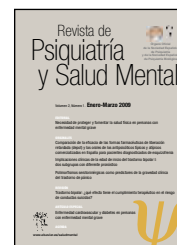


# Revista de Psiquiatría y Salud Mental

www.elsevier.es/ saludmental



## REVIEW ARTICLE

# Bipolar disorder: what effect does treatment adherence have on risk of suicidal behavior?

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Received August 26, 2008, accepted December 1, 2008

### KEYWORDS

Suicide;  
Compliance;  
Comorbidity;  
Lithium

### Abstract

Bipolar disorder is associated with high risk for suicidal behavior. Lack of adherence to treatment is one factor that may be partly responsible for this common complication. We searched MEDLINE with the combination of the key words "compliance" or "adherence" with "suicide" and "bipolar", limited to English language papers published between 1990 and July 2008. We evaluate the existent literature studying the influence of treatment adherence on suicidality among these patients. Our findings show a limited number of studies addressing this issue, mostly conducted with patients enrolled in lithium clinics. Results suggest an association between non-adherence and an increased risk of suicidal behavior among bipolar patients. Whether non-adherence leads to increase risk of suicidality due to specific properties of interventions such as lithium treatment or simply is secondary to mood stabilization is still an open question.

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**PALABRAS CLAVE**

Suicidio;  
Cumplimiento;  
Comorbilidad;  
Litio

**Trastorno bipolar: ¿qué efecto tiene el cumplimiento terapéutico en el riesgo de conductas suicidas?****Resumen**

El trastorno bipolar conlleva un riesgo elevado de conductas suicidas. La falta de cumplimiento terapéutico es uno de los factores que, en parte, puede ser la causa de esta complicación frecuente. Realizamos una búsqueda en MEDLINE con la combinación de las palabras clave "compliance" o "adherence" con "suicide" y "bipolar", y limitada a los artículos publicados en inglés entre 1990 y julio de 2008. Hemos evaluado la literatura médica existente en la que se ha estudiado la influencia del cumplimiento terapéutico en las tendencias suicidas en estos pacientes. Nuestros resultados muestran un número limitado de estudios en los que se ha abordado esta cuestión, la mayoría de ellos llevados a cabo en pacientes registrados en clínicas en que se usa el litio. Los datos obtenidos indican una relación entre la falta de adherencia y el aumento de riesgo de conducta suicida en los pacientes bipolares. Continúa estando sin resolver la cuestión de si la falta de adherencia conduce a un aumento del riesgo de tendencias suicidas a causa de las propiedades específicas de intervenciones como el tratamiento con litio o ello es simplemente secundario a la estabilización del estado de ánimo.

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**Introduction**

Unpredictable and recurrent manic (or hypomanic) and depressive episodes characterize the usual presentation of bipolar affective disorder (BD). BD is a severe lifelong illness with a high mortality rate that is in great measure due to suicidal behaviors.<sup>1,2</sup> In addition, accidents and comorbid entities such as substance abuse or medical disorders increase the mortality rate.<sup>3</sup>

Prevalence of BD has been estimated to be 1-2% across ethnic groups.<sup>4,5</sup> However, recent population studies have shown higher rates of life-prevalence for BD I than previous investigations,<sup>6-10</sup> and it is estimated that its prevalence could approach 5% if bipolar spectrum disorders are included.<sup>11-13</sup>

According to the World Health Organization 2001 report, BD is the fifth cause of disability worldwide for the 15 to 44 year age group, and the ninth when all ages are considered.<sup>14</sup> BD is frequently complicated by family discord, problems with the justice system and workplace problems.<sup>4,15</sup> As a chronic and severe psychiatric disorder, the costs associated with it have been ranked seventh among world-wide causes of non-fatal disease burden. Das Gupta and Guest placed the cost of bipolar disorder in 2002 for the UK at £2 billion; Wyatt and Henter estimated in 1991 that the total 1-year cost for the approximately 2 million cases in the USA was \$45 billion.<sup>16,17</sup> These studies did not include bipolar spectrum disorders.

Considering the growing relevance of bipolar disorder, the aim of this article is to review published studies on the influence of treatment adherence among patients diagnosed with BD and the risk of suicidal behaviors.

