Mixed affective state: a diagnostic and therapeutic challenge

Singh S1, Ho JYH2, Agius M3

1Dr Saurabh Singh BA (Hons), MB BChir, Department of General Surgery, Barnet and Chase Farm Hospitals NHS Trusts, London.
2Dr Jasmine H Y Ho, BA (Hons)MB BChir, Department of Paediatrics, National University Hospital, Singapore.
3Dr Mark Agius MD., Department of Psychiatry, University of Cambridge, South Essex Partnership University Foundation Trust. Clare College Cambridge.

Abstract

Mixed affective states are important phases in bipolar affective disorder. This paper describes the nature of these states and their importance, which is because of the increased risk of suicidal thoughts and actions. Stopping antidepressants, optimising treatment with mood stabilisers and adding an atypical antipsychotic to treatment is effective in treating mixed affective states, reducing suicidal ideation and actions.

Key words: mixed affective state, mixed bipolar depression, dysphoric mania, antidepressants, mangement of mixed affective state, antipsychotics

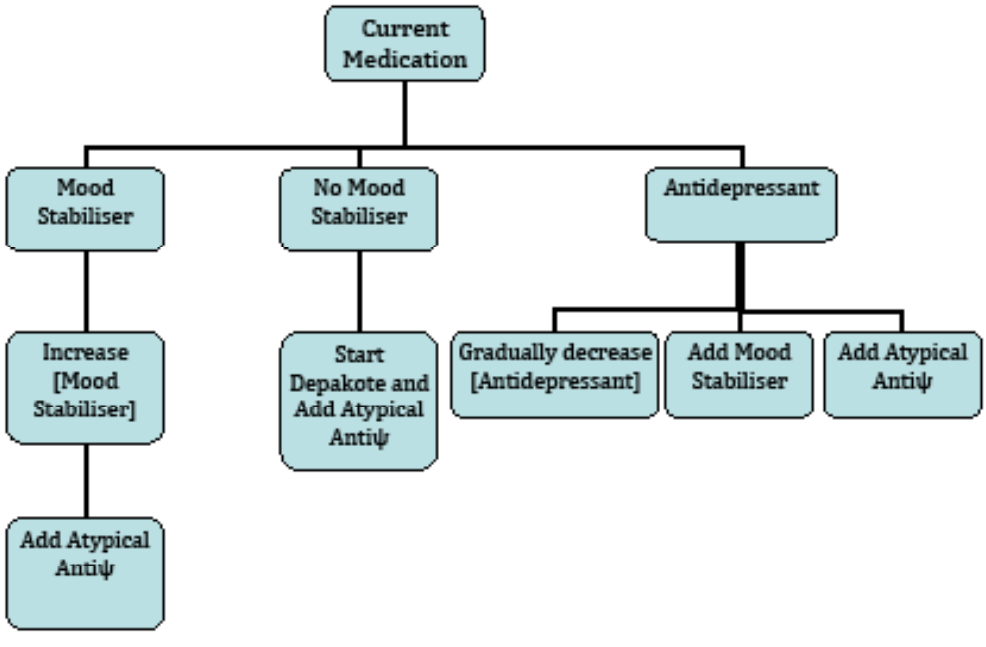
The mixed affective state remains both a diagnostic and therapeutic challenge. In mixed affective states, patients experience both symptoms of depression and mania. It is widely accepted that these patients exhibit an increased risk of suicide. Although it is recognised that these states are important, there is no adequate consensus on the diagnostic criteria or management.
Many terms including 'mixed affective state', 'dysphoric mania', 'mixed bipolar depression' and 'agitated depression' have been used in the literature. These terms allude to different proportions of manic and depressive symptoms that may be classified into three phenotypes; mixed affective episodes (when the proportion of manic and depressive symptoms is equal), dysphoric mania (when manic symptoms are prominent), and mixed (bipolar) depression (when depressive symptoms predominate). These phenotypes are generated because both mania and depression are active processes that can occur both successively and simultaneously (1) (2). Furthermore, agitated depression can be reconceptualised as an affective mixed state (3).
Evidence for a spectrum which encompasses such states is provided by Akiskal et al. (3) who showed that a significant percentage (19.7%) of patients diagnosed with Unipolar depression (n=254) experience 'agitated depression'. In addition, those 19.7% showed a strong clustering of 'non-euphoric hypomanic' symptoms, which suggests a bipolar spectrum link. In fact, Tavormina et al. showed that 28% of bipolar patients had agitated depression (n=300) (4). The overlap in the symptomatology in such patients suggests that mixed affective states are part of the bipolar affective disorder spectrum. Indeed, mixed states can be thought of as transition states between manic and depressive episodes. The notion of a "bipolar spectrum" appeared in the literature in a 1977 paper on a prospective follow-up of cyclothymic individuals (5). Akiskal et al. conceptualised unipolar and bipolar mixed states as 'depressive mixed state' and a part of the bipolar affective spectrum (3).
A conceptual model was proposed by Rhimer et al. who described three entities produced by the combination of two different outputs from two distinct 'mood generators' (1). The manic mood generator produces a manic mood and a depressive mood generator a depressed state. When the dominant input is from the manic mood generator with a smaller input from the depressive mood generator; a state of 'dysphoric mania' is produced. Conversely, in 'mixed bipolar depression' the depressive mood generator dominates over the manic. Equal inputs from both mood generators produce the 'mixed affective state'.
Several studies have shown that patients have a high risk of suicide when in a mixed affective state (6). Therefore clinically it is imperative to find strategies to resolve mixed states quickly. Balázs J et al.

