Rev Bras Psiquiatr 2004;26(Supl III):7-11

Diagnosis and treatment of mixed states

Diagnóstico e tratamento dos estados mistos

Angela Schwartzmann[a] and Beny Lafer[b]

[a]Institute of Psychiatry of the Clinical Hospital of Medical School of the University of São Paulo - HC-FMUSP. Assistance and Research Project on Bipolar Disorder - PROMAN
[b]Department of Psychiatryc of the Clinical Hospital of Medical School of the University of São Paulo - HC-FMUSP. Assistance and Research Project on Bipolar Disorder of the Clinical Hospital of Medical School of the University of São Paulo (PROMAN)

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 asdeemed 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,[1] 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[1] 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[2] describes the 'constant change and fluidity of emotions present in these episodes'. Himmelhoch et al3 describe better depressive, manic and psychotic symptoms.

Viena's[4] 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[5] and Maj et al.[6] 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[7] define MS as the simultaneous presence of any number of depressive and manic symptoms, highlighting their high prevalence.

The RDC, Research Diagnostic Criteria,[8] 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[9] 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[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[11] is shown in Table 1.

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 alternance (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).

SOURCE: DSM-IV adapted

In the clinical practice it is difficult to find both full syndromes simultaneously, and due to this McElroy et al[12] define mixed or dysphoric mania based on Cincinatti's criteria as seen in Table 2.

Table 2 - Cincinatti's criteria for mixed states[12]

A. Presence of manic syndrome according to the DSM-III-R.
B. Simultaneous presence of at least 3 depressive symptoms or 2 in case they are symptoms common to mania and depression (insomnia, psychomotor agitation). In case there are 2 depressive symptoms not common to mania, a diagnosis of possible MS should be performed.
C. Manic and depressive symptoms should occur concomitantly or alternated within minutes
D. Depressive and manic symptoms should be simultaneously present for at least 24 hours

Perugi et al[13] define MS in a more comprehensive way, emphasizing that the symptoms of opposite polarity may occur simultaneously or alternating.

What can be seen in all these attempts to define mixed symptoms is that its concept becomes more or less comprehensive according to the duration of symptoms, inclusion or not of rapid cycling and the minimal number of depressive symptoms considered.

Mixed depressions have been less studied and are not specifically contemplated by the DSM-IV or the ICD-10. The concept derives from involutive melancholy (agitated) from the 19th century and is coincident with Kraepelin's[1] concept of agitated depression. Koukopoulos et al[14] and Benazzi et al,[15] authors who have been dedicated to the study of these conditions, admit that the simultaneous presence of at least two symptoms of mania in a depressive episode suffices to define agitated or mixed depression.

Clinical or epidemiological characteristics

1. Mixed mania

Mixed mania is generally referred to in the literature as a state of severe mania, more frequently developed by women and adolescents, associated with suicide, irritability, psychotic symptoms, substance abuse, neuropsychiatric abnormalities with chronic course, poor evolution in the short- and long-term, poor response to lithium and better to anticonvulsant stabilizers and ECT and higher family predisposition to depression.[16,24] Some patients show higher frequency of this type of episode than others.

Prevalence: In the literature the prevalence of these episodes ranges from 5 to 70%[24] of manias. McElroy et al[12] found a mean prevalence of 31%. Therefore, it is frequent the association of depressive symptoms with mania during the disease's course.

Gender: Mixed mania is more frequently among women, especially when the criterion includes higher depression rates.[13,17-19]

Family history: The mixed pattern of mania is associated with family history of depression, besides bipolar disorder (BD), suggesting a double inheritance in MS.[19] These data are not consensual in the literature.[13,20-21]

Age of manifestation: Kraepelin[1] noted that MS had late onset, what would represent a worsening of the condition. Dell'Osso et al[20] and Strakowski et al[22] confirm this information. As to the disease's onset, it does not change when there is occurrence of MS or pure mania in the patients' history.[13,19,22] Mc Elroy et al[23] found higher incidence of mixed symptomatology among adolescents.

Symptomatology, course and prognosis: the higher severity of the disease among patients who have MS is proved not only by its symptomatology, but also by the higher presence of comorbidities and worse prognosis. As noted by Kraepelin, more recent studies show a worse prognosis and higher severity in the short- and long-term, considering the longer duration of episodes, although they occur in lower number along the disease.[13,19-20,24-26] They also describe worse recovery from episodes, longer duration of the disease, higher presence of psychotic symptoms, higher number of hospitalizations, worse treatment outcomes, higher comorbidity rates with disorders such as obsessive-compulsive disorder and panic disorder, altered basic mood, substance abuse, use of antidepressants and precedent stressor.[13,17,19,24,31,38] It seems that some bipolar patients show a predominantly mixed pattern: onset of disease with mixed episode predicts a course with predominance of this type of phenomenology.[19-20,24,27-29] Psychotic symptoms and irritability seem to be constantly present in episodes with mixed symptomatology.[7,16,24,29-33] MS are associated with higher rates of impulsiveness and suicidality (suicide ideation, attempts and act).[34-37] Therefore, the disease with this pattern shows higher morbidity and mortality.

