Diagnosis and treatment of mixed states
Diagnóstico e tratamento dos estados mistos

Angela Schwartzmann and Beny Lafer

Abstract
Mixed States are described in the literature using based on different definitions resulting in different descriptions of the clinical and demographic characteristics, of these episodes, but although they are always deemed a severe form of Bipolar disorder with worse prognosis and more prevalent than previously described. The aim of this article is to present a review of these different definitions and their impact on the study of mixed states. Pharmacological treatment is also discussed.

Keywords: Mixed states; Bipolar disorder; Mixed mania; Depressive mania; Dysphoric mania

Resumo
Estados mistos (EM) são descritos na literatura usando-se diferentes definições, o que resulta em diferentes descrições das características demográficas e clínicas do quadro, mas sempre como uma forma de transtorno bipolar de pior prognóstico e mais prevalente do que descrito no passado. O objetivo do artigo é apresentar estas diferentes definições e seu impacto no estudo dos estados mistos. O tratamento farmacológico será discutido.

Descritores: Estados mistos; Transtorno bipolar; Mania mista; Mania depressiva; Mania disfórica

Introduction
Mania and depression are seen as clinical syndromes of opposite polarities. It is known, according to the observations described by Kraepelin, that the association of manic or hypomanic symptoms with depressive ones is not infrequent, especially among patients who have BD conditions deemed severe. Besides, their treatment is more difficult due not only to the mixed symptomatology, but also to the instability of their presentation. Most currently studied mixed episodes are mixed manias, also called dysphoric manias, in which depressive symptoms are associated in higher or lesser degree with a manic or hypomanic condition. Besides them, the literature on mixed states (MS) describes mixed depressions, characterized by a predominantly depressive condition associated in a lesser degree with manic symptoms.

Concept
Kraepelin defined MS as a combination of manic and depressive symptoms in three domains: mood, psychomotor activity and ideation. He considered that it occurred in more advanced stages of the disease. He described 6 types of mixed states, based on the several combinations of polarity of these 3 spheres or domains:
1. Excited depression
2. Depression with flight of ideas
3. Depressive-anxious mania
4. Inhibited mania
5. Mania with poverty of thoughts
6. Manic stupor

Campbell describes the ‘constant change and fluidity of emotions present in these episodes’. Himmelhoch et al describe better depressive, manic and psychotic symptoms.

Viena’s research criteria define stable mixed states (simultaneous presence of manic and depressive symptoms) and instable mixed states (rapid oscillation of symptoms), the latter corresponding to the concept of rapid cycling studied by Dunner et al and Maj et al. All of them described a syndrome of rapid alternance of opposite affective states, depression, anxiety, hostility or rapid alternation from inhibition toward behavioral agitation, aggressiveness and always with sleep disturbances.

Goodwin and Jamison define MS as the simultaneous presence of any number of depressive and manic symptoms, highlighting their high prevalence.

The RDC, Research Diagnostic Criteria, used in many researches, defines MS as a period in which manic, hypomanic and depressive symptoms occur simultaneously, or when the subject cycles rapidly to a period of opposite polarity.

The DSM III R requires the simultaneous presence of full criteria for mania and depression (except for the two-week duration) or their alternance within days with prominent depressive symptoms for at least one day.

The ICD-10 defines MS as the combination or rapid alternance of depressive, manic and hypomanic symptoms, with prominent symptoms for at least one week.

The definition of mixed states by the DSM IV is shown in Table 1.
Mixed states are characterized by a period of time (at least one week) in which criteria for both manic and major depressive episodes are met almost every day (criterion A). The subject shows rapid mood alternation (sadness, irritability, euphoria) accompanied by symptoms of a manic and a depressive episode.

The disturbance should suffice to cause pronounced impairment in the social, occupational functioning or to require hospitalization, or it is marked by the presence of psychotic aspects (criterion B).

The disturbance is not due to the direct psychological effects of a substance or to the general medical condition (criterion C).

### Table 1 - DSM IV criteria for mixed state

Mixed states are characterized by a period of time (at least one week) in which criteria for both manic and major depressive episodes are met almost every day (criterion A). The subject shows rapid mood alternation (sadness, irritability, euphoria) accompanied by symptoms of a manic and a depressive episode.

The disturbanc...
females. Tandon et al. obtained different biochemical findings for mixed depression from those described for mixed mania.

