anxious, with only 6% ($n = 4$) of our participants falling into the "moderate to severe" anxiety category, and 20% expressing ($n = 14$) "mild to moderate" anxiety. The rest of the sample, representing about 75% of the participants, reported only mild anxiety.

Overall irritability was not strongly associated with treatment response in the placebo group (mean difference 5.9; 95% CI −17.82, 6.07). However, in the ziprasidone group, baseline irritability was significantly associated with treatment response (mean difference 7.2; 95% CI 3.36, 33.21). Baseline anxiety assessed using the HAM-A was not associated with treatment response in either the placebo or drug group (placebo mean difference 0.23, 95% CI −5.64, 5.19; ziprasidone mean difference 1.75, 95% CI −2.53, 6.03).

Elevated mood did not predict treatment response, independently (placebo mean difference 2.65, 95% CI −11.67, 6.37; drug mean difference 7.91, 95% CI −18.22, 2.39), or when adjusted for diagnosis (for bipolar disorder; ß = −0.83, 95% CI −1.34, 5.23; for MDD, ß = −0.70, 95% CI −13.20, 7.67).

Diagnosis (MDD versus type II bipolar disorder) did not strongly predict treatment response (placebo mean difference 3.24, 95% CI −3.67, 10.15; drug mean difference 4.21, 95% CI −11.68, 3.26).

4. Discussion

The most common symptom presentation of manic symptoms in the depressive mixed state was the triad of irritability, flight of ideas, and distractibility. Almost all patients were highly irritable and agitated, but not anxious. The best predictor of treatment response to a neuroleptic was irritable mood; anxiety or specific manic symptoms did not predict treatment response. Importantly, when mixed depression is present, we found that no strong differential treatment response occurred using the DSM-based distinction between bipolar disorder and MDD.

These data are relevant to DSM-5, since the proposed definitions there for the mixed modifier for MDD specifically exclude irritability and distractibility, which are two of the three most common symptoms of mixed depression in our study. The DSM-5 proposal also excludes agitation. These criteria, though sensitive, may have low specificity, which

may have been the concern of DSM-5 task force members who are concerned about false positives. However, if the mixed state is defined too narrowly, we will also have many false negatives.

These data add to the previous literature on mixed depression. For instance, in an analysis of the Systematic Treatment Enhancement for Bipolar Disorder (STEP-BD) cohort (Goldberg et al., 2009), coexisting subsyndromal manic symptoms (1–3 symptoms associated with manic symptoms) were present in 54.0% of acutely depressed subjects (n = 1380). However, in the application of restrictive DSM-IV-TR criteria requiring full manic and full MDE, only 14.8% of 1380 bipolar patients experiencing a MDE also met the criteria for mania. Flight of ideas and psychomotor agitation were highly correlated with a full DSM-IV mixed episode, but distractibility was more common in the subsyndromal mixed depression group.

The results of our study are partly consistent with a recent large international study (Angst et al., 2011), in which 47% of 5635 consecutive adults with major depressive episodes experienced 3 or more manic symptoms of less than 4 days duration (subsyndromal mania or hypomania). 84% of the total sample met the DSM-IV criteria for MDD (16% met bipolar disorder criteria), thus confirming the frequent presence of mixed depression in MDD, and not only bipolar disorder. In that study, as in ours, distractibility, decreased need for sleep, and irritability were common (40–47% prevalence), but Angst and colleagues found more evidence of increased activities and pressured speech (47–50%), and less flight of ideas (33%), than in our cohort. This study, while huge, did not systematically use rating scales given by reliable interviewers, however, and it did not prospectively assess treatment response.

In sum, these data from a randomized clinical trial setting augment prior large cross-sectional observational reports. As a whole, these studies suggest that important features of mixed depression are irritable mood, distractibility, and flight of ideas, augmented by other manic symptoms. These results should assist in the development of valid definitions for DSM-5 revisions.