The ethiopathogeny of this condition has been debated by several authors, among them.Swann et al.[39,26] When studying the noradrenergic activity, hypothalamic-hipophyseal axis, they concluded that MS is an overlap of a biological condition of mania and depression. These data are not always coincident with previous studies.

2. Mixed depression (MD)

The studies on mixed depressions are scarce: Himmelhoch et al[3] studied agitated psychotic depression, conceptualizing it as bipolar depression, associated with manic or hypomanic symptoms and psychotic symptoms.

Table 3 - Perugi's criteria for mixed states[13]

State of emotional instability and/or perplexity in which the depressive and manic symptoms appear simultaneously or alternating.

A. Manifestation of opposite extremes of at least 2 of the 5 items below:
   1.Mood (anxious/ sad and/or euphoric, irritable)
   2. Course of thought (slowed down and/or accelerated)
   3. Sensoperceptual disturbances (depressive and/or expansive)
   4. Psychomotor activity (slowed down and/or accelerated).
B. At least 2 of the following :
   1. increased affective resonance or mood lability
   2. Low anger/hostility threshold, especially lack of control of impulses
   3. Altered sexual behavior regarding the usual
   4. Remarkable sleep disturbance
   5. Day variation of at least 1 symptom of item (A)
C. Adequate interpersonal relationships and affective responses in the premorbid or inter-phase period.

MD is associated with hyperthymic mood,[17] predominance of bipolar II disorder,[15] atypical symptoms of depression,[15,41] predominance of females[41] and use of antidepressants.[14] Koukopoulos[14] considers that mixed depression is an MS for showing characteristics common to mixed mania, such as treatment response, symptoms instability, great incidence on

females. Tandon et al[40] 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[8] 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[11] describes rapid cycling as a course specifier, in which at least 4 different episodes occur in a 12-month period. Kräemilinger and Post[42] define ultra-rapid and ultra-ultra rapid (ultradian) cycling as BD courses which undergo sudden changes within weeks or a few days, and in the first case with the change occurring in up to 24 hours. The instability of these episodes is the common trait and should be the initial concern of the treatment.

Treatment

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.[43] , Goldberg et al.[44] and Montgomery et al.[45]). The first step in the treatment of MS is the withdrawal of all mood-increasing substances[46]. The association of more than one mood stabilizer or of one mood stabilizer and one antipsychotic is more efficient than using it in monotherapy.[45-48]

1. Lithium

MS is a predictor of bad response to lithium,[43,46-47] and it fails to treat manic symptoms and improves depressive and cognitive symptoms.[27] Poor response does not seem to be related to the severity of the condition, but to the presence of mixed characteristics.[43,45]

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.[45,48] Calabrese et al[49] reported good prophylactic response to valproate.

Carbamazepine: high rates of dysphoria (irritability) in MS were related by Post and Uhde[50] to better response to treatment with carbamazepine, but not regarding depressive symptoms. Dilsaver et al[51] 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 gabapentine, lamotrigine, topiramate, for patients with diagnosis of MS, only for mania (Pande et al[52] and Chengappa et al[46,53-54]).

ECT: It is a good treatment for acute episode (Small et al,[55] Dilsaver et al[47,51]). Devanand et al[56] 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 Ciaparelli et al's.[57]

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.[46,74] Extrapyramidal side-effects and late dyskinesia restrict their use.[58-59]

*Atypical:

Olanzapine: its use in monotherapy is efficient in MS and pure mania, with reduction of time of response of depressive and manic symptoms.[60-61] 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).[60,62] If associated with 2 stabilizers, whose response was partial, it provides advantages (lithium+valproate and lithium+ carbamazepine).[63]

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.[64-65] If associated with other stabilizers (lithium, carbamazepine, valproate) it offers advantages to treat manias in general.[66-68] When associated with lithium, it has an action comparable to the association of lithium with haloperidol.[64]

Quetiapine and Aripiprazol were not specifically studied for MS, although there are good results in the treatment of pure mania.[69-72]

Clozapine: Suppes et al[73] 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.[74]

References

1. Kraepelin E. Manic-depressive insanity and paranoia. Trad. de Robert. M. Barclay. Edinburgh, E & S Livingstone; 1921.

2. Campbell JD. Manic-depressive disease: clinical and psychiatric significance. Philadelphia: JB Lippincott; 1953. apud Goodwin (7).