**Differential diagnosis**

The differential diagnosis of MS is a very difficult issue in the clinical practice. The main ones are:

1. **Anxious depression**: there is no acceleration of thought or increase of the libido.
2. **Borderline personality**: mood lability is common to both pathologies, but there is no cycling as in BD, as well as no previous history of BD.
3. **Agitated depression**, defined by the RDC as a full depressive episode associated with symptoms of psychomotor agitation such as agitation of inferior members or finger tapping. There is no acceleration of thought, increase of libido or of risk activities.
4. **Fast cycling pictures** may hamper the diagnosis and it must be reminded that they may be present concomitantly to MS. The DSM IV describes rapid cycling as a course specifier, in which at least 4 different episodes occur in a 12-month period. Kräemilinger and Post define ultra-rapid and ultra-fast cycling as agitation of inferior members or finger tapping. There is no acceleration of thought, increase of libido or of risk activities.

The response to traditionally efficient treatments for acute mania have presented worse results for MS both in the short- and in the long-term (Prien et al. , Goldberg et al. and Montgomery et al.). The first step in the treatment of MS is the withdrawal of all mood-increasing substances. The association of more than one mood stabilizer or of one mood stabilizer and one antipsychotic is more efficient than using it in monotherapy.  

1. **Lithium**

MS is a predictor of bad response to lithium, and it fails to treat manic symptoms and improves depressive and cognitive symptoms. Poor response does not seem to be related to the severity of the condition, but to the presence of mixed characteristics.

2. **Anticonvulsivants**

Divalproate and valproic acid: Response to divalproate does not seem to differ in mixed and classical mania, being much higher than placebo, what is not related to severity or gender, but only to the presence of depressive symptoms. Calabrese et al. reported good prophylactic response to valproate.

Carbamazepine: high rates of dysphoria (irritability) in MS were related by Post and Uhde to better response to treatment with carbamazepine, but not regarding depressive symptoms. Dilsaver et al. reports better response to depressive symptoms when associated to manic ones than when isolated.

3. **Other anticonvulsivants**

There are no controlled studies for MS with gabapentin, lamotrigine, topiramate, for patients with diagnosis of MS, only for mania (Pande et al. and Chengappa et al.).

ECT: It is a good treatment for acute episode (Small et al. . Dilsaver et al. comparing bipolar subjects in mania versus depression, versus MS, found good response in the 3 groups, but MS patients had longer hospitalization and needed a higher number of applications than bipolar depressed patients, a discordant finding from Ciapparelli et al. . Antipsychotics: studies were not always performed exclusively with mixed patients, being studies on mania with or without depressive symptoms.

*Typical: they were much used in combination with lithium or alone in acute mania and MS. According to several authors, the treatment with this class of antipsychotics reduces the time of response of manic symptoms. Extrapyramidal side-effects and late dyskinesia restrict their use.

**Atypical:**

Olanzapine: its use in monotherapy is efficient in MS and pure mania, with reduction of time of response of depressive and manic symptoms. Associations with lithium or divalproate seem to be more efficient than the use of one of these stabilizers alone, including in the long-term (49-week follow-up). If associated with 2 stabilizers, whose response was partial, it provides advantages (lithium + valproate and lithium + carbamazepine). Risperidone: Studies include pure and mixed mania, and the results are not specified. Studies with bipolar patients show the efficacy of using risperidone on BD in mania, acting on depressive and manic symptoms. If associated with other stabilizers (lithium, carbamazepine, valproate) it offers advantages to treat manias in general. When associated with lithium, it has an action comparable to the association of lithium with haloperidol.

Quetiapine and Aripiprazol were not specifically studied for MS, although there are good results in the treatment of pure mania.

Clozapine: Suppes et al. report improvement in the symptomatology in one study on 6 patients with MS.

**Conclusion**

Mixed states represent an acute condition of bipolar disorder with more difficulty in diagnosis, more severe course and prognosis and therefore more difficult to be treated. When not identified, the use of antidepressants alone worsens not only the episode, with higher suicide risk, but also the disease's course. The patient's and the family history should be investigated not only for the presence of mood disorders, but also for suicide and comorbid psychiatric disorders. Mixed symptomatology in patients who complain of depression with irritable mood, acceleration of thought, increase of energy and aggressiveness should be always specifically investigated and treated. The correct explanation of the disease and its most severe forms to the patient has been an efficient way of improving the prognosis, and the quality of life of these individuals.

**References**

40. Freeman (24).
58. Ghaemi SN. New treatments for bipolar disorder: the role of atypical

Correspondence
Angela Schwartzmann
Projeto de Assistência e Pesquisa em Transtorno Bipolar (PROMAN) do Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
Rua Ovidio Pires de Campos, 785
05403-010 São Paulo, SP
E-mail: schwangela@yahoo.com.br