**Bipolar disorders and risk of suicide**

BD represents a significant risk factor for both suicide attempts and suicide itself.<sup>18,19</sup> Lifetime risk of suicide for BD has been estimated between 6 and 15%.<sup>3,20</sup> Suicide rates, averaging 0.4% per year in men and women diagnosed with BD are at least 20-fold higher than in the general population.<sup>21</sup> Depressive symptoms and episodes often dominate the course of BD and are the most common cause of morbidity and, indeed, of death by suicide.<sup>22</sup> BD lifetime rates of suicide attempts are higher (29.2-48.4%) than unipolar affective disorder (15.4-15.9%) and other Axis I disorders (2.6-4.2%),<sup>23,24</sup> attaining a 3:1 ratio of completed suicide (compared to 30:1 in the general population).<sup>25</sup>

**Non-adherence in bipolar disorder**

According to the WHO, adherence is defined as the extent to which a person's behavior corresponds to the agreed-upon recommendations of a healthcare provider.<sup>26</sup> Consequently, non-adherent behaviors encompass a wide range of possibilities.

Among bipolar patients, non-adherence, with its attendant clinical and economic impact is particularly key. It has been repeatedly associated with increased suicidal risk,<sup>27-29</sup> relapse rates<sup>29</sup> and active symptoms, as well as reductions in quality of life. Differences in efficacy rates between clinical trials and routine clinical practice have been also attributed to non-adherence.<sup>30</sup>

Medication non-adherence among patients with BD has been estimated at a median rate of 41%.<sup>31</sup> Scott and Pope<sup>32</sup>

also reported that one in three persons with BD fail to take at least 30 percent of their medication. However, reports on treatment adherence show a wide range of results mostly because of differences in its definition and assessment.<sup>33</sup> Currently, the presence of more frequent comorbid substance use disorders and atypical forms of BD has been highlighted as contributors to more frequent nonadherence.<sup>34</sup>

### **Adherence and suicide risk: the effect of therapeutic interventions**

Completed suicide among mood disordered patients is by far more common among those who have been treated as inpatients, as shown by Bostwick and Pankratz.<sup>35</sup> Among pharmacological treatments, lithium carbonate is the best established with evidence of improved long-term outcome. Naturalistic studies also implicate its use in reducing rates of completed and attempted suicide.<sup>28,36-39</sup> Moreover, lithium discontinuation is reported to lead to a rapid increase in suicidal risk.<sup>40</sup> Indeed, a recent meta-analysis of naturalistic studies by Baldessarini et al<sup>39</sup> reported that the overall risk of suicidality was five times lower among lithium-treated subjects compared to those not treated with lithium.

Though evidence is weaker for other mood stabilizers, efficacy of these agents has also been reported, especially in atypical cases.<sup>41</sup> In a naturalistic study by Yerevanian et al,<sup>42</sup> rates of non-lethal suicidal behavior (events/100 patient years) were similar during lithium (2.49), divalproex (4.67) and carbamazepine (3.80) monotherapies. Yerevanian et al<sup>43</sup> have reported as well that suicidal behavior event rates among bipolar patients were greatest during treatment with antidepressant monotherapy (25.92), least during mood stabilizer monotherapy (3.48), and intermediate during mood stabilizer + antidepressant combination treatment (9.75). The impact of antipsychotic treatment on suicidal behaviors was measured in the same sample, showing that event rates were 9.4 times greater during antipsychotic monotherapy and 3.5 fold-higher during mood stabilizer + antipsychotic than during mood stabilizer monotherapy.<sup>44</sup> The authors concluded that treatment of bipolar patients with antipsychotics was associated with an increase in non-lethal suicidal behavior. It is worth noting that the growing number of treatment options in recent years has led to more frequent polypharmacy, adding complexity to medication regimens, which may further compromise compliance with suggested treatments.<sup>45</sup>

The reported influence on treatment adherence of the patient's understanding of their illness and their expectations of treatment with pharmacological medication<sup>46</sup> supports supplementation of pharmacotherapy with psychoeducation and psychotherapy.<sup>47</sup> Psychotherapy for BD is also known to improve the outcome of the illness.<sup>48</sup> Family Focused Therapy (FFT) may be of utility in reducing suicidal risk among BD patients.<sup>49</sup> Miklowitz et al (2003) signaled that patients undergoing FFT had higher mean drug adherence scores during the follow-up than patients undergoing less intensive crisis management.<sup>50</sup> However, we found no study

measuring the impact of this improvement on suicidal risk.