3. Himmelhoch JM, Coble P, Kupfer J, Ingenito J. Agitated psychotic depression associated with hypomanic episode: a rare syndrome. Am Journal Psychiatry. 1976;133:765-71. apud Koukopoulos (14).

4. Berner P, Gabriel E, Katsching H, Kieffer W, Koehler K, Lenz G, et al. Diagnostic criteria for schizophrenia ad affective psychoses. (World Psychiatry Association). Washington (DC): American Psychiatry Association; 1983.

5. Dunner DL, Patrick V, Fieve RR. Rapid cycling manic depressive patients. Compr Psychiatry. 1977;18:561-6.

6. Maj M, Magliano L, Pirozzi R, Marasco C, Guarnieri M. Validity of rapid cycling as a course specifier for bipolar disorder. Am J Psychiatry. 1994;151:1015-9.

7. Goodwin FK, Jamison, RK. Manic-depressive ilness. New York, Oxford University Press; 1990.

8. Spitzer RL, Endicott J, Robbins E. Research diagnostic criteria. New York: Biometrics Research, Evaluation Section, New York State Psychiatry Institute; 1978.

9. Spitzer RL, Gibbon M, Skodol AE, Williams JBW, First MB. DSM-IIII-R Diagnostic and statistical manual of mental disorders (Revised Edition).