The results of this analysis are limited by the modest sample size, but the cohort was very well-characterized systematically with standardized rating scales and diagnostic instruments, with treatment response based on double-blind randomized conditions — features which are absent in any prior studies of the mixed depression.

Role of funding source

Funding for this study was provided primarily by an investigator initiated research grant by Pfizer (Groton, CT, USA). None of these funding sources had a role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Conflicts of interest

In the past 12 months, Dr. Ghaemi has received a research grant from Pfizer, Inc. and the NIMH. He provided one-time research trial consultations to Sepracor, Inc. and Pfizer, Inc. Neither he nor his family hold equity positions in these companies.

Acknowledgment

This research was primarily supported by an investigator initiated research grant by Pfizer (Groton, CT, USA).

References

Akiskal, H.S., Benazzi, F., 2004. Validating Kraepelin's two types of depressive mixed states: "depression with flight of ideas" and "excited depression". The World Journal of Biological Psychiatry 5, 107–113.

Angst, J., Azorin, J.M., Bowden, C.L., Perugi, G., Vieta, E., Gamma, A., Young, A.H., 2011. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Archives of General Psychiatry 68, 791–798.

Benazzi, F., 2001. Major depressive episodes with hypomanic symptoms are common among depressed outpatients. Comprehensive Psychiatry 42, 139–143.

Benazzi, F., 2002. Which could be a clinically useful definition of depressive mixed state? Progress in Neuro-Psychopharmacology & Biological Psychiatry 26, 1105–1111.

Benazzi, F., 2008. Reviewing the diagnostic validity and utility of mixed depression (depressive mixed states). European Psychiatry 23, 40–48.

Dilsaver, S.C., Benazzi, F., 2008. Treating depressive mixed states in bipolar disorders. The Journal of Clinical Psychiatry 69, e23.

Dodd, S., Kulkarni, J., Berk, L., Ng, F., Fitzgerald, P.B., de Castella, A.R., Filia, S., Filia, K., Montgomery, W., Kelin, K., Smith, M., Brnabic, A., Berk, M., 2010. A prospective study of the impact of subthreshold mixed states on the 24-month clinical outcomes of bipolar I disorder or schizoaffective disorder. Journal of Affective Disorders 124, 22–28.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders — Patient Edition (SCID — I/P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute, New York.

Galinowski, A., Lehert, P., 1995. Structural validity of MADRS during antidepressant treatment. International Clinical Psychopharmacology 10, 157–161.

Goldberg, J.F., Perlis, R.H., Bowden, C.L., Thase, M.E., Miklowitz, D.J., Marangell, L.B., Calabrese, J.R., Nierenberg, A.A., Sachs, G.S., 2009. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. The American Journal of Psychiatry 166, 173–181.

Jones, S.H., Thornicroft, G., Coffey, M., Dunn, G., 1995. A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). The British Journal of Psychiatry 166, 654–659.

Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., Keller, M.B., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Archives of General Psychiatry 59, 530–537.

Keller, M.B., Lavori, P.W., Coryell, W., Andreasen, N.C., Endicott, J., Clayton, P.J., Klerman, G.L., Hirschfeld, R.M., 1986. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. JAMA : The Journal of the American Medical Association 255, 3138–3142.

Koukopoulos, A., Sani, G., Koukopoulos, A.E., Manfredi, G., Pacchiarotti, I., Girardi, P., 2007. Melancholia agitata and mixed depression. Acta Psychiatrica Scandinavica. Supplementum 50–57.

Patkar, A., Gilmer, W., Pae, C., Ziffra, M., Pirok, E., Mulligan, M., Filkowski, M.M., Whitham, E.A., Thommi, S.B., Loebel, A., Masand, P., Ghaemi, S.N., in press. A 6 week randomized double-blind placebo-controlled trial of ziprasidone for the acute depressive mixed state. Plos One.

Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Research 73, 159–171.