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REVIEW ARTICLE

Medication Adherence in Patients with Bipolar Disorder: A Comprehensive Review

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Abstract Poor medication adherence is a pervasive problem that causes disability and suffering as well as extensive financial costs among individuals with bipolar disorder (BD). Barriers to adherence are numerous and cross multiple levels, including factors related to bipolar pathology and those unique to an individual's circumstances. External factors, including treatment setting, healthcare system, and broader health policies, can also affect medication adherence in people with BD. Fortunately, advances in research have suggested avenues for improving adherence. A comprehensive review of adherence-enhancement interventions for the years 2005–2015 is included. Specific bipolar adherence-enhancement approaches that target knowledge gaps, cognitive patterns, specific barriers, and motivation may be helpful, as may approaches that capitalize on technology or novel drug-delivery systems. However, much work remains to optimally facilitate long-term medication adherence in people with BD. For adherence-enhancement approaches to be widely adapted, they need to be easily accessible, affordable, and practical.

Key Points

To meaningfully address medication adherence in patients with bipolar disorder (BD), both patient-level and external barriers must be identified and targeted.

Psychoeducation, motivational interviewing, and cognitive behavioral treatment strategies can be effective in improving medication adherence in BD.

Future research should incorporate both subjective and objective methods of measuring adherence, with longer follow-up periods and targeted means of delivery that are easily accessible to patients with BD.

1 Introduction

Treatment adherence has been described as the degree to which a patient's behavior matches agreed-upon recommendations from a prescribing clinician [1, 2]. Poor adherence is a major problem for individuals with chronic health conditions, and the World Health Organization notes that half of individuals in developed countries do not take medications as recommended [2]. As Horne [3] notes, most people tend to evaluate a recommended course of treatment according to whether the recommendations make sense based on their personal experience, their beliefs about their illness or health conditions, and their expectations for treatment.

Bipolar disorder (BD) is a chronic and cyclical mood disorder that is responsive to a number of evidence-based

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foundational medication treatments, including lithium, some of the anticonvulsant mood-stabilizing medications, and antipsychotic drugs, particularly second-generation compounds [4]. As with other chronic health conditions, sustaining adherence is a problem for many individuals, with roadblocks to adherence stemming from a variety of factors.

This report on medication adherence in BD reviews the prevalence of poor adherence in BD, the barriers to and facilitators of adherence, and the consequences of poor adherence. Findings from a comprehensive review of interventions that specifically tested BD adherence-enhancement approaches are presented and discussed, as is the important issue of adherence to medications for general medical conditions among people with BD. As the rates of physical comorbidity and premature mortality are high in patients with BD, the latter is particularly important. The last portion of this report pulls together recommendations on psychosocial approaches that may be helpful in addressing poor adherence in BD, drug-delivery methods and logistic support that can enhance adherence, and current gaps in knowledge and directions for future research.

2 The Adherence Landscape in Bipolar Disorder (BD)

2.1 Prevalence

Expert consensus has defined medication non-adherence as missing 20 % or more of prescribed medication [5, 6], although some studies have used a more conservative cutoff of missing 30 % or more of prescribed medications [7, 8]. Psychotropic non-adherence in those with BD contributes to a gap in medication efficacy and effectiveness [9, 10]. Given that these medications are used both to treat active symptomology and as prophylaxis against illness recurrence, it is important to understand and address rates of medication non-adherence to optimize treatment success.

Estimates of medication non-adherence for patients with BD range from 20 to 60 % [10–13]. Rates of non-adherence vary significantly among studies, partly because of the heterogeneity of the patient samples. A 2012 cross-sectional study that included 150 outpatients with BD type I (BD I) found poor adherence in 32 %. This rate was based on patient and caregiver report along with serum drug levels, when available [14]. In a study aimed at determining factors affecting treatment adherence, Col et al. [15] found a non-adherence rate of 42.3 % as measured by the Treatment Adherence Rating Scale in their sample of 78 volunteers diagnosed with remitted BD I disorder. Some studies have found medication non-adherence rates to be closer to 25 %. Examples include a cross-sectional multicenter study using data from the fundamental advanced centers of expertise in bipolar disorder (FACE-BD). This study found that 25 % of the 382 patients with BD studied clearly exhibited poor adherence [16]. Similarly, a prospective cross-sectional study of 140 patients with BD I in a community health center found that 19.3 % of the patients were non-adherent with medication [8]. Finally, in 2015, Levin et al. [5] investigated a sample of 86 patients with BD, all of whom were recruited for poor medication adherence, and found baseline non-adherence rates to be 40.2 % 'in the past week' and 42.8 % 'in the past month'. This rate was based on a self-report of percentage of doses missed measured by the Tablets Routine Questionnaire (TRQ).

Another factor that affects the variable non-adherence rates in the BD population can be attributed to the way medication non-adherence is defined and measured. Studies use objective, subjective, or both types of measurements to quantify medication adherence. Examples of subjective methods used to assess medication adherence include patient self-report, provider or caregiver report, and chart review. Benefits of self-report methods include low cost/effort expenditure, immediate feedback, and being able to administer the method in a variety of settings [17]. While these methods are easy and practical, patients may tend to over-report their level of adherence on self-report scales [18, 19]. For instance, a cross-sectional study that included 114 patients with BD and 166 patients with schizophrenia found that adherence was 61.6 % based on blood levels and 86.3 % based on self-report using the 5-item Medication Adherence Report (MARS-5) [20]. Unfortunately, clinician prediction may be even less reliable than patient self-report, with accuracies of 50–60 % reported [21, 22]. Self-report scales frequently used to assess medication non-adherence include the Morisky-Green Scale [23], the Morisky 8-item Medication Adherence Scale (MMAS), the MARS [24], and the TRQ [7, 21].

Objective methods for measuring medication adherence include pill count, serum drug levels, pharmacy refill records, microchip placement on tablets that indicate when medication is taken, computerized pill caps that record openings, and electronic monitoring packs [9, 17, 25]. Although objective methods benefit from avoiding reliance on patient or caregiver report, they do present their own set of difficulties [26]. Monitoring systems that allow for recording pill bottle openings or pill removal from a blister pack can be expensive and could negatively affect the patient's view of their role as an active and autonomous agent in healthcare decisions [9, 23]. Reliance on the number of pill bottle openings can underestimate adherence if multiple pills are removed at once and overestimate adherence if the patient opens the pill bottle for reasons

other than taking their scheduled dose [27, 28]. Although automated methods of identifying and tracking medication taking might seem to be minimally affected by human error or social desirability bias, it is still possible to end up with missing or inaccurate data. Some patients may unintentionally or intentionally neglect to bring in the bottle with automated caps. Some patients take medications from their old, non-automated pill bottles instead of from the automated pill bottles. Other patients use pill boxes or pill minders that may make dose monitoring difficult. Likewise, pharmacy refill records and pill counts can lead to the overestimation of medication adherence if the patient receives the refill but does not take the medication as prescribed or removes pills without ingesting them.

Serum drug levels may accurately represent adherence if drawn randomly; however, if the patient selectively ingests medication a few hours prior to lab visits, a false appearance of adherence can be created [21, 29]. Additionally, medications that have long half-lives may lead to overestimation of adherence. In light of the potential inaccuracies of various objective methods for assessing medication adherence, use of more than one assessment method, including a subjective measure, is recommended [6].

2.2 Barriers

To determine how best to improve adherence in BD, it is critical to understand adherence barriers from the perspective of the patient as well as external factors (Table 1). Patient-level barriers include sociodemographic and clinical variables, characteristics of the illness, and psychological and cognitive factors. External barriers include such areas as medication/treatment, clinician, and system-level factors.

2.2.1 Patient-Level Barriers

Sociodemographic variables that affect medication adherence in BD include age, marital status, race and ethnicity, culture, and sex. Numerous studies report that a younger age, specifically below 40 years, is associated with worse adherence for BD medications [30–38]. Similarly, being unmarried or living alone has been identified as a risk factor for non-adherence [30, 31, 36, 39, 40]. However, it is important to note that not all studies have replicated this relationship [16]. Being non-White or identifying with a minority ethnic group was also found to predict medication non-adherence [31, 40–42]. This discrepancy may be the result of distrust, misdiagnosis, socio-economic factors, and a lack of non-White mental health professionals. Distrust may stem from the fact that non-White Americans are more negatively affected by prejudice and discrimination [43, 44]. Examples of misdiagnosis of non-White patients include the tendency to over-diagnose African Americans with schizophrenia and under-diagnose them with BD, whereas Asian Americans are generally under-diagnosed because a stereotype exists that the culture is "problem free" [45]. Non-White Americans are more likely to have lower socio-economic status and are thus less likely to have health insurance coverage [46], and the under-representation of non-White mental health professionals may deter some patients from various ethnic minorities from seeking care [44]. Additionally, certain ethnic groups may be more likely to be treated with different medications [47], leading to different side effect profiles, which may negatively affect adherence rates. Furthermore, it has been reported that cultural beliefs may affect adherence [48]. A review of the effects of culture on chronic mental illness suggested that cultural differences in language, communication, personality, and support system must be addressed to increase adherence [47]. For example, studies of African-Americans with BD report that some individuals fear addiction to medication and perceive that medication symbolizes and highlights them as being ill [49]. Additional sociodemographic variables associated with non-adherence include a lack of social support [15, 36] and homelessness [12, 36, 37].