3rd ed. Washington (DC): American Psychiatry Press; 1987.
10. The ICD-10 Classification of Mental and behavioral disorders. Clinical descriptions and diagnostic guidelines. World Health Organization; 1992.
11. Spitzer RL, Gibbon M, Skodol AE, Williams JBW, First MB. DSM-IV Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatry Press; 1994.
12. McElroy SL, Keck PE Jr, Pope HG, Hudson JI, Faedda GL, Swann AC. Clinical and research implications of the diagnosis of mixed mania or mania or hypomania. Am J Psychiatry. 1992;149:1633-44.
13. Perugi G, Akiskal HS, Micheli C, Musettil, Paiano A, Quilici C, et al. Clinical subtypes of bipolar mixed states: validating a broader european definition in 143 cases. J Affect Disord. 1999;43:169-80.
14. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Psych Clin of North Am. 1999;22:547-67.
15. Benazzi F. Depressive mixed states: unipolar and bipolar II. Eur Arch Psych Clin Neurosci. 2000;250:249-53.
16. Ebert D, Loew T, Martus P. Dysphoric or mixed mania. Am J Psychiatry. 1993;150:1907-8.
17. Akiskal HS, Hantouche EG, Bourgeois ML, Azorin JM, Sechter D, Allilaire JF, et al. Gender, temperament, and clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). J Affect Disord. 1998;50:175-86.
18. Himmelhoch JM. Mixed states, manic-depressive illness, and the nature of mood. Psych Clin of North Am. 1979;2:449-59. apud Koukopoulos (14)
19. McElroy SL, Strakowski SM, Keck PE Jr, Tugrul KL, West SA, Lonczak HS. Differences and simmilarities in mixed and pure mania. Compr Psychiatry. 1995;36:187-94.
20. Dell'Osso L, Placidi GF, Nassi R, Freer P, Cassano JB, Akiskal HS. The manic depressive mixed states: Familial, temperamental and psychopathologic Characteristics in 108 female inpatients. Eur Arch Psych Clin Neurosc. 1991;240:234-9.
21. Perugi G, Akiskal HS, Micheli C, Toni C, Madaro D. Clinical characterization of depressive mixed state in bipolar-I patients. J Affect Disord. 2001;67:105-14.
22. Strakowski SM, Tohen M, Stoll AC, Faedda GL, Goodwin DC. Comorbidity in mania at first hospitalization. Am J Psychiatry. 1992;149:544-56.
23. McElroy SL, Strakowski SM, West SA, Keck PE Jr, McConville BJ. Phenomenology of adolescent and adult mania in hospitalized patients with bipolar disorder. Am J Psychiatry. 1997;154:44-9.
24. Freeman M, McElroy SL. Clinical picture and etiologic models of mixed states. Psych Clin of North Am. 1999;22:535-46.
25. Keller MB, Lavori PW, Coryell W, Endicott J, Muellert TI. Bipolar I: a 5-year prospective follow up. J Affect Disord. 1993;181:243-5.
26. Post RM, Rubinow DR, Uhde TW, Roy-Byrne PP, Linnoila M, Rosoff A, et al. Dysphoric mania. Clinical and biological correlates. Arch Gen Psychiatry. 1989;46(4):353-8. apud Freemann (24)
27. Woods SW, Money R, Baker CB. Does the manic /mixed episode distinction in bipolar disorder patients run true overtime? Am J Psychiatry. 2001;158:1324-6.
28. Cassidy F, Carroll BJ. Seasonal variation of mixed and pure episodes of bipolar disorder. J Affect Disord. 2002;69:25-31.
29. Cassidy F, Aheanr E, Murry E, Forest K, Carroll BJ. Diagnosis of depressive symptoms of bipolar episode. Psychol Medicine. 2000;30:403-11.
30. Goldberg J F, Garno JL, Portera L, Leon AC, Kocsis JH. Qualitative differences in manic simptoms during mixed versus pure mania. Compr Psychiatry. 2000;41:237-41.
31. Dilsaver SC. Chen YR, Shoaib AM, Swann AC. Phenomenology of mania: evidence for distinct depressed , dysphoric and euphoric presentations. Am J Psychiatry. 1999;156:426-30.
32. Swann AC, Secunda SK, Katz MM, Croughan J, Bowden CL, Koslow SH, Berman N, et al. Specificity of mixed affective states: clinical comparison of dysphoric mania and agitated depression. J Affect Disord. 1993;28:81-9.
33. Cassidy F, Ahearn E, Murry E, Forest K, Carroll BJ. Signs and symptms of mania in pure and mixed episodes. J Affect Disord. 1998;50:187-201.
34. Swann AC, Janicka PL, Calabrese JR, Bowden CL, Dilsaver SC, Morris DD, et al. Structure of mania: depressive, irritable and psychotic clusters with different retrospectively assessed course patterns of illness in randomized clinical trial participants. J Affect Disord. 2001;67:123-32.
35. Leverich GS, Altshuler LL, Frye MA, Suppes T, Keck PE Jr, McElroy SL, et al. Factors associated with suicide attempts in 648 patients with suicide attempts in Stanley Foundation Bipolar Network. J Clin Psychiatry. 64: 506-15.
36. Oquendo MA, Waternaux C, Bordsky B, Parsons B, Haas EL, Malone KM, et al. Suicidal behavior in bipolar mood disorder: Clinical Characteristics of attempters and non attempters. J Affect Disord. 2000;59:107-17.
37. Strakowsky SM, McElroy SL, Keck PE Jr, West SA. Suicidality among patients with mixed and manic bipolar disorder. Am J Psychiatry. 1996;153:674-6.
38. Dilsaver SC, Swann AC. Mixed mania: apparent induction by tricyclic antidepressant in five consecutively treated patients of bipolar depression. Biol Psychiatry. 1995;37:60-2.
39. Swann AC, Stokes PE, Secunda SK, Maas JW, Bowden CL, Berman N, et al. Depressive manic versus agitated depression: biogenic amine and hypothalamic-pituitary-adrenocortical function. Biol Psychiatry. 1994;35:803-13.
40. Tandon R, Channabasavanna SM, Greden JF. CSF biochemical correlates of mixed affective states. Acta Psych Scand. 1988;78:289-97. apud Swann (41).
41. Benazzi F. Atypical depression with hypomanic symptoms. J Affect Disord. 2001;65:179-83.
42. Krämlinger KG, Post MR. Ultra-rapid and ultradian cycling in bipolar affective illness. Br J Psychiatry. 1996;168:314-23.
43. Prien RF, Himmelhoch JM, Kupffer DJ. Treatment of mixed mania. J Affect Disord. 1988;15:9-15. apud Freeman (24).
44. Montgomery AS, Schatzberg AF, Guelfi JD, Kasper S, Nemeroff C, Swann A, et al. Pharmacotherapy of depression and mixed states in bipolar disorder. J Affect Disord. 2000;59(Suppl1):S39-S56.
45. Goldberg JF, Harrow M, Leon AC. Lithium treatment of bipolar affective disorders under naturalistic follow up conditions. Psychopharmacol Bull. 1996;32:47-54.
46. Sachs GS. Decision tree for the treatment of bipolar disorder. J Clin Psychiatry. 2003;64:35-40.
47. Dilsaver SC, Swann AC, Shoaib AM, Bowers TC, Halle MT. Depressive mania associated with nonresponse to antimanic agents. Am J Psychiatry. 1993;150:1548-51.
48. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, et al. Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry. 1998;54:37-42.
49. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry. 1990;147:431-4.
50. Post RM, Uhde TW, Roy-Byrne PP, Joffe RT. Correlates of antimanic reponse to carbamazepine. Psychiatry Res. 1987;21:71-83. apud Freeman (24)
51. Dilsaver SC, Swann SC, Chen YW, Shoaib A, Joe B, Krajewski KJ, et al. Treatment of bipolar depression with carbamazepine: results of an open study. Biol Psychiatry. 1996;40:935-7.
52. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. Bipolar Disord. 2000;2(3 PT 2):249-55.
53. Chengappa KN, Gherson S, Levine J. The evolving role of topiramate among other mood stabilizers in the management of bipolar disorder. Bipolar Disord. 2001;3:215-32.
54. Chengappa KN, Rathore D, Levine J, Atzert R, Solai L, Parepally H, et al. Topiramate as add-on treatment for patients with bipolar mania. Bipolar Disord. 1999;1:42-53.
55. Small JG, Klapper MH, Kellams JJ, Miller MJ, Milstein V, Sharpley PH, et al. Electroconvulsive treatment compared with lithium in management of manic states. Arch Gen Psychiatry 1988;45:727-32.
56. Devanand DP, Polanco P, Cruz R, Shah S, Paykina N, Singh K, Majors L. The efficacy of ECT in mixed affective states. J ECT. 2000;16:32-7.
57. Ciapparelli A, Dell´Osso L, Tundo A, Pini S, Chiavacci MC, Di Sacco I, et al. Eletroconvulsive therapy in medication nonresponsive patients with mixed mania and bipolar depression. J Clin Psychiatry. 2001;62:552-5.
58. Ghaemi SN. New treatments for bipolar disorder: the role of atypical

