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Medication non-adherence in bipolar disorder: Review of rates, demographic and clinical predictors

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Abstract

AIM

To conduct a systematic search for all studies examining rates and demographic and illness-related determinants

of medication non-adherence in bipolar disorder (BD).

METHODS

A comprehensive literature search was undertaken of six English-language databases to identify published articles on medication non-adherence in BD from inception till December 2016. Any article, either a review or an original-research article was examined for its relevance to the subject. All such articles were manually searched to locate any further articles containing relevant information. Studies were included only if they had adequately described the patient sample, assessment methods and statistical procedures, presented their results systematically and their conclusions were congruent with the results.

RESULTS

The initial search yielded 249 articles on the subject; of these 198 articles were included. Of the 162 original-research studies, 132 had provided information on rates of medication non-adherence in BD. There was a wide variation in rates ranging from universal adherence (100%) to almost universal non-adherence (96%); this discrepancy was more due to methodological differences than true variations in rates. Notwithstanding the significant discrepancies in methodology, based on these 132 studies mean rates of 41.5%-43% and median rates of 40%-41% were obtained for medication non-adherence in BD. Rates of adherence with mood stabilizers were significantly lower than those for antipsychotics, or for medications of all classes. None of the demographic attributes were unequivocally linked to medication non-adherence in BD. Similarly, medication-related variables such as type of medications, doses, treatment regimens and side effects did not demonstrate consistent associations with non-adherence. Among clinical characteristics the presence of comorbid substance use disorder and absence of insight were the only two factors clearly linked to non-adherence in BD.

CONCLUSION

Medication non-adherence is prevalent in about a third

to half of patients with BD. Demographic, illness and treatment related factors do not predict non-adherence with certainty.

Key words: Medications; Demographics; Rates; Non-adherence; Illness characteristics; Treatment variables; Bipolar disorder

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Core tip: Based on existing reviews non-adherence is estimated to be present in 25%-42% of patients with bipolar disorder (BD). The present, more comprehensive review comprising of 198 studies found mean rates of 41.5%-43% and median rates of 40%-41% for medication non-adherence in BD. Neither demographic characteristics nor medication-related variables were unequivocally linked to medication non-adherence in BD, while comorbid substance use disorder and absence of insight were the only two clinical factors consistently associated with non-adherence in BD. The failure of clinical and demographic factors to predict non-adherence emphasizes the importance of other patient orientated factors in determining non-adherence in BD.

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INTRODUCTION

Bipolar disorder (BD) is prototypical of all chronic medical conditions with enduring symptoms, residual disability and the need for long-term care^[1,2]. Like other such conditions, non-adherence with treatment is very common among patients with BD and associated with a range of adverse consequences such as poor clinical outcomes, functional impairment, impaired quality of life, increased health-service utilization and higher costs of care^[2-4].

Several reviews on the subject have estimated non-adherence rates in BD to range from around 8% to 68% with mean rates varying from 25% to 40% across these reviews^[5-8]. Despite this wide variation in rates the median rate of non-adherence, which is probably a more true measure of non-adherence, has been fairly stable at 40% to 42% in different reviews. However, it is somewhat surprising that despite there being over 100 studies on treatment non-adherence in BD, most of these reviews have not included more than a handful of studies. Moreover, the majority of reviews are somewhat dated and have not systematically and comprehensively searched the existing literature to identify all possible studies relating to non-adherence in BD. Those that have systematically reviewed

the existing literature (e.g., Busby and Sajatovic^[3]) appeared to have used very stringent selection criteria limiting the number of studies they have included.

The correlates of non-adherence in BD have been traditionally categorized into patient-related, illness-related, treatment-related and physician-related factors^[9-12]. The majority of studies have, however, examined demographic correlates like age, gender, marital status, or clinical features such as age of onset, longitudinal course, symptom-severity, insight and comorbidity, or medication-related variables such as the class of medications, number and doses of medications and side effects associated with treatment^[3,13,14]. However, results of these studies have been largely inconsistent, leading to considerable uncertainty regarding which of these factors truly influence non-adherence in BD^[8,13]. Consequently, there is little consensus among reviews regarding the clinical, demographic and treatment-related determinants of medication non-adherence in BD. Moreover, similar to the reviews on the rates of non-adherence in BD, reviews examining correlates of non-adherence are based on a limited number of studies.

Given these drawbacks of existing reviews on rates and correlates of medication non-adherence in BD, the present review aimed to conduct a more comprehensive and systematic search for all possible studies of BD, which have investigated these aspects. The principal objective was to estimate rates of medication non-adherence in BD and examine its demographic, illness and medication related correlates based on a much wider selection and a larger number of studies than those that have been included as a part of earlier reviews.

MATERIALS AND METHODS

A comprehensive literature search was undertaken using the following six English-language databases: MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane and Google to identify published articles on medication non-adherence in BD from inception till December 2016. Search terms included BD, bipolar depression or mania used in conjunction with other terms including adherence, compliance, concordance, non-adherence, non-compliance, determinants, predictors, treatment and medication. Any article, either a review or an original research article (based on clinical trials or observational studies) was examined for its relevance to the subject. All such articles were manually searched to locate any further articles, which were judged to be containing information pertaining to the topic. In an effort to identify and include as many studies as possible the initial criteria for selection were broad and inclusive. Any article that had provided information on rates and/or demographic, clinical or treatment correlates of medication non-adherence in BD was included. Articles dealing with other forms of adherence, e.g., appointment adherence or attendance for psychosocial interventions were considered only if they had provided

Table 1 Rates of medication non-adherence in bipolar disorder: Reviews

Ref.	Review based on	Non-adherence rates
Van Putten ^[20] , 1975	7 studies	20%-30% (only lithium)
Jamison and Akiskal ^[21] , 1983	10 studies	33%-50% (only lithium)
Cochran ^[5] , 1986	13 studies from 1966-1986	9%-57% (only lithium)
Goodwin and Jamison ^[22] , 1990	50 studies	18%-53% (only lithium)
Lingam and Scott ^[6] , 2002	3 studies and 1 review	20%-66%, median 41%
Perlick <i>et al</i> ^[7] , 2004	25 papers from 1979-2004	23%-68%, median 42%
Colom <i>et al</i> ^[4] , 2005	6 studies	20%-64%, mean 25%
Gaudio <i>et al</i> ^[18] , 2008	3 reviews	20%-60%, mean 40%
Basco and Smith ^[8] , 2009	9 studies	8%-64%
Busby and Sajatovic ^[3] , 2010	6 studies	20%-60%
Foster <i>et al</i> ^[23] , 2011	7 studies	21%-50%
Leclerc <i>et al</i> ^[12] , 2013	27 studies (rates derived from 6 studies)	12%-64%
García <i>et al</i> ^[16] , 2016	9 studies	23%-60% (only antipsychotics)

Other reviews have also estimated non-adherence rates to be in the range of 20%-68% with a median rate of 41%-42% in BD including Schou^[24] (1988), Guscott and Taylor^[25] (1994), Scott^[26] (1995), Schou^[19] (1997), Berk *et al*^[17] (2004), Sajatovic *et al*^[27] (2004), Byrne *et al*^[28] (2006), Depp and Lebowitz^[29] (2007), Depp *et al*^[14] (2008), Pompili *et al*^[10] (2009), Crowe *et al*^[15] (2011) and Rakofsky *et al*^[11] (2011). BD: Bipolar disorder.

information on medication adherence. Both quantitative and qualitative studies were included. Final selection, however, also depended on the quality of studies, which was assessed partly based on criteria used in previous reviews^[12,15]. Studies were included only if they had adequately described the source and nature of the patient sample, the methods of ascertaining relevant variables and the statistical procedures followed. Additionally, for any study to be incorporated its results should have been presented systematically and the conclusions should have been congruent with the results of the study.

Statistical analysis

Statistical analyses consisted mainly of estimation of mean and median rates. Student's *t* test was used to compare the non-adherence rates among different classes of medications. This was approved by the bio-statistics department of the institution.

RESULTS

The initial search yielded 249 articles on the subject; 43 of these were reviews and 206 were original research articles. Of these 51 articles (7 reviews and 44 original research articles) were excluded. Though these 51 articles did deal with some aspect of treatment adherence in BD the principal reason for excluding them

was the lack of information either on rates of medication non-adherence or on demographic, illness or treatment related correlates of non-adherence in BD. Thus, the final list included 198 articles; 36 of these were reviews and 162 were original research articles.

Rates of medication non-adherence in BD

Reviews: Table 1 lists the reviews on rates of non-adherence in BD. The most commonly quoted reviews are the ones by Lingam and Scott^[6] and Perlick *et al*^[7], both of which have found rates ranging from about 20% to 68% with median rates of about 41% to 42% for non-adherence in BD. Other reviews included in the table also indicate that non-adherence rates vary from 8%-64% with mean rates of 25% to 40% and median rates of 40% to 41% for all classes of medications. Reviews on lithium estimate non-adherence rates to lie between 9% to 57%, while one review found the rates to vary from 23%-60% among patients on antipsychotics^[16]. The wide variation in rates (from 8% to 68%) was most likely to be due to differences in methodology adopted by individual studies^[4]. Moreover, the number of studies, from which these rates are derived was quite small in most reviews. Only Pompili *et al*^[10] have included 104 articles on mood disorders from 1975 to 2009, but the number of studies from which the non-adherence rate for BD was derived was not clear. Despite these disparities and limitations it was evident that about a quarter to half of the patients with BD were fully or partially non-adherent^[15,17]. This rate was similar to other chronic medical disorders including psychiatric and physical disorders^[1,4,18]. There appeared to be no substantial differences between rates of non-adherence for mood stabilizers (principally lithium carbonate) and those for antipsychotics^[4]. Similarly, no differences in rates between older or newer medications were noted. Indeed, studies conducted decades apart have revealed that rates of non-adherence have remained the same over the years despite the availability of many new types of medications^[4,6,10,13,19].

Studies: Tables 2-4 list the 132 studies of this review providing an estimate of medication non-adherence in BD. Studies spanned exactly four decades with the first study conducted by Bech *et al*^[30] among patients on lithium in 1976. The number of studies with patients on all classes of medications (*n* = 69) was the highest followed by studies of patients on mood stabilizers (*n* = 46). There were 15 studies of patients on antipsychotics and only two of patients on antidepressants. The majority of the studies were conducted in Western settings with barely 20 studies from non-Western countries. Not surprisingly, there was a wide variation in rates from universal adherence (100%) to almost universal non-adherence (96%). This was obviously more as a result of methodological differences across studies rather than a true variation in rates. Studies differed in the number of patients included, the duration during which adherence was assessed and the

Table 2 Rates of medication non-adherence in bipolar disorder: Studies of all classes of medications