### **Factors associated with discontinuation of treatment**

According to the classification system described by Baldessarini et al (2008),<sup>45</sup> factors associated with treatment non-adherence among bipolar patients could be divided into demographic, clinical, treatment-related and psychological. In this study alcohol-dependence, followed by age (youth) and the degree of affective morbidity were reported to be the most significant factors in non-adherence, but no association was found with sex, diagnostic subtype, and other comorbidities. Johnson et al (2007)<sup>51</sup> noted that bipolar patients who were white and more educated were more adherent. They reported as well that medication that reduced depressive episodes, and was less likely to cause weight gain or have cognitive effects most significantly affected patients' likely adherence to treatment.

Other studies were performed on patients treated with lithium prophylaxis. Nilsson et al (1989)<sup>52</sup> found that lithium side effects were the major clinical reason for discontinuing treatment, while attitudes towards medication showed scarce importance. Schumann et al (1999),<sup>29</sup> in a retrospective 6-year follow-up of affectively ill patients, reported that the main reason for non-adherence was resistance to the idea that the condition requires long-term treatment for prophylaxis. Gonzalez-Pinto et al (2006)<sup>53</sup> recently reported that treatment non-adherence was associated with substance abuse, being unmarried, being male, and having more hypomanic-manic episodes and hospitalizations.

A putative factor on treatment non-adherence among BD patients is altered neurocognition.<sup>54,55</sup> Individuals diagnosed with bipolar disorder in both the acute and euthymic phases of illness display deficits on a range of neuropsychological tasks. These deficits could mediate treatment adherence, through insight,<sup>56</sup> and suicidality. Few studies have examined these issues in BD. Yen et al. (2008) described no differences in neurocognitive function between remitted bipolar patients that had or had not reported suicidal ideations or attempts over the previous year.<sup>55</sup>

### **Comorbidity**

Extensive comorbidity, frequently calculated over 50% often complicates treatment and contributes to the burden of BD. An increased treatment drop-out has been described among bipolar patients with comorbid substance use disorder,<sup>57</sup> anxiety disorders<sup>58</sup> and personality disorders,<sup>59</sup> which together with attention deficit hyperactivity disorder are the most frequent comorbidities among BD patients. Colom et al (2000) proposed comorbidity, especially with personality disorders, as the main predictor of treatment non-adherence among BD patients.<sup>59</sup> Besides, a higher number of suicide attempts among comorbid BD patients has

TABLE 1 Studies on treatment adherence and suicidality of bipolar patients

Authors	Year	Design	Study period	Sample	Measurement	Main adherence criterion	Suicidal behavior risk
Yerevanian et al	2007	Retrospective	3 years (mean follow-up)	405 BD patients	Review of clinical notes, treatments and suicidal events	Continuation of treatment	16-fold higher after discontinuation
Gonzalez-Pinto et al	2006	Prospective	10 years	72 patients with BD I	Long-term lithium maintenance treatment	$\geq 0.50$ mEq/L in 90% of bimonthly serum lithium assays	5.2-fold higher (95%CI, 1.5-18.6) for non-adherents
Isometsa	2005	Retrospective	2 years	31 suicides committed by patients with BD I	Psychological autopsy	Mean of last three lithium serum levels $\geq 0.60$ mmol/L	Only 6% of cases were compliant.
Kessing et al	2005	Observational cohort	5 years	13,186 patients that purchased lithium	Population-based registers	Purchasing lithium twice or more	0.44-time decreased for adherents
Brodersen et al	2000	Prospective cohort	16 years	133 affectively ill patients (61 with BD)	Prophylactic lithium treatment programme	Uninterrupted intake of lithium and attendance to the programme	Four-fold higher risk of completed suicide for non-adherents (p = 0.06)

been reported in different studies.<sup>60,61</sup> Whether comorbidity acts as an intermediate factor leading from treatment non-adherence to suicidality among bipolar patients remains unclear.

## Literature on adherence and suicidal risk among bipolar patients

A MEDLINE search performed with the combination of the key words "compliance" or "adherence" with "suicide" and "bipolar" and limited to English language papers published between 1990 and July 2008 produced 34 papers (14 reviews). Articles were selected for inclusion when risk associated with treatment non-adherence on suicidality of BD patients was estimated quantitatively. Following these terms five articles were selected:

Gonzalez-Pinto et al (2006)<sup>53</sup> conducted a prospective study for up to 10 years in 72 patients with bipolar I disorder investigating the association between suicidal behaviors with adherence to long-term lithium maintenance treatment. Treatment adherence was considered adequate when at least 90% of bimonthly serum lithium assays remained  $\geq 0.50$  mEq/L and verified by semi-structured interviews semi-annually with both a close family member and the patient. Poorly adherent patients showed a 5.2-fold (95% CI, 1.5-18.6) greater risk of suicidal behaviors compared to highly adherent patients (11.4/2.2 acts/100 person-years). In multivariate analysis, treatment non-adherence's effect on risk for future suicidal behavior was second only to prior suicide attempt.