neuroleptic agents. J Clin Psychiatry. 2000; 61(Suppl14):33-42.
59. Sachs GS, Thase ME. Bipolar disorder therapeutics: mantenaince treatment. Biol Psychiatry. 2000;48:573-81.
60. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry. 1999;156:702-9.
61. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. Arch Gen Psychiatry. 2000;57:841-9.
62. Baker RW, Tohen M, Fawcett J, Risser RC, Schuh LM, Brown E, et al. Acute dysphoric mania: treatment response to olanzapine versus placebo. J Clin Psychopharmacol. 2003;23:132-7.
63. Tohen M, Chengappa KN, Suppes T, Zarate CA Jr, Calabrese JR, Bowden CL, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry. 2002;59:62-9.
64. Segal J, Berck M, Brook S. Risperidone compared with both lithium and haloperidol in mania: double-blind randomized controlled trial. Clin Neuropharmachol. 1998;21:176-8.
65. Vieta E, Goikolea JM, Corbella B, Benabarre A, Reinares M, Martinez G, et al. Risperidone safety and efficacy in the treatment of bipolar disorder and schizoaffective disorders: results from 6-month multicenter, open study. J Clin Psychiatry. 2001;62:818-25.
66. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind placebo-controlled comparison of efficacy and safety. Am J Psychiatry. 2002;159:1146-54.
67. Yatham LN. Risperidone add to mood stabilizers in acute and continuation treatment of mania. Proceedings of the 7th World Congress of Biological Psychiatry; 2001.
68. Vieta E, Gastro C, Colom F, Martinez A, Otero A, Vallejo J. Treatment of refractory rapid cycling bipolar disorder with risperidone. J Clin Psychopharmacol. 1998;18:172-4.
69 . Reinstein MJ, Bar MA, Ginsberg LL. Quetiapine fumarate and risperidone in outpatients with psychotic disorders. Proceedings of the 152nd Annual Meeting of American Psychiatry Association; 1999.
70. Purdon SE, Malla A, Labelle A, Litt. Neuropsychological chance in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci. 2001;26:137-49.
71. Zarate CA, Rothschild A, Fletcher KE, Madrid A, Zapatel J. Clinical predictors of acute response with quetiapine in psychotic mood disorders. J Clin Psychiatry. 2000;61:185-9.
72. Jody D, Ronald M, Keck P, Saha A, Iwamoto T, Tourkodimitris S, Archibald D. 33rd Collegium International Neuropsychpharmachologic Congresss. Aripiprazole in treatment of mania. Montreal; 2002.
73. Suppes T, McElroy SL, Gilbert J, Dessain EC, Cole JO. Clozapine in the treatment of dysphoric mania. Biol Psychiatry. 1992;32:270-80.
74. Collom F, Vieta F, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psych. 2003 april; 60(4):402-7.

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