Ref.	Study	Non-adherence rates
Keck <i>et al</i> ^[47] , 1996a	n = 101; duration-past month; clinical interview and serum levels	64% fully or partially non-adherent
Keck <i>et al</i> ^[48] , 1998	n = 134; duration - 12 mo; clinical interview	53% fully or partially non-adherent
Strakowski <i>et al</i> ^[49] , 1998	n = 109 (83 with BD); duration - 12 mo; clinical interviews	59% fully or partially non-adherent
Weiss <i>et al</i> ^[50] , 1998	n = 44 with BD and SUD; cross-sectional study; clinical interviews	79% fully or partially non-adherent (35% took medications less than 67% of the time)
Colom <i>et al</i> ^[51] , 2000	n = 200; duration 2 yr; clinical interviews with patients and relatives and serum levels for mood stabilizers	40% fully or partially non-adherent
Svarstad <i>et al</i> ^[52] , 2001	n = 67; duration 12 mo; retrospective claims data	33% irregular use
Calabrese <i>et al</i> ^[53] , 2000	n = 324 with RCBD; duration - 6 mo; clinical interview	34%
Greenhouse <i>et al</i> ^[54] , 2000	n = 32; duration - 1 wk; self-report	25%
Lam <i>et al</i> ^[55] , 2003	n = 52; duration - 6 mo; serum levels and self-reports	Serum levels - 7%-22%; self-report - 12%-33%
Calabrese <i>et al</i> ^[56] , 2005	n = 254 with RCBD; duration - 30 mo; clinical interview	20%-28%
Coletti <i>et al</i> ^[57] , 2005	n = 38 adolescents; duration - 1 mo; parent reports	66% fully or partially non-adherent
Fleck <i>et al</i> ^[58] , 2005	n = 50; cross-sectional study; visual analogue scale	52% fully or partially non-adherent
Roy <i>et al</i> ^[33] , 2005	n = 100 (42 with BD); cross-sectional study; clinical interview	91%
Sajatovic <i>et al</i> ^[46] , 2005	n = 52; duration - 3 mo; self-reports and DAI-10	12%
Sajatovic <i>et al</i> ^[59] , 2006a	n = 323; cross-sectional study; clinical interview	36% partially or fully non-adherent
Clatworthy <i>et al</i> ^[36] , 2007	n = 16; cross-sectional study; self-report-qualitative data	81%
DelBello <i>et al</i> ^[60] , 2007	n = 71 adolescents; duration 12 mo; clinical interviews	65% fully or partially non-adherent
Johnson <i>et al</i> ^[61] , 2007	n = 469; cross-sectional study; web-based survey; self-report	30%
Montoya <i>et al</i> ^[62] , 2007	n = 312; cross-sectional study; clinical interviews	40% fully or partially non-adherent
Sajatovic <i>et al</i> ^[63] , 2007c	n = 205 with RCBD; duration - 6 mo; clinical interview	20%
Shabani and Eftekhar ^[64] , 2007	n = 22; duration - 17 mo; clinical interview	38%
Strakowski <i>et al</i> ^[65] , 2007	n = 96 (United States) and 46 (Taiwan); duration - 1 yr (Taiwan) to 8 yr (United States); clinical interviews	21% (Taiwan) - 41% (United States) followed up without full treatment adherence
Baldessarini <i>et al</i> ^[66] , 2008a	n = 429; duration -last 10 d; self-report	34% (psychiatrists rated 6%-18% as non-adherent)
Copeland <i>et al</i> ^[67] , 2008	n = 435; duration - past 4 d; self-report of missed dose and self-report-MMAS	27% on missed dose and 46% on MMAS
Sajatovic <i>et al</i> ^[40] , 2008	n = 302; duration - 3 yr; clinical interview	12%
Zeber <i>et al</i> ^[68] , 2008	n = 435; cross-sectional study; self-report and MMAS	Overall 30%; 23% (self-report) to 46% (MMAS)
Taj <i>et al</i> ^[69] , 2008	n = 23; cross-sectional study; clinical interviews	26%
Azorin <i>et al</i> ^[70] , 2009	n = 766; duration 2 yr; clinical interview	At baseline - 44% (pure mania) - 50% (mixed mania); at 2 yr - 8% (pure mania) - 16% (mixed mania)
Clatworthy <i>et al</i> ^[71] , 2009	n = 223; cross-sectional study; self-report - MARS	30%
Martinez-Aran <i>et al</i> ^[74] , 2009	n = 103; cross-sectional study; clinical interviews with patients and relatives and serum levels for mood stabilizers	41%
Mazza <i>et al</i> ^[75] , 2009	n = 131 (94 with BD); duration - 12 mo; serum levels and relatives' reports	22%
Sajatovic <i>et al</i> ^[72] , 2009a	n = 140; cross-sectional study; self-report-TRQ	19%
Sajatovic <i>et al</i> ^[39] , 2009b	n = 164; duration - 12 mo; self-report	19%
Sharifi <i>et al</i> ^[73] , 2009	n = 76; duration - 8 wk; clinical interview	29%
Bates <i>et al</i> ^[76] , 2010	n = 1052; cross-sectional study; web-based survey; self-report -MMAS	49.50%
Devulapalli <i>et al</i> ^[77] , 2010	n = 140; duration - past month; self-report	19%
González-Pinto <i>et al</i> ^[78] , 2010	n = 1831; duration - 24 mo; clinical interview	23%
Hou <i>et al</i> ^[79] , 2010	n = 35; cross-sectional study; self-report -MMAS	54%
Jónsdóttir <i>et al</i> ^[80] , 2010	n = 280 (114 with BD); duration- past week; self-report, MARS-5, serum levels	Serum levels - 34%; self-report - 16%
Gutiérrez-Rojas <i>et al</i> ^[81] , 2010	n = 108; cross-sectional study; clinical interviews with patients and relatives and serum levels for mood stabilizers	17%
Perlis <i>et al</i> ^[82] , 2010	n = 3640; duration - 12 mo; self-reports and clinical interviews	54% fully or partially non-adherent (24% non-adherent on 20% or more study visits)
Cely <i>et al</i> ^[83] , 2011	n = 124; cross-sectional study; self-report-MMAS	30%
Cruz <i>et al</i> ^[85] , 2011	n = 17 elderly subjects; cross-sectional study; self-report-MMAS	88%
Hong <i>et al</i> ^[84] , 2011	n = 1341; duration - 21 mo; clinical interview	24%
Savaş <i>et al</i> ^[85] , 2011	n = 147; duration - 12 mo; self-report	27%
Sajatovic <i>et al</i> ^[86] , 2011b	n = 140; duration - 1 mo; TRQ	18%
Mahmood <i>et al</i> ^[87] , 2011	n = 40; duration - 1 mo; clinical interview	62%
Barraco <i>et al</i> ^[88] , 2012	n = 650; duration - 12 mo; self-report-SMAQ and DAI-10	60% at baseline; 31% at 9 mo; 33% at 12 mo
Eker and Harkin ^[89] , 2012	n = 71; duration - 6 wk; ANT, self-report-MARS, TOS	60%-61% at baseline; 13%-76% at 6wk
Murru <i>et al</i> ^[90] , 2012	n = 76 schizoaffective disorder-bipolar type; duration - 10 yr; partly retrospective based on clinical interviews with patients and families and serum levels	41%
Miasso <i>et al</i> ^[91] , 2012	n = 101; cross-sectional study; self-report-MMAS	63%
Sajatovic <i>et al</i> ^[92] , 2012	n = 43; duration - 6 mo; self-report-TRQ, MMAS; Pill counts	TRQ - 48%-51% at baseline; 21%-25% at 6 mo - Pill counts - 58% at baseline

Vieta <i>et al</i> ^[93] , 2012	<i>n</i> = 2448 psychiatrists; duration-3 mo; questionnaire survey	57% patients rated fully or partially non-adherent
Sharma <i>et al</i> ^[94] , 2012	<i>n</i> = 127; cross-sectional study; self-report	40%
Belzeaux <i>et al</i> ^[95] , 2013	<i>n</i> = 382; cross-sectional study; self-report - MARS and clinical interviews	25%
de Souza <i>et al</i> ^[96] , 2013	<i>n</i> = 36 cross-sectional study; self-report - MMAS	78%
Gibson <i>et al</i> ^[97] , 2013	<i>n</i> = 24; cross-sectional study; self-report	50%-77% fully or partially non adherent
Hibdye <i>et al</i> ^[98] , 2013	<i>n</i> = 410; cross-sectional study; self-report - MMAS	51%
Jónsdóttir <i>et al</i> ^[99] , 2013	<i>n</i> = 255 (109 with BD); duration - past week; self-report, serum levels	42% fully or partially non-adherent
Murru <i>et al</i> ^[100] , 2013	schizoaffective disorder-bipolar type (<i>n</i> = 75) and BD (<i>n</i> = 151); duration - 10 yr; partly retrospective based on clinical interviews with patients and families and serum levels	BD - 33%; schizoaffective disorder-bipolar type - 44%
Arvilommi <i>et al</i> ^[101] , 2014	<i>n</i> = 168; duration 18 mo; clinical interview	> 50% non-adherent
Kassis <i>et al</i> ^[102] , 2014	<i>n</i> = 76; cross-sectional study; questionnaire based	55%
Ghaffari-Nejad <i>et al</i> ^[103] , 2015	<i>n</i> = 123; duration-6 mo; DAI = 10	61% fully or partially non-adherent
Hajda <i>et al</i> ^[104] , 2015	<i>n</i> = 33; cross-sectional study; self-report - DAI-10	58%
Ibrahim <i>et al</i> ^[105] , 2015	<i>n</i> = 358 (177 with BD); cross-sectional study; self-report-MMAS-8	46%
Levin <i>et al</i> ^[106] , 2015	<i>n</i> = 65; duration-3 mo; self-report-TRQ	32%-59% at baseline; 10%-40% at 3 mo
Mert <i>et al</i> ^[107] , 2015	<i>n</i> = 68; duration - 6 mo; self-reports; relatives' reports, medical records	45%
Azadforouz <i>et al</i> ^[108] , 2016	<i>n</i> = 47; duration-6 mo; clinical interview	36%
Mousavi <i>et al</i> ^[109] , 2016	<i>n</i> = 73 with BD and psychotic symptoms; cross-sectional study; clinical interviews	96%

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CRS: Compliance rating scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: Substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

techniques used to assess adherence. The majority of studies had sample sizes ranging from 100 to 500 patients (*n* = 51; 39%); but about a third had included 50 to 100 patients (*n* = 37; 28%), while 20% of the studies (*n* = 26) had less than 50 patients. Most studies were conducted over the period of 1 mo to 1 year (*n* = 56; 42%), but cross-sectional studies were also very common (*n* = 37; 28%), whereas about a quarter of the studies (*n* = 33; 25%) had extended beyond 1 year, often up to several years in some studies of mood stabilizers. About a third of the studies had used multiple measures to estimate adherence (*n* = 38; 29%), even as studies based only on self-reports (*n* = 37; 28%), or only on clinical interviews (*n* = 34; 26%) were equally common. Fifteen studies (11%) were based on analysis of claims data.

Rates were computed using the highest rate of non-adherence where multiple rates were mentioned and rates at baseline for longitudinal studies. Despite significant discrepancies in methodology across studies, when rates were computed from all the 132 studies the mean rate of non-adherence turned out to be 41.5% (41.52 ± 19.56) and the median rate was 40%. Rates of non-adherence were between 25% to 50% in 65 studies (49%) and greater than 50% in 42 of the 132 studies (32%).

Most studies with very high rates of non-adherence (> 80%) were either part of randomized-controlled trials^[31], or had been conducted among inpatients or mental hospital populations^[32-34], or were studies with qualitative designs^[35,36]. Patient numbers were generally small in these studies. Similarly, studies with very low

rates of non-adherence (< 20%) were either from specialized lithium clinics^[37,38], or were derived from randomized-controlled trials^[39-42]. Others studies with very low rates had relied either exclusively on patient reports to estimate non-adherence^[43-45], or had used qualitative designs with small patient samples^[46]. In contrast, the average rate of non-adherence in the 18 studies with large and more representative samples (naturalistic studies with > 500 patients) was higher at 49% (48.81 ± 14.13). The mean rate of adherence in the studies which had lasted more than 1 year was lower at 36% (36.36 ± 12.90). However, even after excluding the 21 studies with very high or very low rates, the mean rate of non-adherence in BD increased only to 43% (42.81 ± 14.66) and the median rate to 41%.