The literature on sex and medication adherence in BD is inconsistent [19, 48]. While some studies found that men have poorer adherence [39, 48], others did not find a sex difference [7, 11, 50–52], and still others found that women have poorer adherence than men [14, 16, 53, 54]. The relationship between sex and medication adherence in BD is yet to be determined.

Clinical and illness characteristics potentially affecting medication adherence in BD include age of onset, length of illness, severity of symptoms, rapid cycling, and comorbidities, including substance abuse and personality disorders [38, 55]. An earlier age of BD onset has been associated with worse BD adherence in some [33] but not all studies [15, 30], whereas the literature indicates consistently that more severe BD symptoms are associated with worse medication adherence [30, 33, 34, 36, 39, 56]. Studying the relationship between duration of illness and adherence provides inconsistent results. While one study reports a positive correlation between illness duration and medication adherence such that individuals get better at maintaining adherence over time [16], another reports that longer treatment duration is associated with worse adherence [54]. Rapid cycling and high episode frequency have also been associated with worse medication adherence [31, 57] as has being in the midst of a manic/hypomanic episode [34, 36].

Comorbid conditions associated with non-adherence include substance use disorders [8, 35, 39, 40, 56, 58, 59], anxiety disorders [34, 57, 59], and personality disorders,

Table 1 Factors associated with poor adherence to medications for bipolar disorder

Factor	Directionality
Patient-level barriers	
Sociodemographic	
Age	Younger (<40 years)
Marital status	Unmarried or living alone
Race/ethnicity	Non-white or minority
Social support	Weaker
Clinical and illness characteristics	
Severity of symptoms	More severe symptoms
Episode characteristics	Rapid cycling, high episode frequency, manic/hypomanic episodes
Symptom characteristics	Psychotic
BD type	BD Type I
Comorbidities	Substance use and dependence, personality disorders, anxiety disorders
Suicidality	Higher frequency of past suicide attempts
Cognitive	Prospective memory deficits, executive functioning deficits, forgetfulness, working memory deficits, learning and recall deficits
Psychological	
Treatment beliefs	Low perceived need for treatment, negative attitude towards treatment, concerns with negative effects of treatment
Medication beliefs	Negative beliefs about side effects, negative attitude towards medication, fear of dependence, shame about medication taking, belief that medication is unnatural or unhealthy, discomfort with being controlled by medications, belief that one doesn't need medications when they feel better
Illness beliefs	Denial of illness and illness severity, negative attitudes towards illness
Personal beliefs	Poor motivation, limited insight, external locus of control
Influential beliefs of others	Stigma, family or social support belief that medication is unnecessary
External barriers	
Treatment related	
Side effects	Concerns about current and possible future side effects, weight gain, cognitive impairment, tremors, sedation
Treatment complexity	More complex regimens, more frequent dosing
Medication type	Early treatment with antipsychotics, antidepressants, first-generation antipsychotics
Quality of clinician–patient relationship	Low-quality
Systems Related	
Access to care	Poor
Medication cost	High

BD bipolar disorder

including antisocial, borderline, histrionic, and narcissistic personality disorders [14, 48, 59]. A number of studies have also identified the presence of psychotic symptoms and having BD I subtype as being associated with poor adherence [14, 19, 60]. Additionally, having a history of suicide attempts has been found to correlate with poor medication adherence in BD [38, 57, 61].

Prospective memory is an important cognitive variable that affects adherence. This is the ability to remember to carry out a given task at some point in the future and can be impaired in those with BD because of executive functioning deficits such as planning and cognitive flexibility [62, 63]. Thus, even when an individual intends to take medication, they might lack the planning or organizational abilities to do so consistently [63]. The literature indicates that forgetfulness and lack of routines is the most important reason for non-adherence in BD, from the perspective of both the patient and the provider [36]. Worse adherence to psychotropic medications has also been associated with worse performance on tests of working memory, prospective memory, and executive functioning in patients with BD who are positive for HIV [38]. Furthermore, whereas even adherent patients with BD evidence some cognitive impairment, including in the areas of attention, psychomotor speed, and verbal fluency, non-adherent patients are more likely to have impaired executive function

abilities and poor performance on learning and recall, functions vital for following complex medication regimens [60].

Various psychological variables such as medication, illness, and treatment beliefs also play an important role in medication adherence in BD. Low adherence relates to higher levels of concern regarding the adverse effects of treatment and lower levels of perceived need for treatment [58, 64]. Limited insight and denial of illness severity are also significant risk factors for non-adherence [8, 48, 65], as is a patient's inability to accept their disease in general [66]. One study found that almost half of the variance for poor adherence can be explained by the combination of perceived severity of illness and perceived benefits of treatment [67]. Other psychological variables that have been associated with poor adherence include poor motivation [59], stigma, and the perception of family and/or support groups that medication is either unnecessary or undesirable [8].

The literature also points to negative attitudes towards medication in general [38, 59, 68], attitudes towards illness [48], and negative attitudes towards a specific medication treatment [41, 59] as important predictors of medication adherence. Attitudes associated with poor adherence include a fear of dependence on the medication, shame about taking psychiatric medication, considering medication unnatural or unhealthy, discomfort with having one's mood controlled by medication [8, 38, 69], an unwillingness to take medication [66], and low self-efficacy for medication-taking behavior [38]. Similarly, an external locus of control, or a belief that life events are affected by uncontrollable outside forces, is associated with non-adherence [8], whereas an internal health locus of control is associated with better adherence [70]. This is particularly true for younger patients who hold the belief that they have more personal control over their illness [32]. Furthermore, providers perceive that a strong predictor of poor adherence is the patient's belief that they no longer need the medication during periods when they are feeling better [71].

2.2.2 *External Barriers*

Treatment-related adherence barriers with strong evidence in BD include that of perceived side effects, type of medication, number of medications prescribed, complexity of treatment regimens, and the quality of the clinician–patient relationship [72]. A number of studies identify concerns about current medication side effects as well as concerns about fear of possible side effects in the future as being associated with lower adherence [16, 36, 59, 66, 69, 73, 74]. Mago et al. [74] conducted a systematic literature review aimed at identifying the specific adverse effects associated with non-adherence in BD. They reported the most common to be weight gain, perceived cognitive impairment, tremors, and sedation [74].

A larger number of medications, higher doses of medication [54], and a more complex treatment regimen [32] are all associated with poorer adherence. While these associations may be a function of illness severity, an alternate explanation is that patients adhere better to treatments in the short run, but become uncomfortable with long-term medication use, a necessity in the treatment of chronic illnesses. Additionally, while the complexity of treatment could be construed as a reflection of severity of illness, it is also true that, as regimens become more complex, more intact executive functioning is required, an area identified as deficient in individuals with BD [60, 63]. A meta-analysis examining the relationship between dosing frequency and adherence in serious mental illness found an overall trend of worse adherence with more frequent dosing, but these findings were not for BD specifically [75].

A number of studies have identified medication type as an important predictor of non-adherence [9, 35]. Most of this work has focused on the use of antipsychotics in the treatment of BD. Lang et al. [35] report that being in the early stages of treatment with an antipsychotic agent is a predictor for non-adherence and that second-generation antipsychotics are associated with better adherence than are first-generation antipsychotics [76]. Similarly, Gianfrancesco et al. [54] reported that, for the most part, adherence is better with second-generation than with first-generation antipsychotics and that switching from one antipsychotic agent to another (presumably trying to optimize drug response) is associated with better adherence. Another important and consistent finding is that the use of antidepressants for the treatment of BD is associated with worse adherence [35, 39]. Conversely, treatment with a mood stabilizer, anticholinergic medication, or anticonvulsant has been a predictor of better adherence [35].

System-related barriers to medication adherence include poor access to care and unaffordable medication costs [19, 77]. Studies indicate that poor access to psychiatric providers is associated with poor adherence to BD medications [41, 77]. Furthermore, there is a significant relationship between cost-sharing and adherence to BD medication such that the higher the patient cost, the lower the adherence and the shorter time to discontinuation [78].

2.3 Facilitators

To address and improve medication adherence in BD, it is important to identify not only the barriers but also the facilitators of medication adherence. Based on data from a large multicenter treatment program for BD, Sylvia et al.

[77] reported that perceived collaboration with, empathy from, and accessibility to providers facilitate adherence to medication regimens; however, providers' degree of experience and discussion of medication risks and benefits do not predict adherence. Strauss and Johnson [79] also found that strong therapeutic alliance led to improved medication adherence by changing illness and medication attitudes. Similarly, Zeber et al. [80] reported a positive relationship between treatment alliance and medication adherence, and Reilly-Harrington and Sachs [81] recommend the use of collaborative patient–provider treatment contracts that incorporate treatment expectations, including adherence and provider availability and accessibility. In addition to treatment alliance, strong social support has been associated with better medication adherence in patients with BD [15].

Given that better insight into the value of medication in the treatment of BD is associated with improved adherence [39, 82], ensuring that individuals with BD understand how medications can affect symptoms and outcomes may optimize adherence. Similarly, an accepting attitude regarding medication treatment consisting of high levels of treatment necessity beliefs and low levels of concerns regarding treatment is associated with the best medication adherence [64], suggesting that taking the time to explain potential side effects and how these side effects might be dealt with could set the stage for appropriate expectations and accepting attitudes.