A study by Isometsa (2005)<sup>62</sup> reported on 31 bipolar I disorder suicides in a nationwide psychological autopsy study (N = 1397) in Finland from 1987 to 1988. Most subjects had not been prescribed adequate treatment nor were they adherent despite previous contact with psychiatric care. A mean serum lithium level  $>0.60$  mmol/l over the last 3 measurements obtained was the major criterion for adherence. Only five cases out of 31 (16%) were found to be adherent by blood test, but according to psychological autopsy, only two subjects (6%) both received adequate lithium treatment and were compliant. Of those with depression, 11% had received adequate antidepressant treatment.

An observational cohort study was conducted by Kessing et al (2005)<sup>28</sup> examining all prescribed lithium and recorded suicides in Denmark during a five-year period. A total of 13186 persons aged 18 years or older purchased lithium at least once in the study period. Continued lithium treatment was defined as purchasing lithium twice or more and showed a 0.44-time decreased rate of suicide risk in both sexes.

Yerevanian et al (2007)<sup>42-44</sup> recently completed a retrospective study of 405 bipolar disorder patients with a mean follow-up of three years examining the anti-suicidal benefit of mood-stabilizers. They reported a sixteen fold greater suicidal behavior event rate (events/100 patient years) after discontinuation compared with during mood stabilizer monotherapy (55.89 vs. 3.48).

An study to estimate mortality rates from a cohort of 133 affectively ill patients (61 with BD), that commenced

treatment with lithium, over an observation period of 16 years was performed by Brodersen et al.<sup>2</sup> The mortality rates by any cause for compliant and non-compliant patients with two years of lithium treatment were compared between them and with the mortality rates in the general Danish population. Mortality rates for bipolar patients were twice that of the background population, due mainly to the number of suicides. The standardized mortality ratio for suicide was almost four-fold higher among non-compliant (SMR 30.7) than compliant patients (SMR 8.1). However, the difference was not statistically significant ( $p = 0.06$ ). It should be noted that only one of the suicides had BD.

## Comment

Suicidal behaviors are far more common ( $>20$ -fold) in BD patients than among the general population. Among other illness outcomes, suicide risk has been shown to increase in the setting of treatment non-adherence, a situation that is particularly frequent among bipolar patients.

Few studies have examined specifically the impact of treatment non-adherence on suicidal risk among bipolar patients. Further, most studies have been performed on bipolar samples in lithium maintenance treatment.<sup>2,28,42,53,62</sup> However, findings consistently show that treatment adherence reduces suicidal behavior, though, due to the heterogeneous methodology, comparisons cannot be easily made. Suicidal risk ranges from 4-fold to 16-fold higher among non-adherent individuals,<sup>2,42,53</sup> supporting previous reports of improved outcomes and lowered suicide rates<sup>33,63</sup> with treatment adherence. Clearly, development of strategies to enhance treatment adherence are urgently needed.

## References

1. Sachs GS. Unmet clinical needs in bipolar disorder. *J Clin Psychopharmacol*. 2003;23 3 Suppl 1:S2-8.
2. Brodersen A, Licht RW, Vestergaard P, Olesen AV, Mortensen PB. Sixteen-year mortality in patients with affective disorder commenced on lithium. *Br J Psychiatry*. 2000;176:429-33.
3. Sharma R, Markar HR. Mortality in affective disorder. *J Affect Disord*. 1994;31:91-6.
4. Sajatovic M. Bipolar disorder: disease burden. *Am J Manag Care*. 2005;11 Suppl 3:80-3.
5. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA*. 1996;276:293-9.
6. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:627.
7. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord*. 1998;50:143-51.
8. Ten Have M, Vollebbergh W, Bijl R, Nolen WA. Bipolar disorder in the general population in the Netherlands (prevalence, consequences and care utilisation): results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *J Affect Disord*. 2002;68:203-13.
9. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, et al. Prevalence, correlates, and comorbidity of bipolar I

- disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2005;66:1205-15.
10. Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Soc Psychiatry Psychiatr Epidemiol*. 1998;33:581-6.
  11. Dunner DL. Clinical consequences of under-recognized bipolar spectrum disorder. *Bipolar Disorders*. 2003;5:456-63.
  12. Hirschfeld RM. Bipolar spectrum disorder: improving its recognition and diagnosis. *J Clin Psychiatry*. 2001;62:5-9.
  13. Carta MG, Angst J. Epidemiological and clinical aspects of bipolar disorders: controversies or a common need to redefine the aims and methodological aspects of surveys. *Clin Pract Epidemiol Ment Health*. 2007;1:1-4.
  14. World Health Organization. The World Health Report 2001; Mental Health: New Understanding, New Hope. Geneva: World Health Organization; 2001.
  15. Hirschfeld RM, Vornik LA. Bipolar disorder — costs and comorbidity. *Am J Manag Care*. 2005;11 Suppl 3:85-90.
  16. Fini S, de Queiroz V, Pagnin D, Pezawas L, Angst J, Cassano GB, et al. Prevalence and burden of bipolar disorders in European countries. *Eur Neuropsychopharmacol*. 2005;15:425-34.
  17. Chisholm D, van Ommeren M, Ayuso-Mateos JL, Saxena S. Cost-effectiveness of clinical interventions for reducing the global burden of bipolar disorder. *Br J Psychiatry*. 2005;187:559-67.
  18. Angst J, Gamma A, Sellaro R, Lavori PW, Zhang H. Recurrence of bipolar disorders and major depression. A life-long perspective. *Eur Arch Psychiatry Clin Neurosci*. 2003;253:236-40.
  19. Courtet P, Jollant F, Castelnau D, Astruc B, Buresi C, Malafosse A. Implication of genes of the serotonergic system on vulnerability to suicidal behavior. *J Psychiatry Neurosci*. 2004;29:10.
  20. Qin P, Agerbo E, Mortensen PB. Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: a national register-based study of all suicides in Denmark, 1981-1997. *Am J Psychiatry*. 2003;160:765-72.
  21. Tondo L, Isacson G, Baldessarini R. Suicidal behaviour in bipolar disorder: risk and prevention. *CNS Drugs*. 2003;17:491-511.
  22. Emilien G, Septien L, Brisard C, Corruble E, Bourin M. Bipolar disorder: how far are we from a rigorous definition and effective management? *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:975-96.
  23. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biol Psychiatry*. 1996;39:896-9.
  24. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med*. 1997;27:1079-89.
  25. Baldessarini RJ, Pompili M, Tondo L. Suicide in bipolar disorder: Risks and management. *CNS Spectr*. 2006;11:465-71.
  26. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
  27. Tondo L, Jamison KR, Baldessarini RJ. Effect of lithium maintenance on suicidal behavior in major mood disorders. *Ann NY Acad Sci*. 1997;836:339-51.
  28. Kessing LV, Søndergård L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. *Arch Gen Psychiatry*. 2005;62:860-6.
  29. Schumann C, Lenz G, Berghöfer A, Müller-Oerlinghausen B. Non-adherence with long-term prophylaxis: a 6-year naturalistic follow-up study of affectively ill patients. *Psychiatry Res*. 1999;89:247-57.
  30. Guscott R, Taylor L. Lithium prophylaxis in recurrent affective illness. Efficacy, effectiveness and efficiency. *Br J Psychiatry*. 1994;164:741-6.
  31. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand*. 2002;105:164-72.
  32. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. *J Clin Psychiatry*. 2002;63:384-90.
  33. Colom F, Vieta E, Tacchi MJ, Sánchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. *Bipolar Disord*. 2005;7 Suppl 5:24-31.
  34. Schou M. The combat of non-compliance during prophylactic lithium treatment. *Acta Psychiatr Scand*. 1997;95:361-3.
  35. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. *Am J Psychiatry*. 2000;157:1925-32.
  36. Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. Does lithium reduce the mortality of recurrent mood disorders? *J Affect Disord*. 1991;23:1-7.
  37. Greil W, Kleindienst N. Concepts in the treatment of bipolar disorder. *Acta Psychiatr Scand Suppl*. 2003;418:41-6.
  38. Müller-Oerlinghausen B. Arguments for the specificity of the antisuicidal effect of lithium. *Eur Arch Psychiatry Clin Neurosci*. 2001;251 Suppl 2:II72-5.
  39. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disorders*. 2006;8:625-39.
  40. Müller-Oerlinghausen B, Muser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. *J Affect Disord*. 1992;25:261-9.
  41. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology*. 2000;42 Suppl 1:2-10.
  42. Yerevanian BI, Koek RJ, Mintz J. Bipolar pharmacotherapy and suicidal behavior. Part I: Lithium, divalproex and carbamazepine. *J Affect Disord*. 2007;103:5-11.
  43. Yerevanian BI, Koek RJ, Mintz J, Akiskal HS. Bipolar pharmacotherapy and suicidal behaviour Part 2. The impact of antidepressants. *J Affect Disord*. 2007;103:13-21.
  44. Yerevanian BI, Koek RJ, Mintz J. Bipolar pharmacotherapy and suicidal behavior Part 3: impact of antipsychotics. *J Affect Disord*. 2007;103:23-8.
  45. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. *Hum Psychopharmacol*. 2008;23:95-105.
  46. Kleindienst N, Greil W. Are illness concepts a powerful predictor of adherence to prophylactic treatment in bipolar disorder? *J Clin Psychiatry*. 2004;65:966-74.
  47. Vieta E, Rosa AR. Evolving trends in the long-term treatment of bipolar disorder. *World J Biol Psychiatry*. 2007;8:4-11.
  48. Swartz HA, Frank E. Psychotherapy for bipolar depression: a phase-specific treatment strategy? *Bipolar Disord*. 2001;3:11-22.
  49. Miklowitz DJ. Psychotherapy in combination with drug treatment for bipolar disorder. *J Clin Psychopharmacol*. 1996;16 Suppl 1:S56-66.
  50. Miklowitz DJ, George EL, Richards JA, Smoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Arch Gen Psychiatry*. 2003;60:904-12.
  51. Johnson FR, Ozdemir S, Manjunath R, Hauber AB, Burch SP, Thompson TR. Factors that affect adherence to bipolar disorder treatments: a stated-preference approach. *Med Care*. 2007;45:545-52.
  52. Nilsson A, Axelsson R. Factors associated with discontinuation of long-term lithium treatment. *Acta Psychiatr Scand*. 1989;80:221-30.
  53. Gonzalez-Pinto A, Mosquera F, Alonso M, López P, Ramírez F, Vieta E, Baldessarini RJ. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord*. 2006;8:618-24.