The average rate of non-adherence derived from studies where patients received all classes of medication was 45% (44.62 ± 19.61) with a median of 41%; after excluding 11 studies with very high or very low rates the mean rate was still 45% (44.94 ± 14.95), while the median rate increased to 43.5%. The mean rate of non-adherence among patients on mood stabilizers was 34% (34.16 ± 18.35) and the median rate was 31.5%. After excluding 9 studies with very high or very low rates the mean increased to 38% (37.82 ± 13.24) and the median to 34%. Rates derived from studies of antipsychotic medications were the highest with a mean of 51% (50.87 ± 15.87) and a median of 48%. After excluding one study with a very high rate the mean dropped to 48% (48.43 ± 13.44) and the median to 47%. Therefore, rates of non-adherence derived

Table 3 Rates of medication non-adherence in bipolar disorder: Studies of mood stabilizers

Ref.	Study	Non-adherence rates
Bech <i>et al</i> ^[30] , 1976	<i>n</i> = 76 on lithium (49 with BD); duration - 2 yr; retrospective case record data and serum levels	24%
Jamison <i>et al</i> ^[9] , 1979	<i>n</i> = 47 on lithium; cross-sectional study; self-report and psychiatrists' estimations	Patients - 47% non-adherent; psychiatrists - 35% non-adherent
Connelly <i>et al</i> ^[109] , 1982	<i>n</i> = 48 on lithium; duration - 9 mo; serum levels and > 75% clinic attendance	25%
Connelly <i>et al</i> ^[110] , 1984	<i>n</i> = 75 on lithium; duration - 6 mo; serum levels and > 75% clinic attendance	33%
Cochran ^[31] , 1984	<i>n</i> = 28 on lithium; duration - 6 mo; self-report; case notes; clinical interview and serum levels	93% had major or minor non-adherence
Danion <i>et al</i> ^[111] , 1987	<i>n</i> = 73 on lithium (36 with BD); duration - 2 yr; retrospective psychiatric assessments and serum levels	56% - subjective 19%; objective 56%
Aagaard <i>et al</i> ^[112] , 1988	<i>n</i> = 133 on lithium (47 with BD); duration - 6 mo; clinical interview	23%
Maarbjerg <i>et al</i> ^[113] , 1988	<i>n</i> = 48 on lithium (43 with BD); cross-sectional study; patient questionnaires	46% fully or partially non-adherent
Vestergaard and Schou ^[115] , 1988	<i>n</i> = 480 on lithium (187 with BD); duration - 7 yr; medical records based on serum levels and clinical interviews	50% in first 6 mo; 25% per year during the first 2 yr; 10% per year after 4-5 yr
Lenzi <i>et al</i> ^[116] , 1989	<i>n</i> = 67 women on lithium or carbamazepine; duration - 8 mo; self-report and serum levels	45%
Nilsson and Axelsson ^[117] , 1989	<i>n</i> = 64 with mood disorders on lithium; duration - 7 yr; serum levels and medical records	25%
Aagaard and Vestergaard ^[118] , 1990	<i>n</i> = 133 on lithium (61 with BD); duration - 2 yr; clinical interview	42%
Courtney <i>et al</i> ^[38] , 1995	<i>n</i> = 15 on lithium; cross-sectional study; serum levels	0%
Lee <i>et al</i> ^[119] , 1992	<i>n</i> = 50 on lithium; duration 12 mo; self-report; clinical interview; serum levels	30%
Berghöfer <i>et al</i> ^[120] , 1996	<i>n</i> = 86 (55 with BD) on lithium; retrospective follow-up over a mean of 8.9 yr based on clinical interview and serum levels	24%
Keck <i>et al</i> ^[121] , 1997	<i>n</i> = 140 on mood stabilizers; duration - 12 mo; clinical interview	51% fully or partially non-adherent
Maj <i>et al</i> ^[122] , 1998	<i>n</i> = 402 on lithium; duration - 5 yr; clinical interview and serum levels	28%
Schumann <i>et al</i> ^[123] , 1999	<i>n</i> = 75 (31 with BD) on lithium; duration-6 yr; retrospective medical records based on interviews and serum levels	55%
Wong <i>et al</i> ^[124] , 1999	<i>n</i> = 80 with mood disorders on lithium (60 with BD cross-sectional study; self-reports; clinical interviews; serum levels	27.50%
Licht <i>et al</i> ^[125] , 2001	<i>n</i> = 148 on mood stabilizers (132 on lithium): duration 24 mo; retrospective analysis of treatment charts, serum levels and clinical interviews	20%
McCleod and Sharp ^[37] , 2001	<i>n</i> = 30 on lithium; cross-sectional study; self-reports, clinical ratings and serum levels	0%
Svarstad <i>et al</i> ^[52] , 2001	<i>n</i> = 53 on lithium; duration 12 mo; retrospective claims data	26% irregular use
Scott ^[126] , 2002	<i>n</i> = 98 (85 with BD) on mood stabilizers; cross-sectional study; self-reports-ROMI and TRQ	30% partially adherent
Scott and Pope ^[127] , 2002a	<i>n</i> = 98 on mood stabilizers (78 with BD); duration- 24 mo; TRQ and serum levels	partial non-adherence - 47% over 2 yr; 32% over past month; 27% over past week; full non-adherence - 20% over 2 yr
Scott and Pope ^[128] , 2002b	<i>n</i> = 98 on mood stabilizers (78 with BD); duration - 18 mo; TRQ and serum levels	TRQ - 32% partial adherence; serum levels - 36%
Dharmendra and Eagles ^[43] , 2003	<i>n</i> = 411; duration - 3 yr; retrospective study based on self-reports and serum levels	15%
Pope and Scott ^[129] , 2003	<i>n</i> = 72 on lithium (61 with BD); duration - 2 yr; self-report-RSM	46%
Bowden <i>et al</i> ^[130] , 2005	<i>n</i> = 372 on lithium or valproate; duration - 52 wk; clinical interview	54%-75% premature discontinuations
Calabrese <i>et al</i> ^[56] , 2005	<i>n</i> = 254 with RCBD on lithium or valproate; duration 20 mo; clinical interviews and serum levels	10%-28%
Patel <i>et al</i> ^[131] , 2005	<i>n</i> = 32 adolescents on mood stabilizers; duration - 12 mo; clinical interviews and medical records	Treatment time without full adherence in 47%
Salloum <i>et al</i> ^[41] , 2005	<i>n</i> = 59 with BD and alcohol dependence on lithium or lithium and valproate; duration - 24 wk; self-report and serum levels	13%-14%
Gonzalez-Pinto <i>et al</i> ^[132] , 2006	<i>n</i> = 72; duration - 10 yr; clinical interviews and serum levels	22%
Drotar <i>et al</i> ^[133] , 2007	<i>n</i> = 107 adolescents; on lithium and valproate; duration - 20 wk; serum levels, pill counts, self/parent report and clinical interview	16%-34% (average 17%) non-adherent on various measures
Kessing <i>et al</i> ^[134] , 2007	<i>n</i> = 14277 on lithium; duration 6 yr; nation-wide register and pharmacy data	25% stopped lithium within 45 d
Manwani <i>et al</i> ^[135] , 2007	<i>n</i> = 115 on mood stabilizers; duration - 10 mo; clinical interview	34% lifetime adherence in those with SUD 17% in those without SUD
Rosa <i>et al</i> ^[136] , 2007	<i>n</i> = 106; cross-sectional study; self-report-MARS and serum and RBC levels	14% (based on levels) 33% (based on MARS)

Sajatovic <i>et al</i> ^[137] , 2007a	<i>n</i> = 44637 on mood stabilizers; duration - 3 mo or more; retrospective claims data-MPR based	46% partially or fully non-adherent; took medications less than 50%-80% of the time
Baldessarini <i>et al</i> ^[138] , 2008b	<i>n</i> = 2197 on single mood stabilizers; duration - 12 mo; national health plan claims data; MPR based	72% took medications less than 80% of the time
Vega <i>et al</i> ^[139] , 2009	<i>n</i> = 72 on lithium; duration - 5 yr; clinical interviews and serum levels	8% (women)-39% (men)
Bauer <i>et al</i> ^[44] , 2010	<i>n</i> = 312 on mood stabilizers; duration - 6 mo; self-report	11% partially or fully non-adherent
Sajatovic <i>et al</i> ^[86] , 2011b	<i>n</i> = 136; duration - 1 mo; self-report-TRQ	18% in the past week or month
Scott <i>et al</i> ^[140] , 2012	<i>n</i> = 81 on mood stabilizers; cross-sectional study; self-report -TRQ	26% - past month
Bauer <i>et al</i> ^[45] , 2013a	<i>n</i> = 206 on mood stabilizers; duration 100 d; self-report	14% mean percent of days of missing doses
Arvilommi <i>et al</i> ^[101] , 2014	<i>n</i> = 168 on mood stabilizers; duration 18 mo; clinical interview	40% fully or partially non-adherent
Sylvia <i>et al</i> ^[42] , 2014	<i>n</i> = 283 on lithium; duration - 6 mo; self-report-TRQ	4.5%-7% reported missing at least 30% of their medications in the past week
Col <i>et al</i> ^[141] , 2014	<i>n</i> = 78 on mood stabilizers; cross-sectional study; self-report-MARS	42%

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CRS: Compliance Rating Scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: Substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

Table 4 Rates of medication non-adherence in bipolar disorder: studies of antipsychotics and antidepressants

Ref.	Study	Non-adherence rates
Antipsychotics		
Keck <i>et al</i> ^[142] , 1996b	<i>n</i> = 77 on antipsychotics; duration - 6 mo; clinical interview	32%
Svarstad <i>et al</i> ^[52] , 2001	<i>n</i> = 56 on antipsychotics; duration 12 mo; retrospective claims data	23% irregular use
Patel <i>et al</i> ^[131] , 2005	<i>n</i> = 32 adolescents on antipsychotics; duration - 12 mo; clinical interviews and medical records	Treatment time without full adherence in 44%
Sajatovic <i>et al</i> ^[143] , 2006b	<i>n</i> = 32993 on antipsychotics; duration - 3 mo or more; retrospective claims data-MPR based	48% partially or fully non-adherent; took antipsychotics less than 50%-80% of the time
Sajatovic <i>et al</i> ^[144] , 2007b	<i>n</i> = 73964 on antipsychotics; duration - 3 mo or more; retrospective claims data-MPR based	39% among those > 60 yr and 50% in those < 60 yr took antipsychotics less than 50%-80% of the time
Hassan and Lage ^[145] , 2009	<i>n</i> = 1973 on antipsychotics; duration - 12 mo; retrospective claims based data-MPR based	56% took antipsychotics less than 50% of the time and 73% less than 75% of the time
Lage and Hassan ^[146] , 2009	<i>n</i> = 7,769 on antipsychotics; duration- 12 mo; retrospective claims data-MPR based	62% took antipsychotics less than 50% of the time and 79% less than 75% of the time
Lang <i>et al</i> ^[147] , 2011	<i>n</i> = 9410 on antipsychotics; duration - 12 mo; retrospective claims data-MPR based	60% took antipsychotics less than 80% of the time
Rascati <i>et al</i> ^[148] , 2011	<i>n</i> = 2446 on SGAs; duration - 18 mo; retrospective claims data-MPR based	42% took antipsychotics less than 80% of the time
Berger <i>et al</i> ^[34] , 2012	<i>n</i> = 84 on SGAs: Duration-6 mo; retrospective claims data-MPR and CMG based	85% took antipsychotics less than 80% of times (50% according to CMGs)
Stephenson <i>et al</i> ^[149] , 2012	<i>n</i> = 162 patients with BD on SGAs and 153 physicians; duration - 12 mo; retrospective claims data and physician survey	57% with low-moderate adherence; physicians overestimated adherence in 67% patients
Montes <i>et al</i> ^[150] , 2013	<i>n</i> = 303; cross-sectional study; self-reports- DAI-10 and MMAS, CRS	69%
Kutzelnigg <i>et al</i> ^[151] , 2014	Olanzapine alone or in combination with mood stabilizers; <i>n</i> = 891 at entry; 657 at 2 yr; clinical interview	33% at baseline; 20% at 2 yr
Arvilommi <i>et al</i> ^[101] , 2014	<i>n</i> = 168 on SGAs; duration 18 mo; clinical interview	46% fully or partially non-adherent
Sajatovic <i>et al</i> ^[152] , 2016	<i>n</i> = 1114 on lurasidone; duration- 27 mo; retrospective claims data-MPR based	67% took lurasidone less than 80% of the time
Antidepressants		
Svarstad <i>et al</i> ^[52] , 2001	<i>n</i> = 22 on antidepressants; duration 12 mo; retrospective claims data	27% irregular use
Bauer <i>et al</i> ^[153] , 2013b	<i>n</i> = 144 on antidepressants; duration - daily for 100 d; self-report	19% (missing/ changing doses) to 41% (drug holidays)

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CMG: Cumulative medication gaps; CRS: Compliance Rating Scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

from studies of mood stabilizers were significantly lower than rates among patients on all three classes of medications, or among those on antipsychotics ($P < 0.05$ or $P < 0.01$), while there were no differences between rates among patients on all classes of medications and

those on antipsychotics.

Demographic correlates of medication non-adherence in BD

Reviews: The evidence that socio-demographic characte-

ristics of patients influence their medication taking behaviour is largely inconsistent among patients with BD^[154]. Accordingly, most reviews of the subject have concluded that there is no strong support for an association between demographic variables and medication non-adherence in BD^[4,6,8,17,22,26]. Though certain demographic characteristics of patients have been associated with non-adherence in some studies of BD, such associations have not been found in others. There is also some discrepancy between reviews about which demographic parameters might be associated with non-adherence in BD; some reviews have concluded that younger age^[12,14,22,27,29] and male gender^[11,15,22,27] are more likely to be associated with non-adherence, while others have found that being single or living alone^[2,3,7,11,15], being less educated^[3,12,14,15,17] or belonging to ethnic minorities^[3,10,11] were among the most consistent risk factors for non-adherence in BD.