Medication adherence in BD appears better when providers consider patient medication preferences [83, 84]. Going further, Wilder et al. [83] found that using a tool for psychiatric advance directives that identified both preferred medications and medications that patients were unwilling to take improved adherence to psychiatric medications. Finally, Basco and Smith [85] point out that an important consideration is that medication-taking decision-making may change over time; thus, to facilitate long-term medication adherence, providers need to reassess potential barriers throughout the course of treatment.

It should be noted that many of these facilitators are not easily achieved. Many individuals with serious mental illness in the USA are unable to access mental healthcare providers [86] because those with mental illness are less likely to have adequate health insurance [87, 88]. Furthermore, even individuals who do have health insurance coverage may not have access to mental healthcare given the inadequate number of available mental health providers across the USA [89]. Also, collaborative patient–provider treatment contracts and advance directives about preferred medications are not currently in routine practice in the American healthcare system. It is recommended that future comparative adherence research be carried out across health systems in the USA as well as between the USA and countries with more accessible mental healthcare. Also, research comparing adherence between the USA and countries that routinely incorporate patient preferences into the treatment of mental health would add to our knowledge. Finally, it is imperative that steps are taken to disseminate research findings such that they translate into changes in routine clinical care.

2.4 Consequences of Non-Adherence

Providing factual information to patients and families about adherence can help promote medication adherence. Understanding the consequences of poor adherence can also assist clinicians with adherence monitoring and promotion. There is strong evidence that non-adherence to BD medications increases BD symptoms [21, 90–93]. In a recent study, Li et al. [92] reported that adherence to medication was the strongest independent predictor of 1- and 2-year recurrence rates of manic or depressive episodes, performing better as an independent variable than sex, type of BD, medication type, and lack of family support [92]. A large, prospective Pan-European study analyzed 1341 patients from an outpatient setting over 21 months of BD maintenance treatment following an acute manic or mixed episode. Medication non-adherence was associated with lower frequency of remission and recovery and higher frequency of recurrence, relapse, and hospitalization [93]. Furthermore, partial non-adherence has also been shown to be harmful. In BD patients with partial adherence resulting in sub-therapeutic medication concentrations, 18-month hospitalization rates were 81.2 versus 9.7 % for fully adherent participants [21]. Baldessarini et al. [94] found that rapid discontinuation of lithium produced more mania or depression recurrences than gradual discontinuation; they posited that discontinuing treatment may engender more BD recurrences than taking no medication at all due to pharmacodynamic adaptation. Thus, drug discontinuation syndromes could at least partially explain the markedly increased BD symptoms of non-adherent patients.

Non-adherence is also related to other psychological concerns. Suicide attempts, completed suicide, and early mortality in BD have all been linked to poor adherence [21, 93, 95, 96]. In a multivariate analysis relating independent variables to post-treatment suicidality, non-adherence was second only to pre-treatment suicidality, associating more strongly with post-treatment suicidality than having a depressive recurrence during treatment [95]. Additionally, a cross-sectional study identified a correlation between number of manic episodes and neurocognitive dysfunction after accounting for depression, disease chronicity, onset, and medication type [97]. The authors suggest that reducing manic episodes by improving adherence could be neuroprotective [97].

Non-adherence to BD medication increases risks for unstable housing status. The relative odds of lifetime homelessness were greater for non-adherent individuals, even after controlling for incarceration history [98]. In a Florida study in individuals with either schizophrenia or BD, people with a lower medication possession ratio (MPR) had a higher risk of subsequent arrest and a higher mean number of days of incarceration [99]. However, more BD-specific data are needed to fully understand the social impact of non-adherence.

These individual-level consequences precipitate systems-level costs. One study using Medicaid claims data determined that hospitalization rates were 73 % for irregular BD medication users compared with 31 % for regular users [100]. Additionally, average lengths of stay were 37 versus 4 days, and mean costs were $US9701 versus $US1657 for irregular and regular BD medication users, respectively [100]. A series of case studies illustrated that 6-year hospitalization costs (excluding outpatient costs) for one non-adherent BD patient equaled a state Medicaid budget for 13 enrollees with BD [101]. During the 21-month period in the Pan-European study, costs incurred by non-adherent patients were more than double the costs for adherent patients, mainly as a function of inpatient hospitalization cost [93]. In another longitudinal study, a higher MPR (better adherence) was associated with decreased total mental healthcare expenditures [102]. Finally, individuals with BD or schizophrenia who were non-adherent incurred higher incarceration costs [99].

2.5 Medical Morbidities

Given that individuals with BD have a mortality rate two to three times that of the general population [103–105], evaluating the role of medication non-adherence in physical health among people with BD is vital [7, 8, 19]. Cardiovascular disease accounts for the largest number of deaths in individuals with BD [103–105] and has been attributed to risk factors such as higher rates of obesity, hyperlipidemia, hypertension, diabetes, dyslipidemia, higher rates of smoking, and a lack of physical activity in this population [106]. Poor BD medication adherence is likely to worsen overall health in those with BD [7, 8, 18, 19]. Although data on adherence patterns with medication treatments for general medical conditions specific to those with BD are limited, it is plausible that improving adherence to both psychiatric and non-psychiatric medication has the potential to improve the physical health status of individuals with BD overall and may be one approach to reducing premature mortality.

There is widespread evidence that psychological factors such as depression are associated with increased non-adherence to medications for various chronic medical conditions [16, 107–110]. Levin et al. [111] recently reported that there is no significant correlation between psychotropic and non-psychotropic medication adherence in patients with BD, suggesting that medication patterns for one medication are not necessarily the same for all types of medications. Furthermore, while poor adherence to medication for medical conditions is a significant problem for people with BD, adherence rates for BD drugs are even worse [111]. Underscoring the likelihood that BD symptoms impair medication-related decision making generally, there is a significant correlation between more severe psychiatric symptoms as measured by the Brief Psychiatric Rating Scale (BPRS) and the Montgomery-Åsberg Depression Rating Scale (MADRS) and worse adherence with drug treatments for medical conditions among those with BD [111, 112]. Specifically, the physiological manifestations of depression on the MADRS and anxiety, guilt, depressed mood, and somatic concern on the BPRS were correlated with worse adherence to non-psychiatric medications [112]. Thus, targeting psychiatric symptoms in this population has the potential to improve medication adherence for non-psychiatric medications, and may thus lead to improved health outcomes.

2.6 Approaches to Improve Medication Adherence in BD

2.6.1 A Review of Interventions Specific to BD Adherence

The comprehensive review focused on data published in the past 10 years to ensure a streamlined presentation of updated research and to add to literature rather than reiterate the findings of previous systematic reviews. We searched PubMed, OVID MEDLINE, PsycInfo, Cochrane, CINAHL, and Embase for prospective trials to improve adherence in BD available in English between January 2005 and December 2015. Studies that looked at serious mental illness as a whole were included if they reported specific adherence data in a BD population. Studies with other psychological or medical comorbidities were also included as long as all participants had BD. Studies were excluded if they focused only on feasibility, if adherence was not the primary focus, if adherence was just one of a list of multiple outcomes, or if participants were aged <18 years. For each database, the search strategy used a combination of the following keywords: bipolar, manic-depressive, serious mental illness, adherence, compliance, medication adherence, concordance, non-adherence, treatment, clinical trial, intervention, intervention trial, adherence promotion. This search was supplemented with manual searches of the reference sections of relevant articles.

The search strategy identified 1012 citations, including duplicates, from all six databases and from the manual

search. We reviewed 120 titles/abstracts; 110 of these did not meet inclusion criteria or were duplicates. Overall, ten studies met inclusion criteria.

To determine the methodological rigor of the identified included studies, we used the Methodological Quality Rating Scale (MQRS). This 12-item instrument has been used to identify the quality of studies in systematic reviews [113, 114].

Table 2 presents a summary of the ten studies reviewed, including the MQRS score, study design, description of the intervention/s, how adherence was measured, and adherence results. MQRS scores ranged from 7 to 11 with an average of 8.9.

Nine of the ten studies reviewed included a psychoeducation component as either part or the entirety of the intervention [115–123]. Two of the studies, both randomized controlled trials, utilized only psychoeducation. Both of these studies reported an increase in the proportion of patients defined as adherent following psychoeducation but not following the control treatment [118, 119]. Another study evaluated the effectiveness of a standardized psychoeducation intervention, the Life Goals Program, delivered in a group format. Results from this randomized controlled trial found no significant difference on medication attitude scores between the intervention and control groups at the 12-month follow-up [117].

Two uncontrolled studies evaluated 'customized adherence enhancement' (CAE), a modular format intervention that includes psychoeducation, motivational enhancement therapy, communication with providers, and medication routines [115, 116]. The intervention is customized such that only those modules deemed relevant to an individual's specific needs based on predetermined criteria (see Sajatovic et al. [115] for guidelines) are administered. The results of both CAE studies indicate a significant improvement in adherence.

Similar to the motivational enhancement therapy module of CAE, two studies in this review utilized motivational interviewing as the intervention or as a component of the intervention. One non-controlled study used motivational interviewing specifically focused on increasing medication adherence in BD. In this study, each participant's behavior, efficacy, confidence, and readiness to change was reviewed and the intervention was then customized to the participant's needs. Results from this study found a significant increase in adherence [120]. Another study that included both motivational and psychoeducational elements comprised four components: education, motivational training, medication management, and symptom management. This intervention was derived from interventions utilized for adults with BD and was adapted for older adults. The results of this uncontrolled study indicated a decrease in the percentage of participants reporting missed medication doses and problems taking medication [121].