showed that psychomotor agitation and irritability are strong predictors of increased suicide risk (6). There is scant literature about the management of mixed states. A few principles emerge from the limited studies available. The need to discontinue antidepressants is apparent (7). Logically there is a need to stabilise the mood and among mood stabilisers, divalproate has been more effective (7). There is little evidence on the use of adjuncts. A recent case series suggested three-pronged regimens, including increasing/adding mood stabilisers and/or increasing/adding antipsychotics as well as decreasing antidepressants (8).

From reviewing the literature, a mixed affective state should be considered when symptoms of mania and depression occur; especially agitation, insomnia, changes in appetite, psychotic symptoms and suicidal ideation (ICD-10: F31.6, DSM-IV: 296.6x). Agitation is a powerful predictor of increased suicide risk.

If a patient experiences such a mental state, it is likely they lie on the bipolar affective disorder spectrum. Hence it is important to take a longitudinal history, screening for hypomanic and manic episodes. Given an increased risk of suicide, a comprehensive suicide risk assessment is necessary. As already discussed, three treatment strategies emerge from the literature which could be used simultaneously. In essence, it is necessary to decrease or discontinue medication that may push the patient's mood in one direction, for example antidepressants, and also stabilise the mood. If a patient is on an antidepressant then a decreasing and subsequent discontinuing it is helpful. To stabilise the mood, if a patient is currently on a mood stabiliser, the dose should be increased. If not, then a mood stabiliser such as divalproate should be started. Because of the necessity of stabilising the mood, an adjunct such as an antipsychotic may be required.

Regular review is necessary to screen for adverse effects and to assess suicide risk.
The following algorithm summarises our recommendations
(Depakote=semisodium valproate=divalproate, Antiψ = Antipsychotic drug).



GP Comment

What have I learned from this paper?

I was interested to learn that agitated depression is part of the bipolar spectrum and associated with a high risk of suicide. Also that it is best treated, not with antidepressants but with mood stabilisers. These facts would encourage me to refer these patients early to the mental health services.

Dr Stephen Cakebread, GP, Bedfordshire.

References

1. Rihmer Z, Gonda X. Prediction and prevention of suicide in bipolar illness. The second dual congress on Psychiatry and the Neurosciences, 1st European Congress of the International Neuropsychiatric Association; 2nd Mediterranean congress of the World Federation of Societies of Biological Psychiatry Athens 2006;Book of Abstracts:p 30.
2. Agius M. The Consequences of the Model of the Bipolar Spectrum for the Choice of Treatment for Bipolar Illness. Psychiatrie 11 2007;Suppl4:8-12.
3. Akiskal HS, Benazzi F, Perugi G, Rihmer Z. Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. J Affect Disord. 2005;85 (3):245-58.
4. Tavormina G, Agius M. A study of the incidence of bipolar spectrum disorders in a private psychiatric practice. PsychiatrDanub. 2007;19 (4):370-4.
5. Akiskal HS, Djenderedjian AM, Rosenthal RH, Khani MK. Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Am J Psychiatry 1977;134 (11):1227-33.
6. Balázs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. J Affect Disord. 2006;91 (2-3):133-8
7. Thuile J, Even C, Guelfi JD. Mixed states in bipolar disorders: a review of current therapeutic strategies. Encephale 2005;31 (5 Pt 1):617-23.
8. Ho J, Singh S, Agius M, Zaman R. Mixed affective states: a study within a community mental health team with treatment recommendations. Psychiatr Danub. 2011 Sep;23 Suppl 1:S25-8. PubMed PMID: 21894097.