Studies: Table 5 list the studies, which have examined the demographic correlates of medication non-adherence in BD. In keeping with the reviews on demographic variables influencing non-adherence in BD, these studies also demonstrate that there is very little to support the notion that demographic attributes of patients have a significant influence on their medication taking behaviour. Firstly, a large number of studies ($n = 29$) have been unable to find an association between medication non-adherence and any demographic variable. Among individual variables young age has often been cited as a correlate of non-adherence in BD^[12,14,22,27,29], but the number of studies which have found an association with young age ($n = 22$) was almost similar to those that have been unable to demonstrate such an association ($n = 19$). Studies that have found associations with male gender, single marital status, lower levels of education, unemployment or low socioeconomic status or income were fewer than those unable to find such as association, or those that have found the obverse association. There appeared to be some link with a general "social disadvantage" factor including ethnic minority status, homelessness and dysfunctional family atmospheres, but the aggregate number of studies finding a positive association ($n = 25$) was not substantially different from those finding no such association ($n = 16$).

Clinical correlates of medication non-adherence in BD

Reviews: The relationship between several clinical features and medication non-adherence has been examined in a number of studies of BD. Clinical characteristics, which have been explored have included overall severity of the illness, severity of manic, depressive and psychotic symptoms as well as variables such as age of onset, duration of illness or episode-length, episode polarity and subtypes of BD. The impact of factors such as cognitive impairment, lack of insight and comorbidity on treatment-adherence has also been examined. The overall conclusion of reviews on the subject is that non-

adherence in BD is a complex phenomenon and the association with clinical variables is ambiguous. Not only are the results of such associations inconsistent and equivocal, but the causal direction of any positive associations, *i.e.*, whether the clinical variable in question led to non-adherence or vice-versa, is often unclear^[4,8,15,28]. Overall severity of illness in terms of number of episodes, number of hospitalizations or suicidality has been found to be associated with non-adherence in a few studies, but this is not a consistent finding^[2-4,6,7,12]. Similarly, severity of manic symptoms have been found to impact adherence negatively quite commonly, though not all studies have found this association^[2-4,6,15,22,23]. The influence of depressive or mixed symptoms and psychotic symptoms have not been examined often enough to reach any firm conclusions about their effect on non-adherence in BD^[2-4,12,18,27,28]. It is postulated that cognitive impairment may adversely affect adherence in BD, but the evidence for this appears to be derived from only a few studies^[2-4,8,14]. The evidence linking other clinical variables such as age of onset, duration of illness or episode-length, polarity and bipolar subtypes with non-adherence in BD is limited^[3,8,12]. The adverse effects of comorbid personality disorders and anxiety disorders on adherence in BD has also found mention, though the evidence seems limited to a few studies^[2-4,8,15]. In contrast, almost every review on the subject has concurred in finding that the presence of comorbid substance use disorders (SUD) has a significant negative impact on adherence in BD^[6,8,12,14,23]. Current rather than past substance abuse is more likely to be associated with non-adherence in BD^[3,163-166]. Finally, lack of insight and denial of illness has been consistently found to be associated with non-adherence in BD, though studies finding an association between insight and adherence in BD are still few in number^[2,11,12,167,168].

Studies: Table 6 include studies examining the clinical correlates of medication non-adherence in BD. As is evident from the two tables there was no evidence of a consistent association with non-adherence for the majority of the clinical variables examined. Certain studies did find positive associations between non-adherence and clinical variables such as early age of onset, shorter durations of illness, greater number of hospitalizations, higher number of total, manic, depressive or mixed episodes, rapid cycling course, bipolar vs unipolar disorders and bipolar I vs bipolar II disorders, polarity of episodes, overall severity of illness and severity of depressive, mixed and psychotic symptoms, family history of psychiatric disorders, comorbid personality disorders and comorbid anxiety or hyperkinetic disorders. However, the number of studies, which were unable to find such associations either equalled or outnumbered those with positive associations. The exceptions to this trend were associations of more severe manic symptoms (21 studies with positive associations and 16 without) and cognitive impairment

Table 5 Studies of demographic correlates of medication non-adherence in bipolar disorder

Demographic correlates	Studies with positive associations	Studies without positive associations	Others
Any demographic variable		Jamison <i>et al</i> ^[9] , 1979; Aagaard and Vestergaard ^[118] , 1990; Maj <i>et al</i> ^[122] , 1998; Schumann <i>et al</i> ^[123] , 1999; Colom <i>et al</i> ^[51] , 2000; Licht <i>et al</i> ^[125] , 2001; Scott ^[126] , 2002; Scott and Pope ^[127] , 2002a; Kliendienst and Griel ^[156] , 2004; Revicki <i>et al</i> ^[155] , 2005; Yen <i>et al</i> ^[157] , 2005; Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[40] , 2008; Taj <i>et al</i> ^[69] , 2008; Sajatovic <i>et al</i> ^[72] , 2009a; Clatworthy <i>et al</i> ^[71] , 2009; Martinez-Aran <i>et al</i> ^[74] , 2009; Sharifi <i>et al</i> ^[73] , 2009; González-Pinto <i>et al</i> ^[78] , 2010; Cely <i>et al</i> ^[83] , 2011; Murru <i>et al</i> ^[90] , 2012; Bauer <i>et al</i> ^[45] , 2013a; Bauer <i>et al</i> ^[153] , 2013b; Jónsdóttir <i>et al</i> ^[99] , 2013; Col <i>et al</i> ^[141] , 2014; Sylvia <i>et al</i> ^[42] , 2014; Ghaffari-Nejad <i>et al</i> ^[103] , 2015; Levin <i>et al</i> ^[106] , 2015; Mert <i>et al</i> ^[107] , 2015	
Young age	Frank <i>et al</i> ^[158] , 1985; Kleindienst and Greil ^[156] , 2004; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[137] , 2007a; Sajatovic <i>et al</i> ^[144] , 2007b; Johnson <i>et al</i> ^[61] , 2007; Baldessarini <i>et al</i> ^[66] , 2008a; Baldessarini <i>et al</i> ^[138] , 2008b; Copeland <i>et al</i> ^[67] , 2008; Mazza <i>et al</i> ^[75] , 2009; Bates <i>et al</i> ^[76] , 2010; Bauer <i>et al</i> ^[144] , 2010; Hou <i>et al</i> ^[79] , 2010; Perlis <i>et al</i> ^[82] , 2010; Lang <i>et al</i> ^[147] , 2011; Savaş <i>et al</i> ^[85] , 2011; Barraco <i>et al</i> ^[88] , 2012; Montes <i>et al</i> ^[150] , 2013; Hajda <i>et al</i> ^[104] , 2015; Levin <i>et al</i> ^[106] , 2015; Mousavi <i>et al</i> ^[32] , 2016	Danion <i>et al</i> ^[111] , 1987; Maarbjerg <i>et al</i> ^[113] , 1988; Lenzi <i>et al</i> ^[116] , 1989; Colom <i>et al</i> ^[51] , 2000; Licht <i>et al</i> ^[125] , 2001; Coletti <i>et al</i> ^[57] , 2005; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Drotar <i>et al</i> ^[133] , 2007; Rosa <i>et al</i> ^[136] , 2007; Sajatovic <i>et al</i> ^[144] , 2007b; Sajatovic <i>et al</i> ^[63] , 2007c; Zeber <i>et al</i> ^[68] , 2008; Savaş <i>et al</i> ^[85] , 2011; Belzeaux <i>et al</i> ^[95] , 2013; Hibdye <i>et al</i> ^[98] , 2013; Murru <i>et al</i> ^[100] , 2013; Kutzelnigg <i>et al</i> ^[151] , 2014; Azadforouz <i>et al</i> ^[108] , 2016	Both young and old age- Kessing <i>et al</i> ^[134] , 2007 Old age - Lehman and Rabins ^[59] , 2006; Rascati <i>et al</i> ^[148] , 2011; Sharma <i>et al</i> ^[94] , 2012
Male gender	Frank <i>et al</i> ^[158] , 1985; Aagaard <i>et al</i> ^[112] , 1988; Vestergaard and Schou ^[115] , 1988; McCleod and Sharp ^[37] , 2001; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Drotar <i>et al</i> ^[133] , 2007; Vega <i>et al</i> ^[139] , 2009; Savaş <i>et al</i> ^[85] , 2011; Mousavi <i>et al</i> ^[32] , 2016	Danion <i>et al</i> ^[111] , 1987; Maarbjerg <i>et al</i> ^[113] , 1988; Licht <i>et al</i> ^[125] , 2001; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Rosa <i>et al</i> ^[136] , 2006; Rosa <i>et al</i> ^[136] , 2007; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[137] , 2007a; Sajatovic <i>et al</i> ^[144] , 2007b; Sajatovic <i>et al</i> ^[63] , 2007c; Johnson <i>et al</i> ^[61] , 2007; Baldessarini <i>et al</i> ^[66] , 2008a; Baldessarini <i>et al</i> ^[138] , 2008b; Mazza <i>et al</i> ^[75] , 2009; Bauer <i>et al</i> ^[144] , 2010; Hou <i>et al</i> ^[79] , 2010; Perlis <i>et al</i> ^[82] , 2010; Rascati <i>et al</i> ^[148] , 2011; Sajatovic <i>et al</i> ^[86] , 2011b; Barraco <i>et al</i> ^[88] , 2012; Sharma <i>et al</i> ^[94] , 2012; Hibdye <i>et al</i> ^[98] , 2013; Montes <i>et al</i> ^[150] , 2013; Kutzelnigg <i>et al</i> ^[151] , 2014; Hajda <i>et al</i> ^[104] , 2015; Azadforouz <i>et al</i> ^[108] , 2016	Female gender - Keck <i>et al</i> ^[142] , 1997; Jose <i>et al</i> ^[161] , 2003; Sajatovic <i>et al</i> ^[46] , 2005; Kessing <i>et al</i> ^[134] , 2007; Copeland <i>et al</i> ^[67] , 2008; Zeber <i>et al</i> ^[68] , 2008; Bates <i>et al</i> ^[76] , 2010; Belzeaux <i>et al</i> ^[95] , 2013; Murru <i>et al</i> ^[100] , 2013
Not married	Frank <i>et al</i> ^[158] , 1985; Aagaard <i>et al</i> ^[112] , 1988; Connelly <i>et al</i> ^[109] , 1982; Connelly <i>et al</i> ^[110] , 1984; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Sajatovic <i>et al</i> ^[137] , 2007a; Vega <i>et al</i> ^[139] , 2009; Perlis <i>et al</i> ^[82] , 2010; Sajatovic <i>et al</i> ^[162] , 2011a; Hajda <i>et al</i> ^[104] , 2015	Lenzi <i>et al</i> ^[116] , 1989; Licht <i>et al</i> ^[125] , 2001; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Sajatovic <i>et al</i> ^[144] , 2007b; Sajatovic <i>et al</i> ^[63] , 2007c; Zeber <i>et al</i> ^[68] , 2008; Mazza <i>et al</i> ^[75] , 2009; Bauer <i>et al</i> ^[144] , 2010; Hou <i>et al</i> ^[79] , 2010; Savaş <i>et al</i> ^[85] , 2011; Barraco <i>et al</i> ^[88] , 2012; Sharma <i>et al</i> ^[94] , 2012; Belzeaux <i>et al</i> ^[95] , 2013; Hibdye <i>et al</i> ^[98] , 2013; Murru <i>et al</i> ^[100] , 2013; Azadforouz <i>et al</i> ^[108] , 2016; Mousavi <i>et al</i> ^[32] , 2016	
Poorly educated	Frank <i>et al</i> ^[158] , 1985; Connelly <i>et al</i> ^[110] , 1984; Danion <i>et al</i> ^[111] , 1987; Johnson <i>et al</i> ^[61] , 2007; Sajatovic <i>et al</i> ^[63] , 2007c; Bates <i>et al</i> ^[76] , 2010; Savaş <i>et al</i> ^[85] , 2011; Hajda <i>et al</i> ^[104] , 2015; Mousavi <i>et al</i> ^[32] , 2016	Aagaard <i>et al</i> ^[112] , 1988; Maarbjerg <i>et al</i> ^[113] , 1988; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Zeber <i>et al</i> ^[68] , 2008; Bauer <i>et al</i> ^[144] , 2010; Hou <i>et al</i> ^[79] , 2010; Perlis <i>et al</i> ^[82] , 2010; Sharma <i>et al</i> ^[94] , 2012; Belzeaux <i>et al</i> ^[95] , 2013; Hibdye <i>et al</i> ^[98] , 2013	
Unemployment	Aagaard <i>et al</i> ^[112] , 1988; Perlis <i>et al</i> ^[82] , 2010; Hibdye <i>et al</i> ^[98] , 2013; Montes <i>et al</i> ^[150] , 2013	Sajatovic <i>et al</i> ^[63] , 2007c; Bauer <i>et al</i> ^[44] , 2010; Hou <i>et al</i> ^[79] , 2010; Perlis <i>et al</i> ^[82] , 2010; Savaş <i>et al</i> ^[85] , 2011; Barraco <i>et al</i> ^[88] , 2012; Sharma <i>et al</i> ^[94] , 2012; Murru <i>et al</i> ^[100] , 2013; Hajda <i>et al</i> ^[104] , 2015	
Low socioeconomic status or income	DelBello <i>et al</i> ^[60] , 2007; Perlis <i>et al</i> ^[82] , 2010	Aagaard <i>et al</i> ^[112] , 1988; Maarbjerg <i>et al</i> ^[113] , 1988; Lenzi <i>et al</i> ^[116] , 1989; Aagaard and Vestergaard ^[118] , 1990; Johnson <i>et al</i> ^[61] , 2007; Zeber <i>et al</i> ^[68] , 2008; Savaş <i>et al</i> ^[85] , 2011; Sharma <i>et al</i> ^[94] , 2012	
Ethnic minority status	Keck <i>et al</i> ^[121] , 1997; Strakowski <i>et al</i> ^[49] , 1998; Kleindienst and Greil ^[156] , 2004; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[137] , 2007a; Sajatovic <i>et al</i> ^[144] , 2007b; Sajatovic <i>et al</i> ^[63] , 2007c; Johnson <i>et al</i> ^[61] , 2007; Copeland <i>et al</i> ^[67] , 2008; Zeber <i>et al</i> ^[68] , 2008; Perlis <i>et al</i> ^[82] , 2010; Rascati <i>et al</i> ^[148] , 2011; Sajatovic <i>et al</i> ^[162] , 2011a; Sajatovic <i>et al</i> ^[92] , 2012	Fleck <i>et al</i> ^[58] , 2005; Patel <i>et al</i> ^[131] , 2005; Drotar <i>et al</i> ^[133] , 2007; Baldessarini <i>et al</i> ^[66] , 2008a; Baldessarini <i>et al</i> ^[138] , 2008b; Bates <i>et al</i> ^[76] , 2010; Hibdye <i>et al</i> ^[98] , 2013; Kutzelnigg <i>et al</i> ^[151] , 2014	
Living alone/homeless	Lenzi <i>et al</i> ^[116] , 1989; Kleindienst and Greil ^[156] , 2004; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[137] , 2007a; Sajatovic <i>et al</i> ^[144] , 2007b	Zeber <i>et al</i> ^[68] , 2008; Montes <i>et al</i> ^[150] , 2013; Murru <i>et al</i> ^[100] , 2013; Hajda <i>et al</i> ^[104] , 2015	