Another two studies evaluated the effectiveness of psychosocial interventions. The first randomized controlled trial utilized the 'integrated treatment adherence program', an intervention that incorporates a cognitive behavioral model of therapy to help patients transition from acute care to maintenance treatment [122]. Although this study did not focus entirely on enhancing medication adherence, the results showed a trend over time for increasing the relative number of adherent patients but not the degree of adherence in the treatment compared with the control group. This study recruited patients with comorbid BD and substance use [122]. Another randomized controlled trial incorporated cognitive behavioral theory with a novel method of delivery aimed to improve adherence in individuals with comorbid BD who were HIV positive. 'Individualized texting for adherence building' (iTAB) stems from the theory of planned behavior and used reminders and reinforcement text messages that were automated and individualized for each participant. The study results indicated that the treatment group took their medication significantly closer to the intended time than the control group, but no differences were observed when their adherence was marked on a visual analog scale [123].

The only study that did not incorporate psychoeducation as part of the intervention utilized financial incentives to improve adherence. This cluster randomized controlled trial offered patients a financial incentive for every long-acting injection (LAI) they received, with a common interval between injections of 1–4 weeks. The results indicated a significant improvement in adherence compared with the control group [124].

It is notable that our review of current adherence interventions revealed the use of many similar components as well as methodological limitations. The only studies that did not report an improvement in adherence were the Life Goals group-format intervention, which may not have had adequate participation, the iTAB mobile intervention, which may have had a ceiling effect given that rates of adherence were very high across the board, and the 'integrated treatment adherence program', which did not solely focus on medication adherence. All of the interventions utilized a psychosocial approach, most incorporating a psychoeducational component.

A major limitation of published studies featuring BD adherence interventions is that there was no standard for measuring adherence. Almost all of the studies utilized different methods of assessing adherence, making it difficult to compare adherence results. Even studies using the same measures did not always administer or score them in the same way. Furthermore, while most of the studies measured adherence using some type of self-report, some outcomes

Table 2 An updated review of studies on bipolar disorder adherence enhancement

Study	Sample	Study design	Intervention	Control	Adherence measurement	Adherence results	MQRS score
McKenzie et al. [120]	15 pts from a private outpatient psychiatry office	Pre–post	3-week motivational interviewing: 1 face-to-face session (45–60 min) and two scripted follow-up phone sessions	None	MARS: 10 yes/no style questions; higher scores indicate worse adherence TLFB: a semi-structured interview that determined % of pills taken in the past 30 days	Significant improvement on MARS score such that non-adherence decreased from 4.3 to 2.2. Adherence on the TLFB increased from 67.8 to 94.3 %	8
Depp et al. [121]	21 community-dwelling pts with BD aged >50 y	Quasi-experimental	12-week medication adherence skills training for older adults: combined educational, motivational, medication-management skills and symptom-management training	None	Two items from the Modified TRQ: "how many doses of medications did you miss in the past week?" and "do you have any trouble taking all of your prescribed medications?" Pts dichotomized into adherent or non-adherent; those reporting any missed doses on the first question considered non-adherent	Percentage of pts reporting non-adherence to BD medications declined by 15 % Percentage of pts reporting problems with taking medications declined by 31 %	7
Eker and Karkin [118]	71 (36 in tx group, 35 controls) pts at a University Hospital-based mood disorder outpatient clinic	Semi-experimental: utilized both randomized control groups and pretest–post-test	6 weekly 90- to 120-min psychoeducation sessions	Control group trained by doctor about medication in outpatient setting for 5–10 min	Pts dichotomized into adherent/non-adherent; non-adherent if failed to meet adherence criteria on two or more of the following: (1) ANT: a score of <75 % = non-adherent; (2) MARS: a score of 1–7 = non-adherent; (3) McEvoy Treatment Observation Form completed by caregivers; anything other than active adherence = non-adherent; (4) Changed dosage without prescriber's direction = non-adherent; (5) Quit tx = non-adherent	Significant increase in proportion of adherent individuals from 40 % before to 86.7 % following psychoeducation Significant difference between intervention and control groups in proportion of adherent pts with active tx leading to a higher proportion of adherence	10
Moore et al. [123]	50 (25 in tx group, 25 controls) with HIV and BD	RCT	Automated, personalized, two-way text messaging system that sends educational, motivational, and reminder text messages via cellphone	Active control – standard of care adherence including psychoeducation and daily text mood inquiries	MEMs takes an electronic record of frequency and time cap is removed VAS: pts mark a line anchored from 1 to 100 representing their adherence to tracked medication	Tx group took medication significantly closer to the intended time Both tx and control groups showed high levels of 30-day MEMS adherence Non-adherence rates by VAS were not significantly different between control (54.5 %) and tx groups (41.7 %) No significant change in adherence rates by intervention group on MEMS and VAS	10

Table 2 continued

Study	Sample	Study design	Intervention	Control	Adherence measurement	Adherence results	MQRS score
Priebe et al. [124]	131 (75 in tx group, 56 controls) from community mental health teams	Cluster RCT	Pts given $22 for each depot injection over a year	Tx as usual	Percentage of prescribed depots given	Significant improvement in adherence from 69 % pre-tx to 85 % post-tx	11
Javadpour et al. [119]	108 (54 in tx group, 54 controls) recently discharged inpatients	RCT	Individual psychoeducation delivered in 8, 50-min weekly sessions followed by monthly phone follow-up care and psychological support for 18 months	Pharmacotherapy alone	MARS: higher scores indicative of more adherence	Pts in the psychoeducation group scored higher than controls on MARS at 6-, 12-, and 18-month follow-up	9
Sajatovic et al. [115]	43 non-adherent BD pts prescribed atypical antipsychotics, receiving care at academic medical center or affiliated sites	Pre–post	CAE: 6-week individual needs-based manualized modular intervention focused on medication adherence	None	TRQ: self-report measure that identifies % of days with missed doses in previous 7 or 30 days Morisky Rating: 4-item self-report measure of adherence	Non-adherence decreased from 32 % at BL to 13 % at 3 month follow-up for past week Morisky scores improved significantly from BL to 3 months	7
Sajatovic et al. [116]	43 non-adherent BD pts prescribed mood stabilizers or antipsychotics, recruited from community mental health centers	Pre–post	CAE: 6-week individual needs-based manualized modular intervention focused on medication adherence	None	TRQ: self-report measure identifies % of days with missed doses in previous 7 or 30 days	Non-adherence decreased from 48 % in past week at BL to 25 % at 6-month follow- up Non-adherence decreased from 51 % in past month at BL to 21 % at 6-month follow- up	8
Wenze et al. [122]	30 (14 in tx group, 16 controls) pts with BD and comorbid substance use from inpatient hospital units and at-risk outpatients	RCT	Integrated Treatment Adherence Program: 6-month cognitive behavioral approach including three individual sessions, one family session with significant other, and 11 brief phone contacts	Enhanced Assessment and Monitoring: pt providers were mailed feedback letters after study assessments	Adapted MCQ – self-reported number of missed doses based on pt or pt's significant other. Degree of non-adherence determined on a 0–4 scale (0 = never missed, 1 = missed 1–2, 2 = missed 3–7, 3 = missed >7, 4 = stopped completely) and a dichotomous scale (missed 0–2 versus missed ≥3 or stopped against medical advice)	Trend towards increased adherence over time in the tx group as measured by dichotomous categories of adherent/non-adherent but not degree of non-adherence	9
Sajatovic et al. [117]	164 (84 tx group, 80 controls) pts with BD from a community mental health center	Randomized controlled study	Life Goals Program: 6 weekly manual-driven structured group psychotherapy sessions focused on illness education, management, and problem solving followed by optional unstructured monthly group sessions	Tx as usual	DAI: self-report, true–false format questionnaire Self-reported medication adherence estimate rated on a scale of (0, 25, 50, 75, or 100 %) within the past 30 days	No significant difference between intervention and control at 12-month follow-up in DAI scores or self-reported adherence estimate	10

ANT attitude toward neuroleptic treatment, *BL* baseline, *BD* bipolar disorder, *CAE* customized adherence enhancement, *DAI* Drug Attitude Inventory, *MARS* Medication Adherence Rating Scale, *MCQ* Medication Compliance Questionnaire, *MEMS* medication event monitoring system, *MQRS* Methodological Quality Rating Scale, *pt(s)* patient(s), *RCT* randomized controlled trial, *TLFB* Timeline Followback Interview, *TRQ* Tablets Routine Questionnaire, *tx* treatment, *VAS* visual analogue scale

categorized adherence as a dichotomous variable (adherent versus non-adherent), whereas others reported an ordinal variable such as the percentage of days with missed doses or a continuous variable such as the number of doses missed. Few studies included an objective measure of adherence aside from iTAB and the direct observation of receiving a depot injection [123, 124]. Another methodological issues was the absence of a control group in a number of studies. Finally, for any prospective trial on medication adherence, it is likely that patients with the worst adherence will not agree to participate in a research study to begin with; thus, findings cannot be generalized to the entire population of poorly adherent individuals with BD.

Overall, this comprehensive review suggests that psychoeducation, motivational interviewing, financial incentives, and cognitive behavioral treatment strategies can be effective in improving medication adherence in BD. However, no single intervention stands out as having sufficient efficacy to recommend it above others. There is a clear need for future research that incorporates both subjective and objective methods to measure adherence, sustains adherence for longer follow-up periods, and can be scaled-up to be easily accessible to patients with BD.