54. Cavanagh JT, Van Beck M, Muir W, Blackwood DH. Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. *Br J Psychiatry*. 2002;180:320-6.
55. Yen CF, Cheng CP, Ko CH, Yen JY, Huang CF, Chen CS. Suicidality and its association with insight and neurocognition in Taiwanese patients with bipolar I disorder in remission. *J Nerv Ment Dis*. 2008;196:462-7.
56. Amador XF, Friedman JH, Kasapis C, Yale SA, Flaum M, Gorman JM. Suicidal behavior in schizophrenia and its relationship to awareness of illness. *Am J Psychiatry*. 1996;153:1185-8.
57. Mazza M, Mandelli L, Di Nicola M, Harnic D, Catalano V, Tedeschi D et al. Clinical features, response to treatment and functional outcome of bipolar disorder patients with and without co-occurring substance use disorder: 1-year follow-up. *J Affect Disord* 2008 Oct 7 (Epub ahead of print).
58. Kilbane EJ, Gokbayrak NS, Galynker I, Cohen L, Tross S. A review of panic and suicide in bipolar disorder: Does comorbidity increase risk? *J Affect Disord* 2008 Nov 8 (Epub ahead of print).
59. Colom F, Vieta E, Martínez-Arán A. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *J Clin Psychiatry*. 2000;61:549-55.
60. Vieta E, Colom F, Corbella B, Martínez-Arán A, Reinares M, Benabarre A, et al. Clinical correlates of psychiatric comorbidity in bipolar I patients. *Bipolar Disorders*. 2001;3:253-8.
61. Leverich GS, Altshuler LL, Frye MA, Suppes T, Keck PE Jr, McElroy SL, et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry*. 2003;64:506-15.
62. Isometsä E. Suicide in bipolar I disorder in Finland: psychological autopsy findings from the National Suicide Prevention Project in Finland. *Arch Suicide Res*. 2005;9:251-60.
63. Sajatovic M, Biswas K, Kilbourne AK, Fenn H, Williford W, Bauer MS. Factors associated with prospective longterm treatment adherence among individuals with bipolar disorder. *Psychiatr Serv*. 2008;59:753-9.