Family factors:	Aagaard <i>et al</i> ^[112] , 1988; Drotar <i>et al</i> ^[133] , 2007; Cely <i>et al</i> ^[83] , 2011; Sajatovic <i>et al</i> ^[62] , 2011a; Scott <i>et al</i> ^[140] , 2012; support, negative attitudes	Sajatovic <i>et al</i> ^[72] , 2009a; Sajatovic <i>et al</i> ^[86] , 2011b
	Sharma <i>et al</i> ^[94] , 2012; Col <i>et al</i> ^[141] , 2014	

BD: Bipolar disorder.

Table 6 Studies of clinical correlates of medication non-adherence in bipolar disorder

Clinical correlates	Studies with positive associations	Studies without positive associations	Others
Early age of onset	Aagaard <i>et al</i> ^[112] , 1988; Maarbjerg <i>et al</i> ^[113] , 1988; Drotar <i>et al</i> ^[133] , 2007; Perlis <i>et al</i> ^[82] , 2010; Barraco <i>et al</i> ^[88] , 2012	Colom <i>et al</i> ^[51] , 2000; Scott and Pope ^[127] , 2002a; Sajatovic <i>et al</i> ^[59] , 2006a; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; González-Pinto <i>et al</i> ^[78] , 2010; Murru <i>et al</i> ^[90] , 2012; Levin <i>et al</i> ^[106] , 2015; Azadforouz <i>et al</i> ^[108] , 2016	Later onset - Col <i>et al</i> ^[141] , 2014 Hajda <i>et al</i> ^[104] , 2015
Short durations of illness	Aagaard <i>et al</i> ^[112] , 1988; Maarbjerg <i>et al</i> ^[113] , 1988; González-Pinto <i>et al</i> ^[78] , 2010; Belzeaux <i>et al</i> ^[95] , 2013; Azadforouz <i>et al</i> ^[108] , 2016	Danion <i>et al</i> ^[111] , 1987; Aagaard and Vestergaard ^[118] , 1990; Schumann <i>et al</i> ^[123] , 1999; Colom <i>et al</i> ^[51] , 2000; Licht <i>et al</i> ^[125] , 2001; Scott and Pope ^[127] , 2002a; Jose <i>et al</i> ^[61] , 2003; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Taj <i>et al</i> ^[69] , 2008; Sajatovic <i>et al</i> ^[72] , 2009a; Hou <i>et al</i> ^[79] , 2010; Savaş <i>et al</i> ^[85] , 2011; Murru <i>et al</i> ^[90] , 2012; Sharma <i>et al</i> ^[94] , 2012; Montes <i>et al</i> ^[150] , 2013; Col <i>et al</i> ^[141] , 2014	Longer durations - Coletti <i>et al</i> ^[57] , 2005; Belzeaux <i>et al</i> ^[95] , 2013
Greater number of hospitalizations	Aagaard <i>et al</i> ^[112] , 1988; Maarbjerg <i>et al</i> ^[113] , 1988; Aagaard and Vestergaard ^[118] , 1990; Colom <i>et al</i> ^[51] , 2000; Svarstad <i>et al</i> ^[52] , 2001; Scott ^[126] , 2002; Scott and Pope ^[128] , 2002b; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Baldessarini <i>et al</i> ^[138] , 2008b; Gianfrancesco <i>et al</i> ^[168] , 2008; Hassan and Lage ^[145] , 2009; Lage and Hassan ^[146] , 2009; Martinez-Aran <i>et al</i> ^[74] , 2009; Vega <i>et al</i> ^[139] , 2009; Bates <i>et al</i> ^[76] , 2010; González-Pinto <i>et al</i> ^[78] , 2010; Hong <i>et al</i> ^[84] , 2011; Lang <i>et al</i> ^[147] , 2011; Savaş <i>et al</i> ^[85] , 2011; Scott <i>et al</i> ^[140] , 2012; Kutzelnigg <i>et al</i> ^[151] , 2014	Johnson and McFarland ^[169] , 1996; Keck <i>et al</i> ^[47] , 1996a; Schumann <i>et al</i> ^[123] , 1999; Jose <i>et al</i> ^[61] , 2003; Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[144] , 2007b; Sajatovic <i>et al</i> ^[40] , 2008; Clatworthy <i>et al</i> ^[71] , 2009; Sharifi <i>et al</i> ^[73] , 2009; Bauer <i>et al</i> ^[44] , 2010; González-Pinto <i>et al</i> ^[78] , 2010; Hou <i>et al</i> ^[79] , 2010; Murru <i>et al</i> ^[90] , 2012; Sharma <i>et al</i> ^[94] , 2012; Montes <i>et al</i> ^[150] , 2013; Hajda <i>et al</i> ^[104] , 2015; Azadforouz <i>et al</i> ^[108] , 2016	Fewer hospitalizations - Sajatovic <i>et al</i> ^[137] , 2007a; Col <i>et al</i> ^[141] , 2014
Higher total number of episodes	Danion <i>et al</i> ^[111] , 1987; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Vega <i>et al</i> ^[139] , 2009; Gutiérrez-Rojas <i>et al</i> ^[81] , 2010; Murru <i>et al</i> ^[100] , 2013	Lenzi <i>et al</i> ^[116] , 1989; Keck <i>et al</i> ^[47] , 1996a; Jose <i>et al</i> ^[61] , 2003; Martinez-Aran <i>et al</i> ^[74] , 2009; Murru <i>et al</i> ^[90] , 2012; Belzeaux <i>et al</i> ^[95] , 2013; Col <i>et al</i> ^[141] , 2014	Fewer episodes - Colom <i>et al</i> ^[51] , 2000
Higher number of manic episodes	Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Vega <i>et al</i> ^[139] , 2009; Murru <i>et al</i> ^[100] , 2013	Johnson <i>et al</i> ^[74] , 2009; Bates <i>et al</i> ^[76] , 2010; Gutiérrez-Rojas <i>et al</i> ^[81] , 2010; Murru <i>et al</i> ^[90] , 2012; Col <i>et al</i> ^[141] , 2014	Fewer hypomanic episodes - Colom <i>et al</i> ^[51] , 2000
Higher number of depressive episodes	Danion <i>et al</i> ^[111] , 1987; Gutiérrez-Rojas <i>et al</i> ^[81] , 2010; Col <i>et al</i> ^[141] , 2014	Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Johnson <i>et al</i> ^[61] , 2007; Martinez-Aran <i>et al</i> ^[74] , 2009; Vega <i>et al</i> ^[139] , 2009; Bates <i>et al</i> ^[76] , 2010; Murru <i>et al</i> ^[90] , 2012	Fewer depressive episodes - Colom <i>et al</i> ^[51] , 2000
Higher number of mixed episodes/rapid cycling	Calabrese <i>et al</i> ^[56] , 2005; Perlis <i>et al</i> ^[82] , 2010	Maarbjerg <i>et al</i> ^[113] , 1988; Colom <i>et al</i> ^[51] , 2000; Sajatovic <i>et al</i> ^[59] , 2006a; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Sajatovic <i>et al</i> ^[40] , 2008; Martinez-Aran <i>et al</i> ^[74] , 2009; Murru <i>et al</i> ^[90] , 2012; Murru <i>et al</i> ^[100] , 2013	
BD vs UP disorders	Arvilommi <i>et al</i> ^[101] , 2014; Mert <i>et al</i> ^[107] , 2015	Connelly <i>et al</i> ^[109] , 1982; Maarbjerg <i>et al</i> ^[113] , 1988; Lenzi <i>et al</i> ^[116] , 1989; Aagaard and Vestergaard ^[118] , 1990; Schumann <i>et al</i> ^[123] , 1999; McCleod and Sharp ^[37] , 2001; Scott and Pope ^[127] , 2002a; Taj <i>et al</i> ^[69] , 2008; Ghaffari-Nejad <i>et al</i> ^[103] , 2015	
BP I vs BP II	Martinez-Aran <i>et al</i> ^[74] , 2009; Mazza <i>et al</i> ^[75] , 2009	Jamison <i>et al</i> ^[9] , 1979; Colom <i>et al</i> ^[51] , 2000; Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[40] , 2008; Baldessarini <i>et al</i> ^[66] , 2008a; Baldessarini <i>et al</i> ^[138] , 2008b; Bauer <i>et al</i> ^[44] , 2010; Perlis <i>et al</i> ^[82] , 2010; Montes <i>et al</i> ^[150] , 2013; Sylvia <i>et al</i> ^[42] , 2014	Higher in BP II - Murru <i>et al</i> ^[100] , 2013
Polarity of episodes	Gutiérrez-Rojas <i>et al</i> ^[81] , 2010; Montes <i>et al</i> ^[150] , 2013	Danion <i>et al</i> ^[111] , 1987; Maarbjerg <i>et al</i> ^[113] , 1988; Sajatovic <i>et al</i> ^[59] , 2006a; Col <i>et al</i> ^[141] , 2014	
Overall severity of illness	Baldessarini <i>et al</i> ^[66] , 2008a; Sajatovic <i>et al</i> ^[72] , 2009a; Sajatovic <i>et al</i> ^[40] , 2008; Bates <i>et al</i> ^[76] , 2010; González-Pinto <i>et al</i> ^[78] , 2010; Cely <i>et al</i> ^[83] , 2011; Barraco <i>et al</i> ^[88] , 2012; Sharma <i>et al</i> ^[94] , 2012; Kutzelnigg <i>et al</i> ^[151] , 2014; Hajda <i>et al</i> ^[104] , 2015	Danion <i>et al</i> ^[111] , 1987; Nilsson and Axelsson ^[117] , 1989; Sajatovic <i>et al</i> ^[63] , 2007 c; Sajatovic <i>et al</i> ^[72] , 2009a; Mazza <i>et al</i> ^[75] , 2009; Hong <i>et al</i> ^[84] , 2011; Sajatovic <i>et al</i> ^[86] , 2011b; Montes <i>et al</i> ^[150] , 2013; Sylvia <i>et al</i> ^[42] , 2014; Azadforouz <i>et al</i> ^[108] , 2016; Sajatovic <i>et al</i> ^[152] , 2016	
Manic symptoms	Van Putten ^[20] , 1975; Connelly <i>et al</i> ^[109] , 1982; Keck <i>et al</i> ^[47] , 1996a; Keck <i>et al</i> ^[142] , 1996b; Lenzi <i>et al</i> ^[116] , 1989; Miklowitz <i>et al</i> ^[171] , 2000; Miklowitz <i>et al</i> ^[172] , 2003; Bowden <i>et al</i> ^[130] , 2005; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Gaudiano and Miller ^[173] , 2006; Baldessarini <i>et al</i> ^[66] , 2008a; Copeland <i>et al</i> ^[67] , 2008; Bauer <i>et al</i> ^[44] , 2010; González-Pinto <i>et al</i> ^[78] , 2010; Perlis <i>et al</i> ^[82] , 2010; Hong <i>et al</i> ^[84] , 2011; Barraco <i>et al</i> ^[88] , 2012; Montes <i>et al</i> ^[150] , 2013; Sylvia <i>et al</i> ^[42] , 2014; Levin <i>et al</i> ^[106] , 2015	Colom <i>et al</i> ^[51] , 2000; Rosa <i>et al</i> ^[136] , 2007; Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[63] , 2007 c; Sajatovic <i>et al</i> ^[40] , 2008; Clatworthy <i>et al</i> ^[71] , 2009; Mazza <i>et al</i> ^[75] , 2009; Martinez-Aran <i>et al</i> ^[74] , 2009; Sajatovic <i>et al</i> ^[86] , 2011b; Murru <i>et al</i> ^[90] , 2012; Belzeaux <i>et al</i> ^[95] , 2013; Hibdye <i>et al</i> ^[98] , 2013; Jónsdóttir <i>et al</i> ^[99] , 2013; Ghaffari-Nejad <i>et al</i> ^[103] , 2015; Azadforouz <i>et al</i> ^[108] , 2016; Sajatovic <i>et al</i> ^[152] , 2016	