2.7 Optimizing Medication Taking in People with BD

2.7.1 Psychosocial Interventions

Psychosocial interventions can be divided into two main categories: those aimed at self-management of BD more broadly and those that focus on enhancing medication adherence more specifically. The results from the literature review taken together with a more general review of the literature on this topic support the use of psychoeducation, motivational interviewing, immediate positive reinforcement in the form of financial incentives, family-based interventions, and cognitive behavioral therapy, when delivered in an individual format, to improve medication adherence [125, 126]. There is also some support that reminders improve the timing of doses. However, a number of unanswered questions remain, including which interventions work for which individuals, how many sessions are sufficient, how adherence can be maintained long term, and how interventions can be pushed out or scaled up to reach all sectors of the population with BD.

2.7.2 Making Drugs Easier to Remember to Take

How drugs are packaged, delivered, or ingested, and the logistics of aiding people to remember to take drugs are all important in drug adherence. Studies on novel drug-delivery systems and logistic strategies to improve medication adherence in BD patients are sparse, and most evidence at this stage is extrapolated from studies in general medical settings or from experience with other mental health conditions. Studies have suggested that simplification of dosing, such as less frequent administration, avoiding medications with special or complicated dosing requirements, use of pill boxes or medication organizers, and coordinating dosing time with activities of daily living may be helpful in maximizing adherence [127–130]. Studies of blister packaging of medications, often including a calendar of days, have shown a positive effect on medication adherence [131, 132]. Evidence from general medical populations could have applicability to patients with BD. For example, Vrijens et al. [133] found enhanced atorvastatin adherence following the introduction of a device programmed to beep at dosing time for patients with high cholesterol. Personal programmable pill boxes holding up to 1 month of medication can feature alarms, dosage, and mode of administration indicators. Tracking occurs upon removing dosages from the box, and providers can be sent information regarding adherence [134]. Similarly, electronic monitoring systems contained in blister pack labels can record removal of a unit dose from a blister pack [28]. Further, Proteus Digital Health recently combined aripiprazole with an ingestible digital sensor that could send adherence information to healthcare providers [135].

Specific to BD, Sajatovic et al. [136] used a technology-facilitated multi-component adherence-enhancement system in five individuals with BD. The system components included (1) an automated pill cap with remote monitoring sensor; (2) a multimedia adherence-enhancement program; and (3) a treatment incentive program. This study evaluated system usability, patient satisfaction, and effects on adherence (Morisky Scale), knowledge (Treatment Knowledge Test [TKT]), and symptoms (Internal State Scale [ISS]). Usability scores were high overall, mean Morisky scores improved, and means on all four subscales of the ISS were all in the direction of improvement. The TKT showed a 40 % increase in mean scores [136]. Another BD-specific study demonstrated that a 2-week ecological momentary intervention (EMI) delivered via personal digital assistants (PDAs) was feasible and had the potential to improve adherence, with participants in this pilot reporting missing medication only 3 % of the time [137]. This intervention involved twice-daily prompts asking patients to report their adherence behaviors as well as symptoms and other non-adherence risk factors. Other studies on EMI approaches have also reported high feasibility and efficacy in treating BD more broadly [138, 139]. Given the promise of this area, it is recommended that future research assess the efficacy of EMI approaches for improving adherence.

Alternatives to standard oral drugs need exploration in BD, as different or novel drug-delivery formats have the potential to improve adherence. LAI forms of antipsychotic medication are used for people with serious mental illness and may be particularly helpful for patients who are unintentionally non-adherent [140, 141]. A number of LAI antipsychotic agents are currently available, although only LAI risperidone is approved for maintenance treatment of BD in the USA, Taiwan, and most European countries [142]. A recent consensus of experts from Taiwan recommended LAI antipsychotics in BD patients with poor adherence [143]. This group of experts specified that LAI antipsychotics should be considered in patients with multiple episodes and low adherence or rare but serious illness exacerbations and in those at high risk for low adherence based on clinician judgment, according to patient preference for an injectable medication, and to target residual symptoms despite the use of multiple oral agents [143]. The 2013 update of the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines also include long-acting risperidone injection as a first-line agent for maintenance treatment of BD [144]. It is important to note that another benefit of the use of LAIs is that it allows the provider to promptly identify and address non-adherence if the injection appointment is missed [145].

While injectable drugs may be a solid alternative, it is also important to consider alternative oral formulations that do not require swallowing a standard pill. Patients may have anxiety regarding swallowing pills or true physical difficulties that impair this ability. As such, palatable gummies (oral chewable formulations) have been used to deliver certain medications and vitamins. A recent publication described aripiprazole gummi drops, which have the potential to increase patient adherence as gummi drops are easily chewed and swallowed and do not require water [146]. Additionally, liquid formulations, orally disintegrating tablets (ODTs), or fast-dissolving sublingual formulations may be preferable [147, 148]. A study of 97 individuals with mood disorders (including BD) who had pill-swallowing difficulties and were receiving the anticonvulsant mood stabilizer lamotrigine were switched from standard immediate-release pills to ODTs. Patient satisfaction and convenience were measured using the Treatment Satisfaction Questionnaire for Medication (TSQM). Also measured were global psychopathology using the Clinical Global Impression—Severity (CGI-S) index and depressive symptoms using the Beck Depression Inventory (BDI)-II. The study found that lamotrigine ODT was significantly more convenient than standard pills, with no other differences in TSQM, CGI-S, or BDI-II scores [149].

Overall, building technology-facilitated supports into drug-delivery systems may help individuals remember to take BD medications as directed. Both LAI medications and non-standard oral formulations hold promise for improving adherence in some patients. Given the heavy personal and societal burden of poor adherence, longer-term and more rigorous studies using technology and novel drug delivery are necessary.

3 Conclusions

As noted in our review, poor adherence in BD is a pervasive problem that causes disability and suffering as well as extensive financial costs. Barriers to adherence are many and cross multiple levels, including factors related to BD pathology and factors unique to an individual's genetic, psychological, and social circumstances. The treatment setting, healthcare system, and broader health policies can all affect medication adherence in BD.

Fortunately, advances in research suggest avenues for improving BD adherence. Specific psychotherapeutic approaches that target knowledge gaps, cognitive patterns, specific adherence barriers, and motivation may all be helpful in improving adherence. However, for adherence-enhancement approaches to be widely adapted, they need to be easily accessible, affordable, and practical. Using technology-facilitated approaches could help address accessibility and maximize generalizability. Future research needs to include the testing of dissemination approaches and to partner with large health systems to use the electronic health record for simultaneously tracking medication prescribing, adherence, and BD outcomes. A key component in scaling adherence promotions to real-world settings is ensuring that care approaches that use health professionals be reimbursed by standard payers, including Medicaid. For this, it will be critical to engage patients and family advocates and other stakeholders to press for policy that provides this essential support.

Alternative drug-delivery formats are showing promise in adherence promotion. Second-generation drugs, which are widely used to treat BD, can be administered in LAI formulations that eliminate the need for daily dosing and daily risk of non-adherence. Recently, formulations of antipsychotics that last beyond 30 days have become available, and how these newer formulations may impact BD adherence over the long-term needs further investigation. Brissos et al. [150] conducted an excellent review of long-acting antipsychotic drugs in schizophrenia. It summarizes a number of exciting new formulations that may also be highly relevant for people with BD, such as transdermal patches and subcutaneous antipsychotic drug implants [150]. These and other novel drug-delivery systems should be tested in BD.

Finally, an important gap in our understanding is how best to enhance adherence with medications for general

medical conditions in people with BD. The research specific to this topic is quite limited. Whereas it is likely that some of the barriers are similar to adherence barriers with BD drugs, there is evidence to suggest that roadblocks (and solutions) are likely not identical. Development and testing of approaches to improve adherence to treatments such as antihypertensive drugs and cholesterol-lowering agents in people with BD are critically needed to address the premature mortality due to cardiovascular risk that we see in this group of individuals.