Depressive symptoms	Bowden <i>et al</i> ^[130] , 2005; Gaudio and Miller ^[173] , 2006; Johnson <i>et al</i> ^[61] , 2007; Martinez-Aran <i>et al</i> ^[74] , 2009; Bates <i>et al</i> ^[76] , 2010; Bauer <i>et al</i> ^[44] , 2010; Perlis <i>et al</i> ^[82] , 2010; Hong <i>et al</i> ^[84] , 2011; Barraco <i>et al</i> ^[88] , 2012; Montes <i>et al</i> ^[150] , 2013; Arvilommi <i>et al</i> ^[101] , 2014; Bauer <i>et al</i> ^[45] , 2013a; Bauer <i>et al</i> ^[153] , 2013b; Murru <i>et al</i> ^[100] , 2013; Gibson <i>et al</i> ^[97] , 2013; Levin <i>et al</i> ^[106] , 2015; Azadforouz <i>et al</i> ^[108] , 2016; Sajatovic <i>et al</i> ^[152] , 2016	Colom <i>et al</i> ^[51] , 2000; Miklowitz <i>et al</i> ^[171] , 2000; Miklowitz <i>et al</i> ^[172] , 2003; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[63] , 2007c; Rosa <i>et al</i> ^[136] , 2007; Sajatovic <i>et al</i> ^[40] , 2008; Sajatovic <i>et al</i> ^[72] , 2009a; Clatworthy <i>et al</i> ^[71] , 2009; González-Pinto <i>et al</i> ^[78] , 2010; Sajatovic <i>et al</i> ^[86] , 2011b; Murru <i>et al</i> ^[90] , 2012; Hibdye <i>et al</i> ^[96] , 2013; Sylvia <i>et al</i> ^[42] , 2014; Ghaffari-Nejad <i>et al</i> ^[105] , 2015	Better adherence with depression - Lenzi <i>et al</i> ^[116] , 1989
Mixed symptoms	Bowden <i>et al</i> ^[130] , 2005; González-Pinto <i>et al</i> ^[78] , 2010; Perlis <i>et al</i> ^[82] , 2010	Licht <i>et al</i> ^[125] , 2001; Azorin <i>et al</i> ^[70] , 2009; Hibdye <i>et al</i> ^[96] , 2013; Ghaffari-Nejad <i>et al</i> ^[103] , 2015	
Psychotic symptoms	Miklowitz <i>et al</i> ^[174] , 1992; Maj <i>et al</i> ^[122] , 1998; Yen <i>et al</i> ^[157] , 2005; Martinez-Aran <i>et al</i> ^[74] , 2009; González-Pinto <i>et al</i> ^[78] , 2010; Murru <i>et al</i> ^[90] , 2012; Murru <i>et al</i> ^[100] , 2013; Levin <i>et al</i> ^[106] , 2015; Sajatovic <i>et al</i> ^[152] , 2016	Danion <i>et al</i> ^[111] , 1987; Aagaard and Vestergaard ^[118] , 1990; Colom <i>et al</i> ^[51] , 2000; Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[40] , 2008; Sajatovic <i>et al</i> ^[72] , 2009a; Perlis <i>et al</i> ^[82] , 2010; Belzeaux <i>et al</i> ^[95] , 2013; Azadforouz <i>et al</i> ^[108] , 2016	
Cognitive impairment	Danion <i>et al</i> ^[111] , 1987; Jose <i>et al</i> ^[161] , 2003; Baldessarini <i>et al</i> ^[66] , 2008a; Depp <i>et al</i> ^[175] , 2008; Martinez-Aran <i>et al</i> ^[74] , 2009; Eker and Harkin ^[89] , 2012	Maarbjerg <i>et al</i> ^[113] , 1988; Jónsdóttir <i>et al</i> ^[99] , 2013	
Familial psychiatric disorder	Drotar <i>et al</i> ^[133] , 2007	Colom <i>et al</i> ^[51] , 2000; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Martinez-Aran <i>et al</i> ^[74] , 2009; Savas <i>et al</i> ^[85] , 2011; Murru <i>et al</i> ^[90] , 2012; Col <i>et al</i> ^[141] , 2014; Hajda <i>et al</i> ^[104] , 2015	
Poor insight	Schumann <i>et al</i> ^[123] , 1999; Greenhouse <i>et al</i> ^[54] , 2000; Jose <i>et al</i> ^[161] , 2003; Fleck <i>et al</i> ^[58] , 2005; Yen <i>et al</i> ^[157] , 2005; Rosa <i>et al</i> ^[160] , 2006; Rosa <i>et al</i> ^[136] , 2007; Copeland <i>et al</i> ^[67] , 2008; Sajatovic <i>et al</i> ^[72] , 2009a; González-Pinto <i>et al</i> ^[78] , 2010; Cely <i>et al</i> ^[83] , 2011; Sajatovic <i>et al</i> ^[86] , 2011b; Savaş <i>et al</i> ^[85] , 2011; Vieta <i>et al</i> ^[93] , 2012; Kutzelnigg <i>et al</i> ^[151] , 2014; Mert <i>et al</i> ^[107] , 2015; Novick <i>et al</i> ^[176] , 2015	Wong <i>et al</i> ^[124] , 1999; Jonsdottir <i>et al</i> ^[99] , 2013	
Comorbid SUD	Aagaard <i>et al</i> ^[112] , 1988; Maarbjerg <i>et al</i> ^[113] , 1988; Weiss <i>et al</i> ^[50] , 1998; Aagaard and Vestergaard ^[118] , 1990; Keck <i>et al</i> ^[121] , 1997; Keck <i>et al</i> ^[48] , 1998; Strakowski <i>et al</i> ^[49] , 1998; Licht <i>et al</i> ^[125] , 2001; Fleck <i>et al</i> ^[58] , 2005; Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[137] , 2007a; Sajatovic <i>et al</i> ^[144] , 2007b; DelBello <i>et al</i> ^[60] , 2007; Manwani <i>et al</i> ^[135] , 2007; Baldessarini <i>et al</i> ^[38] , 2008b; Copeland <i>et al</i> ^[67] , 2008; Darling <i>et al</i> ^[177] , 2008; Zeber <i>et al</i> ^[68] , 2008; Sajatovic <i>et al</i> ^[72] , 2009a; van Rossum <i>et al</i> ^[78] , 2009; Vega <i>et al</i> ^[139] , 2009; Bates <i>et al</i> ^[76] , 2010; González-Pinto <i>et al</i> ^[78] , 2010; Perlis <i>et al</i> ^[82] , 2010; Cely <i>et al</i> ^[83] , 2011; Hong <i>et al</i> ^[84] , 2011; Lang <i>et al</i> ^[147] , 2011; Sajatovic <i>et al</i> ^[162] , 2011a; Teter <i>et al</i> ^[179] , 2011; Barraco <i>et al</i> ^[88] , 2012; Vieta <i>et al</i> ^[93] , 2012; Hibdye <i>et al</i> ^[96] , 2013; Jónsdóttir <i>et al</i> ^[99] , 2013; Montes <i>et al</i> ^[150] , 2013; Arvilommi <i>et al</i> ^[101] , 2014	Nilsson and Axelsson ^[117] , 1989; Schumann <i>et al</i> ^[123] , 1999; Colom <i>et al</i> ^[51] , 2000; Sajatovic <i>et al</i> ^[63] , 2007c; Sajatovic <i>et al</i> ^[40] , 2008; Mazza <i>et al</i> ^[75] , 2009; Sharifi <i>et al</i> ^[73] , 2009; Rascati <i>et al</i> ^[148] , 2011; Sajatovic <i>et al</i> ^[86] , 2011b; Murru <i>et al</i> ^[90] , 2012; Sharma <i>et al</i> ^[94] , 2012; Murru <i>et al</i> ^[100] , 2013; Col <i>et al</i> ^[141] , 2014; Kutzelnigg <i>et al</i> ^[151] , 2014; Sylvia <i>et al</i> ^[42] , 2014; Mert <i>et al</i> ^[107] , 2015; Ghaffari-Nejad <i>et al</i> ^[103] , 2015	
Comorbid personality disorders	Danion <i>et al</i> ^[111] , 1987; Aagaard <i>et al</i> ^[112] , 1988; Maarbjerg <i>et al</i> ^[113] , 1988; Colom <i>et al</i> ^[51] , 2000; Murru <i>et al</i> ^[100] , 2013; Arvilommi <i>et al</i> ^[101] , 2014	Aagaard and Vestergaard ^[118] , 1990; Schumann <i>et al</i> ^[123] , 1999; Kliendienst and Griel ^[156] , 2004; Mazza <i>et al</i> ^[75] , 2009; Murru <i>et al</i> ^[90] , 2012; Kutzelnigg <i>et al</i> ^[151] , 2014	
Comorbid anxiety disorders or ADHD	DelBello <i>et al</i> ^[60] , 2007; Baldessarini <i>et al</i> ^[66] , 2008a; Taj <i>et al</i> ^[69] , 2008; Perlis <i>et al</i> ^[82] , 2010; Arvilommi <i>et al</i> ^[101] , 2014	Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[144] , 2007b; Drotar <i>et al</i> ^[133] , 2007; Sajatovic <i>et al</i> ^[40] , 2008; Cely <i>et al</i> ^[83] , 2011; Rascati <i>et al</i> ^[148] , 2011; Murru <i>et al</i> ^[90] , 2012; Belzeaux <i>et al</i> ^[95] , 2013; Kutzelnigg <i>et al</i> ^[151] , 2014; Sylvia <i>et al</i> ^[42] , 2014	Better adherence with comorbid anxiety disorder - Baldessarini <i>et al</i> ^[138] , 2008b

ADHD: Attention deficit hyperactivity disorder; BD: Bipolar disorder; SUD: Substance use disorders; UP: Unipolar disorder.