Compliance with Ethical Standards

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References

1. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2008;(2):CD000011.
2. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: WHO; 2003. p. 3.
3. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest. 2006;130(1 Suppl):65S–72S.
4. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016;30(6):495–553.
5. Levin JB, Tatsuoka C, Cassidy KA, Aebi ME, Sajatovic M. Trajectories of medication attitudes and adherence behavior change in non-adherent bipolar patients. Compr Psychiatry. 2015;58:29–36.
6. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70(Suppl 4):1–46 **(quiz 7–8)**.
7. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry. 2002;63(5):384–90.
8. Sajatovic M, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, et al. Predictors of nonadherence among individuals with bipolar disorder receiving treatment in a community mental health clinic. Compr Psychiatry. 2009;50(2):100–7.
9. Berk L, Hallam KT, Colom F, Vieta E, Hasty M, Macneil C, et al. Enhancing medication adherence in patients with bipolar disorder. Hum Psychopharmacol. 2010;25(1):1–16.
10. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatr Scand. 2002;105(3):164–72.
11. Colom F, Vieta E, Martinez-Aran A, Reinares M, Benabarre A, Gasto C. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. J Clin Psychiatry. 2000;61(8):549–55.
12. Sajatovic M, Valenstein M, Blow FC, Ganoczy D, Ignacio RV. Treatment adherence with antipsychotic medications in bipolar disorder. Bipolar Disord. 2006;8(3):232–41.
13. Licht RW, Vestergaard P, Rasmussen NA, Jepsen K, Brodersen A, Hansen PE. A lithium clinic for bipolar patients: 2-year outcome of the first 148 patients. Acta Psychiatr Scand. 2001;104(5):387–90.
14. Murru A, Pacchiarotti I, Amann BL, Nivoli AM, Vieta E, Colom F. Treatment adherence in bipolar I and schizoaffective disorder, bipolar type. J Affect Disord. 2013;151(3):1003–8.
15. Col SE, Caykoylu A, Karakas Ugurlu G, Ugurlu M. Factors affecting treatment compliance in patients with bipolar I disorder during prophylaxis: a study from Turkey. Gen Hosp Psychiatry. 2014;36(2):208–13.
16. Belzeaux R, Correard N, Boyer L, Etain B, Loftus J, Bellivier F, et al. Depressive residual symptoms are associated with lower adherence to medication in bipolar patients without substance use disorder: results from the FACE-BD cohort. J Affect Disord. 2013;151(3):1009–15.
17. Voils CI, Maciejewski ML, Hoyle RH, Reeve BB, Gallagher P, Bryson CL, et al. Initial validation of a self-report measure of the extent of and reasons for medication nonadherence. Med Care. 2012;50(12):1013–9.
18. Sajatovic M, Chen PJ, Dines P, Shirley ER. Psychoeducational approaches to medication adherence in patients with bipolar disorder. Dis Manage Health Outcomes. 2007;15(2):181–92.
19. Busby KK, Sajatovic M. REVIEW: patient, treatment, and systems-level factors in bipolar disorder nonadherence: a summary of the literature. CNS Neurosci Ther. 2010;16(5):308–15.
20. Jónsdóttir H, Opjordsmoen S, Birkenaes AB, Engh JA, Ringen PA, Vaskinn A, et al. Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. J Clin Psychopharmacol. 2010;30(2):169–75.
21. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. Am J Psychiatry. 2002;159(11):1927–9.
22. Byerly M, Fisher R, Whatley K, Holland R, Varghese F, Carmody T, et al. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. Psychiatry Res. 2005;133(2–3):129–33.
23. Koschack J, Marx G, Schnakenberg J, Kochen MM, Himmel W. Comparison of two self-rating instruments for medication adherence assessment in hypertension revealed insufficient psychometric properties. J Clin Epidemiol. 2010;63(3):299–306.
24. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res. 2000;42(3):241–7.
25. Velligan DI, Kamil SH. Enhancing patient adherence: introducing smart pill devices. Ther Deliv. 2014;5(6):611–3.
26. Levin JB, Sams J, Tatsuoka C, Cassidy KA, Sajatovic M. Use of automated medication adherence monitoring in bipolar disorder research: pitfalls, pragmatics, and possibilities. Ther Adv Psychopharmacol. 2015;5(2):76–87.
27. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. J Psychosom Res. 2010;69(6):591–9.
28. van Onzenoort HA, Neef C, Verberk WW, van Iperen HP, de Leeuw PW, van der Kuy PH. Determining the feasibility of objective adherence measurement with blister packaging smart technology. Am J Health Syst Pharm. 2012;69(10):872–9.

29. Vieta E, Pacchiarotti I, Scott J, Sánchez-Moreno J, Di Marzo S, Colom F. Evidence-based research on the efficacy of psychologic interventions in bipolar disorders: a critical review. Curr Psychiatry Rep. 2005;7(6):449–55.
30. Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J Affect Disord. 2013;149(1–3):247–52.
31. Pompili M, Venturini P, Palermo M, Stefani H, Seretti ME, Lamis DA, et al. Mood disorders medications: predictors of nonadherence—review of the current literature. Expert Rev Neurother. 2013;13(7):809–25.
32. Hou R, Cleak V, Peveler R. Do treatment and illness beliefs influence adherence to medication in patients with bipolar affective disorder? A preliminary cross-sectional study. Eur Psychiatry. 2010;25(4):216–9.
33. Barraco A, Rossi A, Nicolò G, Group ES. Description of study population and analysis of factors influencing adherence in the observational Italian study "Evaluation of Pharmacotherapy Adherence in Bipolar Disorder" (EPHAR). CNS Neurosci Ther. 2012;18(2):110–8.
34. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. Hum Psychopharmacol. 2008;23(2):95–105.
35. Lang K, Korn J, Muser E, Choi JC, Abouzaid S, Menzin J. Predictors of medication nonadherence and hospitalization in Medicaid patients with bipolar I disorder given long-acting or oral antipsychotics. J Med Econ. 2011;14(2):217–26.
36. Sajatovic M, Levin J, Fuentes-Casiano E, Cassidy KA, Tatsuoka C, Jenkins JH. Illness experience and reasons for nonadherence among individuals with bipolar disorder who are poorly adherent with medication. Compr Psychiatry. 2011;52(3):280–7.
37. Sajatovic M, Blow FC, Kales HC, Valenstein M, Ganoczy D, Ignacio RV. Age comparison of treatment adherence with antipsychotic medications among individuals with bipolar disorder. Int J Geriatr Psychiatry. 2007;22(10):992–8.
38. Casaletto KB, Kwan S, Montoya JL, Obermeit LC, Gouaux B, Poquette A, et al. Predictors of psychotropic medication adherence among HIV+ individuals living with bipolar disorder. Int J Psychiatry Med. 2016;51(1):69–83.
39. González-Pinto A, Reed C, Novick D, Bertsch J, Haro JM. Assessment of medication adherence in a cohort of patients with bipolar disorder. Pharmacopsychiatry. 2010;43(7):263–70.
40. Sajatovic M, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. Psychiatr Serv. 2007;58(6):855–63.
41. Zeber JE, Miller AL, Copeland LA, McCarthy JF, Zivin K, Valenstein M, et al. Medication adherence, ethnicity, and the influence of multiple psychosocial and financial barriers. Adm Policy Ment Health. 2011;38(2):86–95.
42. Sajatovic M, Elhaj O, Youngstrom EA, Bilali SR, Rapport DJ, Ganocy SJ, et al. Treatment adherence in individuals with rapid cycling bipolar disorder: results from a clinical-trial setting. J Clin Psychopharmacol. 2007;27(4):412–4.
43. Johnson RL, Saha S, Arbelaez JJ, Beach MC, Cooper LA. Racial and ethnic differences in patient perceptions of bias and cultural competence in health care. J Gen Intern Med. 2004;19(2):101–10.
44. Smedley BD, Stith AY, Colburn L, Evans CH, (US) IoM. Increasing racial and ethnic diversity among physicians: an intervention to address health disparities? The right thing to do, the smart thing to do: enhancing diversity in the health professions. Washington, D.C.: National Academies Press (US); 2001.
45. Office of the Surgeon General (US), Center for Mental Health Services (US), National Institute of Mental Health (US). Culture counts: the influence of culture and society on mental health. Mental Health: culture, race, and ethnicity: a supplement to mental health: a report of the surgeon general. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2001.
46. Smith JC, Medalia C. Health Insurance Coverage in the United States: 2014. In: Bureau USC, editor. Washington, D.C.: US Government Printing Office; 2015. p. 60–253.
47. Bhugra D. Severe mental illness across cultures. Acta Psychiatr Scand Suppl. 2006;429:17–23.
48. Colom F, Vieta E, Tacchi MJ, Sanchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. Bipolar Disord. 2005;7(Suppl 5):24–31.
49. Fleck DE, Keck PE, Corey KB, Strakowski SM. Factors associated with medication adherence in African American and white patients with bipolar disorder. J Clin Psychiatry. 2005;66(5):646–52.
50. Danion JM, Neunreuther C, Krieger-Finance F, Imbs JL, Singer L. Compliance with long-term lithium treatment in major affective disorders. Pharmacopsychiatry. 1987;20(5):230–1.
51. Sajatovic M, Micula-Gondek W, Tatsuoka C, Bialko C. The relationship of gender and gender identity to treatment adherence among individuals with bipolar disorder. Gend Med. 2011;8(4):261–8.
52. Maarbjerg K, Aagaard J, Vestergaard P. Adherence to lithium prophylaxis: I. Clinical predictors and patient's reasons for nonadherence. Pharmacopsychiatry. 1988;21(3):121–5.
53. Kessing LV, Søndergård L, Kvist K, Andersen PK. Adherence to lithium in naturalistic settings: results from a nationwide pharmacoepidemiological study. Bipolar Disord. 2007;9(7):730–6.
54. Gianfrancesco FD, Rajagopalan K, Sajatovic M, Wang RH. Treatment adherence among patients with bipolar or manic disorder taking atypical and typical antipsychotics. J Clin Psychiatry. 2006;67(2):222–32.
55. Crowe M, Wilson L, Inder M. Patients' reports of the factors influencing medication adherence in bipolar disorder—an integrative review of the literature. Int J Nurs Stud. 2011;48(7):894–903.
56. Montes JM, Maurino J, de Dios C, Medina E. Suboptimal treatment adherence in bipolar disorder: impact on clinical outcomes and functioning. Patient Pref Adherence. 2013;7:89–94.
57. Perlis RH, Ostacher MJ, Miklowitz DJ, Hay A, Nierenberg AA, Thase ME, et al. Clinical features associated with poor pharmacologic adherence in bipolar disorder: results from the STEP-BD study. J Clin Psychiatry. 2010;71(3):296–303.
58. Keck PE Jr, McElroy SL, Strakowski SM, Bourne ML, West SA. Compliance with maintenance treatment in bipolar disorder. Psychopharmacol Bull. 1997;33(1):87–91.
59. Arvilommi P, Suominen K, Mantere O, Leppämäki S, Valtonen H, Isometsä E. Predictors of adherence to psychopharmacological and psychosocial treatment in bipolar I or II disorders - an 18-month prospective study. J Affect Disord. 2014;155:110–7.
60. Martinez-Aran A, Scott J, Colom F, Torrent C, Tabares-Seisdedos R, Daban C, et al. Treatment nonadherence and neurocognitive impairment in bipolar disorder. J Clin Psychiatry. 2009;70(7):1017–23.
61. Sajatovic M, Biswas K, Kilbourne AK, Fenn H, Williford W, Bauer MS. Factors associated with prospective long-term treatment adherence among individuals with bipolar disorder. Psychiatr Serv. 2008;59(7):753–9.
62. Lee E, Xiang YT, Man D, Au RW, Shum D, Tang WK, et al. Prospective memory deficits in patients with bipolar disorder: a preliminary study. Arch Clin Neuropsychol. 2010;25(7):640–7.
63. Zogg JB, Woods SP, Sauceda JA, Wiebe JS, Simoni JM. The role of prospective memory in medication adherence: a review of an emerging literature. J Behav Med. 2012;35(1):47–62.