(6 studies with positive associations and 2 without) with non-adherence in BD. Finally, a clear association with medication non-adherence was evident only in the case of two clinical parameters, that is comorbid SUD and lack of insight, where the number of studies with positive associations far outnumbered the studies without such associations.

Treatment-related correlates of medication non-adherence in BD

Reviews: Several studies have examined the effects

of different classes of medications, the duration of treatment with medications, intensity of treatment, *i.e.*, the number of medications and their doses, and the complexity of medication regimens on medication non-adherence in BD. Reviews of literature have found occasional differences in adherence between some of the second-generation antipsychotics (SGAs), but rates of non-adherence with mood stabilizers and antipsychotics have been largely similar^[2]. No differences have been found between older and newer medications; indeed rates of non-adherence in BD

appear to have remained unchanged over the years despite the availability of newer medications^[4,6,15,17,19]. The influence of duration of treatment has been uncertain with non-adherence occurring both in the early as well as late phases of treatment^[4,15,17,22]. The number of medications, higher doses and more complicated medication regimens are all expected to increase the risk of non-adherence, but even this has not been reported consistently^[4,10,15,17,18]. The bulk of studies, however, have been about side effects of treatment. Reviews of non-adherence in BD have found a link with side effects among certain studies^[3,12,21,23], both for side effects associated with mood stabilizers and antipsychotics^[16,181-184]. However, many others have concluded that side effects are often not among the major reasons for non-adherence^[2,4,6,14,17]. The latter reviews also agree in finding that it is the fear or concern about side effects that frequently leads to non-adherence, rather than the actual presence of side effects. Inadequate efficacy of medication-treatment has also been proposed as a risk factor for non-adherence in BD, with efficacy in reducing depressive symptoms being particularly important from the patient's perspective^[3,12,23].

Studies: Similar to the results of studies examining demographic and illness related correlates of non-adherence in BD, studies examining medication-related variables have also yielded few unequivocal associations. Thus, drug classes, the duration of treatment, greater number or higher doses of medications and more complex medication regimens were associated with non-adherence only in a few studies, while the number of studies without such associations were either equal in number or far greater. A positive association with the presence of side effects was reported in 35 studies; more than a-third of these involved lithium. However, 26 studies did not find a positive association and 17 studies found that fear of side effects than their actual presence had a greater impact on non-adherence. Efficacy of treatment had a positive association with non-adherence, but only among 12 studies. These results are depicted in Table 7.

DISCUSSION

Given its chronic, relapsing and remitting nature as well as attendant disability, comorbidity and frequent negative therapeutic outcomes, BD is expected to be characterized by high rates of treatment non-adherence. The existing reviews on medication non-adherence in BD (included in Table 1) support this notion by finding that about 40% to 50% of the patients with BD do not take their medications properly. However most of these reviews are several years old and have included about 25 studies or less in most instances. The current review spanned four decades from 1976 to 2016 and was based on a more comprehensive search of the existing literature on medication non-adherence in BD. It also

used somewhat broader selection criteria in an effort to include data from as many studies as possible. This resulted in a much larger list of close to 200 reviews and studies on the subject; 132 of these studies were used to derive rates of medication non-adherence in BD. The obvious disadvantage of casting such a broad net was the substantial difference in methodologies across the studies that formed a part of this review. Though this significant heterogeneity did not allow a meta-analysis of the data, the results probably reflected a truer and a more up to date picture of medication non-adherence in BD than some of the existing reviews, simply because of the large number of studies included and the longer period covered by this review.

The results of the review yielded some notable findings about the rate of medication non-adherence in BD. To start with there was a wide variation in rates of non-adherence ranging from 0%-96%, which was more a result of the methodological disparities across studies. Nevertheless, the entire group of studies yielded an average rate of 41.5% and a median rate of 40% for medication non-adherence. When the rates were computed excluding outliers with very high or low rates, the mean rate of non-adherence rose to 43% and the median rate to 41%. These rates were remarkably similar to those found in the majority of previously published reviews (Table 1), which have found rates of non-adherence in BD to vary from 8% to 68% with a mean rate of about 40% and a median rate of 41%-42%. Rates of non-adherence were the highest for studies of patients on treatment with antipsychotics (mean 48%-51%; median 47%-48%) followed by studies of patients on all three classes of medications (mean 45%; median 41%-43.5%). Surprisingly, the rates were significantly lower in studies of patients being treated with mood stabilizers (mean 34%-38%; median 31.5%-34%). It was not exactly clear why this was so, particularly since other studies and reviews have not found rates to differ among different classes of medications^[2,5,6,21,22].

However, studies of mood stabilizers mainly included lithium; a significant proportion of them (41%) had been conducted in the 1970s to 1990s; and, the number of studies with very low rates was higher than the other two groups. In direct contrast, studies of patients on antipsychotics were conducted more recently and were based mostly on claims data, which also meant that the sample sizes were very large in many of these studies.

Thus, the overall conclusion from the group of studies included in this review is that between a third to about half of the patients with BD are medication non-adherent. However, there is reason to treat these rates with caution because of the considerable divergence in study designs. Differences in rates of non-adherence across studies usually arise principally from the definition of adherence used, the nature and size of the patient sample included, the setting in which the study is conducted, the duration of assessment and

Table 7 Studies of treatment correlates of medication non-adherence in bipolar disorder

Treatment correlates	Studies with positive associations	Studies without positive associations	Others
Differences between mood stabilizers	Weiss <i>et al</i> ^[50] , 1998; Revicki <i>et al</i> ^[155] , 2005; Baldessarini <i>et al</i> ^[138] , 2008b; Sajatovic <i>et al</i> ^[137] , 2007a	Baldessarini <i>et al</i> ^[66] , 2008a; Darling <i>et al</i> ^[177] , 2008; Bauer <i>et al</i> ^[45] , 2013a; Col <i>et al</i> ^[141] , 2014	
Differences between antipsychotics	Gianfrancesco <i>et al</i> ^[184] , 2005; Gianfrancesco <i>et al</i> ^[185] , 2006; Hassan <i>et al</i> ^[186] , 2007; Sajatovic <i>et al</i> ^[144] , 2007b; Rascati <i>et al</i> ^[148] , 2011; Ibrahim <i>et al</i> ^[105] , 2015	Patel <i>et al</i> ^[131] , 2005; Sajatovic <i>et al</i> ^[143] , 2006b; Baldessarini <i>et al</i> ^[66] , 2008a	
Differences between mood stabilizers and antipsychotics or antidepressants	González-Pinto <i>et al</i> ^[78] , 2010; Lang <i>et al</i> ^[147] , 2011; Murru <i>et al</i> ^[100] , 2013; Arvilommi <i>et al</i> ^[101] , 2014; Ibrahim <i>et al</i> ^[105] , 2015	Danion <i>et al</i> ^[111] , 1987; Keck <i>et al</i> ^[48] , 1998; Colom <i>et al</i> ^[51] , 2000; Patel <i>et al</i> ^[131] , 2005; Sajatovic <i>et al</i> ^[143] , 2006b; Baldessarini <i>et al</i> ^[66] , 2008a; Azorin <i>et al</i> ^[70] , 2009; Clatworthy <i>et al</i> ^[71] , 2009; Gianfrancesco <i>et al</i> ^[187] , 2009; Martinez-Aran <i>et al</i> ^[74] , 2009; Mazza <i>et al</i> ^[75] , 2009; Bates <i>et al</i> ^[76] , 2010; Cely <i>et al</i> ^[83] , 2011; Savaş <i>et al</i> ^[85] , 2011; Murru <i>et al</i> ^[90] , 2012; Bauer <i>et al</i> ^[153] , 2013b; Hibdye <i>et al</i> ^[98] , 2013; Arvilommi <i>et al</i> ^[101] , 2014; Hajda <i>et al</i> ^[104] , 2015	
Shorter duration of treatment	Johnson and McFarland ^[69] , 1996; Colom <i>et al</i> ^[51] , 2000; Lang <i>et al</i> ^[147] , 2011; Azadforouz <i>et al</i> ^[108] , 2016	Gonzalez-Pinto <i>et al</i> ^[132] , 2006; Drotar <i>et al</i> ^[133] , 2007; Darling <i>et al</i> ^[177] , 2008; Sharma <i>et al</i> ^[94] , 2012; Hibdye <i>et al</i> ^[98] , 2013; Col <i>et al</i> ^[141] , 2014	Longer durations - Jamison <i>et al</i> ^[9] , 1979; Scott and Pope ^[127] , 2002a; Kessing <i>et al</i> ^[134] , 2007; Sharifi <i>et al</i> ^[73] , 2009; Short and long durations - Kutzelnigg <i>et al</i> ^[151] , 2014
Greater number of medications	Keck <i>et al</i> ^[47] , 1996a; Revicki <i>et al</i> ^[155] , 2005; Baldessarini <i>et al</i> ^[138] , 2008b; Gianfrancesco <i>et al</i> ^[187] , 2009; Bates <i>et al</i> ^[76] , 2010; Hou <i>et al</i> ^[79] , 2010; Perlis <i>et al</i> ^[82] , 2010; Cruz <i>et al</i> ^[35] , 2011; Rascati <i>et al</i> ^[148] , 2011; Bauer <i>et al</i> ^[45] , 2013a; Bauer <i>et al</i> ^[153] , 2013b; Ibrahim <i>et al</i> ^[105] , 2015	Colom <i>et al</i> ^[51] , 2000; Licht <i>et al</i> ^[125] , 2001; Rosa <i>et al</i> ^[136] , 2007; Baldessarini <i>et al</i> ^[66] , 2008a; Darling <i>et al</i> ^[177] , 2008; Depp <i>et al</i> ^[175] , 2008; Taj <i>et al</i> ^[69] , 2008; Martinez-Aran <i>et al</i> ^[74] , 2009; Bauer <i>et al</i> ^[44] , 2010; Sajatovic <i>et al</i> ^[86] , 2011b; Savaş <i>et al</i> ^[85] , 2011; Miasso <i>et al</i> ^[91] , 2012; Sharma <i>et al</i> ^[94] , 2012; Col <i>et al</i> ^[141] , 2014; Ghaffari-Nejad <i>et al</i> ^[103] , 2015	Less intensive treatment - Johnson and McFarland ^[69] , 1996; Keck <i>et al</i> ^[121] , 1997; Sajatovic <i>et al</i> ^[59] , 2006a; Sajatovic <i>et al</i> ^[143] , 2006b; Sajatovic <i>et al</i> ^[137] , 2007a; Sajatovic <i>et al</i> ^[144] , 2007b; Sajatovic <i>et al</i> ^[40] , 2008
Higher doses of medications	McCleod and Sharp ^[37] , 2001; Gianfrancesco <i>et al</i> ^[185] , 2006	Baldessarini <i>et al</i> ^[66] , 2008a; Col <i>et al</i> ^[141] , 2014; Hajda <i>et al</i> ^[104] , 2015	Lower doses of medications - Mazza <i>et al</i> ^[75] , 2009; Bauer <i>et al</i> ^[44] , 2010
Complex medication regimens	Baldessarini <i>et al</i> ^[138] , 2008b; Sajatovic <i>et al</i> ^[72] , 2009a; Hibdye <i>et al</i> ^[98] , 2013; Ibrahim <i>et al</i> ^[105] , 2015	Keck <i>et al</i> ^[48] , 1998; Baldessarini <i>et al</i> ^[66] , 2008a; Miasso <i>et al</i> ^[91] , 2012; Col <i>et al</i> ^[141] , 2014	Fear of side effects - Cochran <i>et al</i> ^[31] , 1984;
Side effects	Bech <i>et al</i> ^[30] , 1976; Vestergaard and Amdisen ^[88] , 1983; Maarbjerg <i>et al</i> ^[113] , 1988; Gitlin <i>et al</i> ^[189] , 1989; Nilsson and Axelsson ^[117] , 1989; Aagaard and Vestergaard ^[118] , 1990; Maj <i>et al</i> ^[122] , 1998; Weiss <i>et al</i> ^[50] , 1998; Licht <i>et al</i> ^[125] , 2001; Kliendienst and Griel ^[156] , 2004; Lewis ^[190] , 2005; Bowden <i>et al</i> ^[130] , 2005; Calabrese <i>et al</i> ^[56] , 2005; Fleck <i>et al</i> ^[58] , 2005; Revicki <i>et al</i> ^[155] , 2005; Johnson <i>et al</i> ^[61] , 2007; Baldessarini <i>et al</i> ^[66] , 2008a; Baldessarini <i>et al</i> ^[138] , 2008b; Bates <i>et al</i> ^[76] , 2010; Mączka <i>et al</i> ^[191] , 2010; Wang and Henning ^[192] , 2010; Cely <i>et al</i> ^[83] , 2011; Cruz <i>et al</i> ^[35] , 2011; Miasso <i>et al</i> ^[193] , 2011; Sajatovic <i>et al</i> ^[162] , 2011a; Teter <i>et al</i> ^[179] , 2011; Eker and Harkin ^[89] , 2012; Sharma <i>et al</i> ^[94] , 2012; Belzeaux <i>et al</i> ^[95] , 2013; Gibson <i>et al</i> ^[97] , 2013; Arvilommi <i>et al</i> ^[101] , 2014; Sylvia <i>et al</i> ^[42] , 2014; Ibrahim <i>et al</i> ^[105] , 2015; Mert <i>et al</i> ^[107] , 2015; Ghaffari-Nejad <i>et al</i> ^[103] , 2015	Van Putten ^[20] , 1975; Jamison <i>et al</i> ^[9] , 1979; Connelly <i>et al</i> ^[109] , 1982; Danion <i>et al</i> ^[111] , 1987; Lenzi <i>et al</i> ^[116] , 1989; Johnson and McFarland ^[69] , 1996; Schuman <i>et al</i> ^[123] , 1999; Scott ^[196] , 2000; Scott ^[126] , 2002; Scott and Pope ^[127] , 2002a; Morselli <i>et al</i> ^[194] , 2003; Morselli <i>et al</i> ^[195] , 2004; Pope and Scott ^[129] , 2003; Roy <i>et al</i> ^[133] , 2005; Sajatovic <i>et al</i> ^[143] , 2006b; Drotar <i>et al</i> ^[133] , 2007; Rosa <i>et al</i> ^[160] , 2006; Rosa <i>et al</i> ^[136] , 2007; Perlis <i>et al</i> ^[82] , 2010; Savaş <i>et al</i> ^[85] , 2011; Barraco <i>et al</i> ^[88] , 2012; Vieta <i>et al</i> ^[93] , 2012; Hibdye <i>et al</i> ^[98] , 2013; Jónsdóttir <i>et al</i> ^[99] , 2013; Kutzelnigg <i>et al</i> ^[151] , 2014; Col <i>et al</i> ^[141] , 2014	Schumann <i>et al</i> ^[123] , 1999; Scott ^[196] , 2000; Scott ^[126] , 2002; Scott and Pope ^[127] , 2002a; Scott and Tacchi ^[197] , 2002; Morselli <i>et al</i> ^[194] , 2003; Morselli <i>et al</i> ^[195] , 2004; Fleck <i>et al</i> ^[58] , 2005; Rosa <i>et al</i> ^[160] , 2006; Rosa <i>et al</i> ^[136] , 2007; Clatworthy <i>et al</i> ^[136] , 2007; Clatworthy <i>et al</i> ^[71] , 2009; Sajatovic <i>et al</i> ^[198] , 2009c; Kriegshauser <i>et al</i> ^[199] , 2010; Cruz <i>et al</i> ^[35] , 2011; Sajatovic <i>et al</i> ^[162] , 2011a
Efficacy	Bech <i>et al</i> ^[30] , 1976; Jamison <i>et al</i> ^[9] , 1979; Miklowitz <i>et al</i> ^[171] , 2000; Miklowitz <i>et al</i> ^[172] , 2003; Lewis ^[190] , 2005; Fleck <i>et al</i> ^[58] , 2005; Patel <i>et al</i> ^[131] , 2005; Gaudiano and Miller ^[173] , 2006; Drotar <i>et al</i> ^[133] , 2007; Johnson <i>et al</i> ^[61] , 2007; Sajatovic <i>et al</i> ^[198] , 2009c; Cely <i>et al</i> ^[83] , 2011		