64. Clatworthy J, Bowskill R, Parham R, Rank T, Scott J, Horne R. Understanding medication non-adherence in bipolar disorders using a necessity-concerns framework. J Affect Disord. 2009;116(1–2):51–5.
65. Jónsdóttir H, Opjordsmoen S, Birkenaes AB, Simonsen C, Engh JA, Ringen PA, et al. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Acta Psychiatr Scand. 2013;127(1):23–33.
66. Mert DG, Turgut NH, Kelleci M, Semiz M. Perspectives on reasons of medication nonadherence in psychiatric patients. Patient Prefer Adherence. 2015;9:87–93.
67. Adams J, Scott J. Predicting medication adherence in severe mental disorders. Acta Psychiatr Scand. 2000;101(2):119–24.
68. Fuller M, Sajatovic M. Drug information handbook for psychiatry. 7th ed. Cleveland: Lexi-Comp; 2009.
69. Morselli PL, Elgie R, Cesana BM. GAMIAN-Europe/BEAM survey II: cross-national analysis of unemployment, family history, treatment satisfaction and impact of the bipolar disorder on life style. Bipolar Disord. 2004;6(6):487–97.
70. Darling CA, Olmstead SB, Lund VE, Fairclough JF. Bipolar disorder: medication adherence and life contentment. Arch Psychiatr Nurs. 2008;22(3):113–26.
71. Vieta E, Azorin JM, Bauer M, Frangou S, Perugi G, Martinez G, et al. Psychiatrists' perceptions of potential reasons for non- and partial adherence to medication: results of a survey in bipolar disorder from eight European countries. J Affect Disord. 2012;143(1–3):125–30.
72. Cochran SD, Gitlin MJ. Attitudinal correlates of lithium compliance in bipolar affective disorders. J Nerv Ment Dis. 1988;176(8):457–64.
73. Clatworthy J, Bowskill R, Rank T, Parham R, Horne R. Adherence to medication in bipolar disorder: a qualitative study exploring the role of patients' beliefs about the condition and its treatment. Bipolar Disord. 2007;9(6):656–64.
74. Mago R, Borra D, Mahajan R. Role of adverse effects in medication nonadherence in bipolar disorder. Harv Rev Psychiatry. 2014;22(6):363–6.
75. Medic GHK, Littlewood KJ, Diez T, Granström O, Kahn RS. Dosing frequency and adherence in chronic psychiatric disease: systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2013;9:119–31.
76. Dolder CR, Lacro JP, Dunn LB, Jeste DV. Antipsychotic medication adherence: is there a difference between typical and atypical agents? Am J Psychiatry. 2002;159(1):103–8.
77. Sylvia LG, Hay A, Ostacher MJ, Miklowitz DJ, Nierenberg AA, Thase ME, et al. Association between therapeutic alliance, care satisfaction, and pharmacological adherence in bipolar disorder. J Clin Psychopharmacol. 2013;33(3):343–50.
78. Gibson TB, Jing Y, Kim E, Bagalman E, Wang S, Whitehead R, et al. Cost-sharing effects on adherence and persistence for second-generation antipsychotics in commercially insured patients. Manag Care. 2010;19(8):40–7.
79. Strauss JL, Johnson SL. Role of treatment alliance in the clinical management of bipolar disorder: stronger alliances prospectively predict fewer manic symptoms. Psychiatry Res. 2006;145(2–3):215–23.
80. Zeber JE, Copeland LA, Good CB, Fine MJ, Bauer MS, Kilbourne AM. Therapeutic alliance perceptions and medication adherence in patients with bipolar disorder. J Affect Disord. 2008;107(1–3):53–62.
81. Reilly-Harrington N, Sachs GS. Psychosocial strategies to improve concordance and adherence in bipolar disorder. J Clin Psychiatry. 2006;67(7):e04.
82. Copeland LA, Zeber JE, Salloum IM, Pincus HA, Fine MJ, Kilbourne AM. Treatment adherence and illness insight in veterans with bipolar disorder. J Nerv Ment Dis. 2008;196(1):16–21.
83. Wilder CM, Elbogen EB, Moser LL, Swanson JW, Swartz MS. Medication preferences and adherence among individuals with severe mental illness and psychiatric advance directives. Psychiatr Serv. 2010;61(4):380–5.
84. 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(6):545–52.
85. Basco M, Smith J. Faulty decision-making: impact on treatment adherence in bipolar disorder. Primary Psychiatry. 2009;16(8):53–8.
86. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):629–40.
87. Rowan K, McAlpine DD, Blewett LA. Access and cost barriers to mental health care, by insurance status, 1999–2010. Health Aff (Millwood). 2013;32(10):1723–30.
88. Pearson WS, Dhingra SS, Strine TW, Liang YW, Berry JT, Mokdad AH. Relationships between serious psychological distress and the use of health services in the United States: findings from the behavioral risk factor surveillance system. Int J Public Health. 2009;54(Suppl 1):23–9.
89. US Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Report to Congress on the Nation's Substance Abuse and Mental Health Workforce Issues. Hyde PS, administrator; 2013.
90. Keck PE, McElroy SL, Strakowski SM, West SA, Sax KW, Hawkins JM, et al. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. Am J Psychiatry. 1998;155(5):646–52.
91. Hassan M, Lage MJ. Risk of rehospitalization among bipolar disorder patients who are nonadherent to antipsychotic therapy after hospital discharge. Am J Health Syst Pharm. 2009;66(4):358–65.
92. Li C, Chen C, Qiu B, Yang G. A 2-year follow-up study of discharged psychiatric patients with bipolar disorder. Psychiatry Res. 2014;218(1–2):75–8.
93. Hong J, Reed C, Novick D, Haro JM, Aguado J. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. Psychiatry Res. 2011;190(1):110–4.
94. Baldessarini RJ, Tondo L, Viguera AC. Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. Bipolar Disord. 1999;1(1):17–24.
95. Gonzalez-Pinto A, Mosquera F, Alonso M, López P, Ramírez F, Vieta E, et al. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disord. 2006;8(5 Pt 2):618–24.
96. Müller-Oerlinghausen B, Wolf T, Ahrens B, Glaenz T, Schou M, Grof E, et al. Mortality of patients who dropped out from regular lithium prophylaxis: a collaborative study by the International Group for the Study of Lithium-treated patients (IGSLI). Acta Psychiatr Scand. 1996;94(5):344–7.
97. López-Jaramillo C, Lopera-Vásquez J, Gallo A, Ospina-Duque J, Bell V, Torrent C, et al. Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord. 2010;12(5):557–67.
98. Copeland LA, Miller AL, Welsh DE, McCarthy JF, Zeber JE, Kilbourne AM. Clinical and demographic factors associated with homelessness and incarceration among VA patients with bipolar disorder. Am J Public Health. 2009;99(5):871–7.
99. Robertson AG, Swanson JW, Van Dorn RA, Swartz MS. Treatment participation and medication adherence: effects on