BD: Bipolar disorder. References in Tables 2-4 and text (No. 155-199).

the way non-adherence is estimated^[4,15,18,80]. Larger studies with more representative samples and longer

durations may be more likely to yield more accurate rates of non-adherence. In this review, about half of

the studies had less than 100 patients (48%) while studies with 100-500 patients formed a significant proportion of the total number of studies (39%) Studies with large and more representative samples (naturalistic studies with > 500 patients) were fewer (14%) but the mean rate of 49% obtained from them was higher than the mean rate of 41.5%-43% obtained for the entire group. Studies with longer durations (> 1-10 years) formed 25% of the sample. However, the mean rate of non-adherence (36%) among studies with longer durations was lower than the average rate of 41.5%-43% of the entire group. This was possibly due to fact that the bulk of studies with long durations involved mood stabilizers, a group in which mean rates of non-adherence (34%-38%) were lower than that for other medication classes. Different types of subjective and objective methods are often used to estimate adherence. In the absence of a "gold standard" the use of more than one method is recommended as the next best alternative^[2,6,12,14,27]. In this review the majority of studies (54%) had used either self-reports or clinical interviews to estimate adherence; a smaller proportion (11%) used claims data. The low proportion of studies using multiple measures of adherence (29%) could thus cast some doubts on the rates of non-adherence obtained in this review.

A major problem of research in the area of determinants of non-adherence in BD has been the exclusive focus on demographic, illness and treatment related predictors of non-adherence^[3,6,13,15,127]. This has been largely driven by the traditional medical model and compliance-based approaches to the problem of non-adherence in BD. As demonstrated in this review, studies examining demographic, illness and treatment related variables (numbering close to 160) far exceeded those that focused on patient-related factors such as attitudes and beliefs about medications, relationship with the clinician, knowledge about the illness and the influence of the wider socio-cultural environment on medication taking in BD. Social and cultural factors are of potential importance and likely to play a major role in determining treatment-adherence in BD^[154]. However, despite the large number of studies and the long list of variables examined, the search to identify demographic, illness and treatment related factors associated with non-adherence in BD has yielded little of note. This review found that none of the demographic attributes of patients such as age, gender, marital status, education, employment, income or social disadvantage were consistently linked to medication non-adherence in BD. Among clinical characteristics the presence of comorbid SUD and the absence of insight were the only two factors consisted associated with non-adherence with BD. The severity of manic symptoms appeared to show some association with non-adherence among studies of BD included in this review, as did cognitive impairment in a few studies. Given that about half or more of the patients with BD might have a comorbid SUD, the usefulness of this determinant has been questioned^[8].

Lack of insight is expected to adversely affect adherence more so among patients in acute symptomatic phases of mania. However, the role of insight is less certain in other phases such as depression or in the inter-episodic period. Moreover, lack of insight is only one among several influences on non-adherence in BD; therefore, the presence of adequate insight by itself may not be enough to ensure adherence. In accordance with several previous reviews^[2,4,6,10,15] medication-related variables such as the types of medications, duration of treatment, greater number of medications, higher doses and complexity of treatment regimens did not demonstrate consistent associations with non-adherence among studies of BD included in this review. Earlier reviews of non-adherence in BD have found a link with side effects of medications^[3,12,21,23]. A positive association with the presence of side effects was reported in 35 studies of this review; more than a-third of these involved lithium. At the same time almost an equal number of studies did not find a positive association and many found that fear of side effects than their actual presence had a greater impact on non-adherence. This indicates that side effects are often not among the major reasons for non-adherence in BD and that fear or concern about side effects (an attitudinal variable) may be the more important determinant^[2,4,6,17,167].

There could be several reasons for the unequivocal findings regarding clinical and socio-demographic determinants of non-adherence in BD. The simplified and dichotomous approach to examining the association between these parameters and non-adherence in BD has usually ignored the complex relationship between several such variables. For example, the link with manic symptoms could well be related to the lack of insight or cognitive impairment during episodes rather than the severity of symptoms. Moreover, the pathways through which demographic and illness or medication related variables influence could include subjective factors such as attitudes, knowledge or other socio-environmental influences. Therefore, though some of these factors such as comorbid SUD or lack of insight may identify patient groups at higher risk for non-adherence, they cannot identify which of the patients from these high risk groups will go on to develop non-adherence.

Despite being based on a comprehensive search and a much larger number of studies than earlier reviews, the findings of this review were not without their limitations. Many reviews on the management of BD, which mention the problem of non-adherence in passing have not been included. In all likelihood the number of studies on medication non-adherence in BD is larger than the current list of studies, because some studies especially those publications not in English were probably missed. The relative lack of studies from non-Western countries was also a handicap. However, the principal shortcoming was the difficulty of drawing reliable conclusions from studies with such widely disparate methodologies. Nevertheless, it was quite evident that the rate of medication non-

adherence in BD was quite high and no different from other chronic psychiatric or medical disorders. The failure of demographic, illness and treatment related factors to predict non-adherence was also not entirely unexpected. However, this emphasizes the importance of other patient orientated factors in determining non-adherence in BD. Research over the last two decades or so has consistently endorsed the significance of several such factors including patients' attitudes and beliefs about medications, their treatment alliance with the health-care provider, their knowledge and causal beliefs about the illness, the influence of the family, and the role of stigma and treatment-access in determining non-adherence in BD^[200]. A patient-centred approach to non-adherence in BD is also in consonance with the current theoretical perspectives on medication-taking behaviour and the emphasis on combining pharmacological and psychosocial strategies to enhance adherence in BD^[201]. Therefore, future research which combines some of more consistent clinical and demographic correlates with patient-centred determinants is likely to predict non-adherence in BD with a greater degree of accuracy. Such an approach may also lead to a better understanding of this complex phenomenon and suggest more effective ways to deal with the continuing challenge of medication non-adherence in BD.

COMMENTS

Background

Previously published reviews on medication non-adherence in bipolar disorder (BD) have estimated rates to vary from around 8% to 68%, with mean rates ranging from 25% to 40% and median rates from 40% to 42%. However, these most of these reviews are based on a relatively small number of studies, are somewhat dated and have not comprehensively searched the existing literature. Given these drawbacks, the present review aimed to conduct a more comprehensive and systematic search for all studies estimating rates of medication non-adherence in BD and/or providing information on demographic, illness and medication related determinants of non-adherence.

Research frontiers

Treatment non-adherence in BD has attracted a lot of research attention lately because not only is it common in BD, but it also has a number of negative effects on outcome, and enhancing adherence has proved to be challenging.

Innovations and breakthroughs

The current review spanned four decades from 1976 to 2016 and was based on a more comprehensive search of the existing literature on medication non-adherence in BD. This resulted in a much larger list of close to 200 reviews and studies on the subject. Nevertheless, the results endorsed the consensus in existing literature that medication non-adherence is present in a third to about half of the patients with BD. There is also little consensus among earlier reviews regarding the association of clinical, demographic and treatment-related variables with medication non-adherence in BD. The present review clearly demonstrated that demographic and medication-related factors have little influence on medication non-adherence in BD, while among clinical factors only comorbid substance use disorder and absence of insight were clearly linked to non-adherence in BD.

Applications

The failure of clinical and demographic factors to predict non-adherence emphasizes the importance of other patient orientated factors in determining non-adherence in BD. Therefore, future research should also focus on patient-

centred determinants of medication non-adherence in BD and adherence interventions should emphasize the role of these factors.

Terminology

Adherence has been defined as "the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".

Peer-review

The manuscript is well organized and written, the used methodology is rigorous and the conclusions are coherent with the main findings.

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