criminal justice costs of persons with mental illness. Psychiatr Serv. 2014;65(10):1189–91.
100. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. Psychiatr Serv. 2001;52(6):805–11.
101. Durrenberger S, Rogers T, Walker R, de Leon J. Economic grand rounds: the high costs of care for four patients with mania who were not compliant with treatment. Psychiatr Serv. 1999;50(12):1539–42.
102. Gianfrancesco FD, Sajatovic M, Rajagopalan K, Wang RH. Antipsychotic treatment adherence and associated mental health care use among individuals with bipolar disorder. Clin Ther. 2008;30(7):1358–74.
103. Birkenaes AB, Opjordsmoen S, Brunborg C, Engh JA, Jonsdottir H, Ringen PA, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry. 2007;68(6):917–23.
104. Ramsey CM, Leoutsakos JM, Mayer LS, Eaton WW, Lee HB. History of manic and hypomanic episodes and risk of incident cardiovascular disease: 11.5 year follow-up from the Baltimore Epidemiologic Catchment Area Study. J Affect Disord. 2010;125(1–3):35–41.
105. Ramsey CM, Spira AP, Mojtabai R, Eaton WW, Roth K, Lee HB. Lifetime manic spectrum episodes and all-cause mortality: 26-year follow-up of the NIMH Epidemiologic Catchment Area Study. J Affect Disord. 2013;151(1):337–42.
106. Young AH, Grunze H. Physical health of patients with bipolar disorder. Acta Psychiatr Scand Suppl. 2013;442:3–10.
107. Wheeler KJ, Roberts ME, Neiheisel MB. Medication adherence part two: predictors of nonadherence and adherence. J Am Assoc Nurse Pract. 2014;26(4):225–32.
108. King RM, Vidrine DJ, Danysh HE, Fletcher FE, McCurdy S, Arduino RC, et al. Factors associated with nonadherence to antiretroviral therapy in HIV-positive smokers. AIDS Patient Care STDS. 2012;26(8):479–85.
109. Eze-Nliam CM, Thombs BD, Lima BB, Smith CG, Ziegelstein RC. The association of depression with adherence to antihypertensive medications: a systematic review. J Hypertens. 2010;28(9):1785–95.
110. Osborn CY, Egede LE. The relationship between depressive symptoms and medication nonadherence in type 2 diabetes: the role of social support. Gen Hosp Psychiatry. 2012;34(3):249–53.
111. Levin JB, Aebi ME, Tatsuoka C, Cassidy KA, Sajatovic M. Adherence to psychotropic and nonpsychotropic medication among patients with bipolar disorder and general medical conditions. Psychiatr Serv. 2016;67(3):342–5.
112. Levin JB, Krivenko A, Bukach A, Tatsuoka C, Cassidy KA, Sajatovic M. A reexamination of non-psychiatric medication adherence in individuals with bipolar disorder and medical comorbidities. J Nerv Ment Dis (**Epub 10 June 2016**).
113. Cabassa LJ, Ezell JM, Lewis-Fernández R. Lifestyle interventions for adults with serious mental illness: a systematic literature review. Psychiatr Serv. 2010;61(8):774–82.
114. Siantz E, Aranda MP. Chronic disease self-management interventions for adults with serious mental illness: a systematic review of the literature. Gen Hosp Psychiatry. 2014;36(3):233–44.
115. Sajatovic M, Levin J, Tatsuoka C, Micula-Gondek W, Williams TD, Bialko CS, et al. Customized adherence enhancement for individuals with bipolar disorder receiving antipsychotic therapy. Psychiatr Serv. 2012;63(2):176–8.
116. Sajatovic M, Levin J, Tatsuoka C, Micula-Gondek W, Fuentes-Casiano E, Bialko CS, et al. Six-month outcomes of customized adherence enhancement (CAE) therapy in bipolar disorder. Bipolar Disord. 2012;14(3):291–300.
117. Sajatovic M, Davies MA, Ganocy SJ, Bauer MS, Cassidy KA, Hays RW, et al. A comparison of the life goals program and treatment as usual for individuals with bipolar disorder. Psychiatr Serv. 2009;60(9):1182–9.
118. Eker F, Harkın S. Effectiveness of six-week psychoeducation program on adherence of patients with bipolar affective disorder. J Affect Disord. 2012;138(3):409–16.
119. Javadpour A, Hedayati A, Dehbozorgi GR, Azizi A. The impact of a simple individual psycho-education program on quality of life, rate of relapse and medication adherence in bipolar disorder patients. Asian J Psychiatr. 2013;6(3):208–13.
120. McKenzie K, Chang Y-P. The effect of nurse-led motivational interviewing on medication adherence in patients with bipolar disorder. Perspect Psychiatr Care. 2015;51(1):36–44.
121. Depp CA, Lebowitz BD, Patterson TL, Lacro JP, Jeste DV. Medication adherence skills training for middle-aged and elderly adults with bipolar disorder: development and pilot study. Bipolar Disord. 2007;9(6):636–45.
122. Wenze SJ, Gaudiano BA, Weinstock LM, Tezanos KM, Miller IW. Adjunctive psychosocial intervention following Hospital discharge for Patients with bipolar disorder and comorbid substance use: a pilot randomized controlled trial. Psychiatry Res. 2015;228(3):516–25.
123. Moore DJ, Poquette A, Casaletto KB, Gouaux B, Montoya JL, Posada C, et al. Individualized texting for adherence building (iTAB): improving antiretroviral dose timing among HIV-infected persons with co-occurring bipolar disorder. AIDS Behav. 2015;19(3):459–71.
124. Priebe S, Yeeles K, Bremner S, Lauber C, Eldridge S, Ashby D, et al. Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics: cluster randomised controlled trial. BMJ. 2013;347:f5847.
125. MacDonald L, Chapman S, Syrett M, Bowskill R, Horne R. Improving medication adherence in bipolar disorder: a systematic review and meta-analysis of 30 years of intervention trials. J Affect Disord. 2016;194:202–21.
126. Gaudiano BA, Weinstock LM, Miller IW. Improving treatment adherence in bipolar disorder: a review of current psychosocial treatment efficacy and recommendations for future treatment development. Behav Modif. 2008;32(3):267–301.
127. van Dulmen S, Sluijs E, van Dijk L, de Ridder D, Heerdink R, Bensing J, et al. Furthering patient adherence: a position paper of the international expert forum on patient adherence based on an internet forum discussion. BMC Health Serv Res. 2008;8:47.
128. Domino FJ. Improving adherence to treatment for hypertension. Am Fam Physician. 2005;71(11):2089–90.
129. Santschi V, Wuerzner G, Schneider MP, Bugnon O, Burnier M. Clinical evaluation of IDAS II, a new electronic device enabling drug adherence monitoring. Eur J Clin Pharmacol. 2007;63(12):1179–84.
130. Heneghan CJ, Glasziou P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database Syst Rev. 2006;(1):CD005025.
131. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA. 2006;296(21):2563–71.
132. Schneider PJ, Murphy JE, Pedersen CA. Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. J Am Pharm Assoc (2003). 2008;48(1):58–63.
133. Vrijens B, Belmans A, Matthys K, de Klerk E, Lesaffre E. Effect of intervention through a pharmaceutical care program on patient adherence with prescribed once-daily atorvastatin. Pharmacoepidemiol Drug Saf. 2006;15(2):115–21.

134. Berkowitz AC, Goddard DM. Novel drug delivery systems: future directions. J Neurosci Nurs. 2009;41(2):115–20.
135. Wong S, Chan V. The digital pill: tracking medication adherence through electronic modalities. Med Technol. 2016;85(1): 38–40.
136. Sajatovic M, Davis MS, Cassidy KA, Nestor J, Sams J, Fuentes-Casiano E. A technology-enabled adherence enhancement system for people with bipolar disorder: results from a feasibility and patient acceptance analysis. Patient Prefer Adherence. 2015;9:753–8.
137. Wenze SJ, Armey MF, Miller IW. Feasibility and acceptability of a mobile intervention to improve treatment adherence in bipolar disorder: a pilot study. Behav Modif. 2014;38(4):497–515.
138. Depp CA, Mausbach B, Granholm E, Cardenas V, Ben-Zeev D, Patterson TL, et al. Mobile interventions for severe mental illness: design and preliminary data from three approaches. J Nerv Ment Dis. 2010;198(10):715–21.
139. Depp CA, Ceglowski J, Wang VC, Yaghouti F, Mausbach BT, Thompson WK, et al. Augmenting psychoeducation with a mobile intervention for bipolar disorder: a randomized controlled trial. J Affect Disord. 2015;174:23–30.
140. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res. 2011;127(1–3):83–92.
141. Vieta E, Nieto E, Autet A, Rosa AR, Goikolea JM, Cruz N, et al. A long-term prospective study on the outcome of bipolar patients treated with long-acting injectable risperidone. World J Biol Psychiatry. 2008;9(3):219–24.
142. Wu CS, Hsieh MH, Tang CH, Chang CJ. Comparative effectiveness of long-acting injectable risperidone vs. long-acting injectable first-generation antipsychotics in bipolar disorder. J Affect Disord. 2016;197:189–95.
143. Chou YH, Chu PC, Wu SW, Lee JC, Lee YH, Sun IW, et al. A systemic review and experts' consensus for long-acting injectable antipsychotics in bipolar disorder. Clin Psychopharmacol Neurosci. 2015;13(2):121–8.
144. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15(1):1–44.
145. Gigante AD, Lafer B, Yatham LN. Long-acting injectable antipsychotics for the maintenance treatment of bipolar disorder. CNS Drugs. 2012;26(5):403–20.
146. Uchida S, Hiraoka S, Namiki N. Development of gummi drugs of aripiprazole as hospital formulations. Chem Pharm Bull (Tokyo). 2015;63(5):354–60.
147. Fagiolini A, Forgione RN, Morana B, Maccari M, Goracci A, Bossini L, et al. Asenapine for the treatment of manic and mixed episodes associated with bipolar I disorder: from clinical research to clinical practice. Expert Opin Pharmacother. 2013;14(4):489–504.
148. San L, Casillas M, Ciudad A, Gilaberte I. Olanzapine orally disintegrating tablet: a review of efficacy and compliance. CNS Neurosci Ther. 2008;14(3):203–14.
149. Sajatovic M, Thompson TR, Nanry K, Edwards S, Manjunath R. Prospective, open-label trial measuring satisfaction and convenience of two formulations of lamotrigine in subjects with mood disorders. Patient Prefer Adherence. 2013;7:411–7.
150. Brissos S, Veguilla MR, Taylor D, Balanzá-Martinez V. The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. Ther Adv Psychopharmacol. 2014;4(5): 198–219.