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Second Generation Long-Acting Antipsychotics in the Treatment of Bipolar Disorder: A Clinical Viewpoint

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Abstract

Bipolar Disorder (BD) is a severe, chronic and disabling condition. The gold standard of treatment is lithium, but the introduction of Second Generation Long-Acting Antipsychotics (SGA-LAIs) has been addressed several problems in the administration of oral SGAs in BD such as the patient's adherence to the treatment. The aim of this commentary was to provide an overview of the use of SGA-LAIs in the treatment of BD. All considered, the use of SGA-LAIs such as Risperidone Long-Acting and Aripiprazole Long-Acting may have an important impact on the maintenance treatment of BD both in monotherapy or in association with mood stabilizers. In our opinion, the treatment with a SGA-LAI should be initiated as early as possible in BD, especially when non-adherence is suspected. Moreover, as personality disorders (PD) and BD may often coexist, it is worthy to note that the PD-BD comorbidity may further decrease treatment adherence and, therefore, we believe that the early use of a SGA-LAI both in monotherapy or in association with mood stabilizers may dramatically improve the compliance and the overall outcomes in such cases. However, he safety profile should be always kept in mind when choosing an SGA-LAI in the treatment of BD.

Keywords: Bipolar Disorder; Second Generation; Long-Acting; Antipsychotics; Lithium; Mood Stabilizers; Adherence; Compliance; Personality disorders

Introduction

Bipolar Disorder (BD) is a severe and disabling condition characterized by recurrent episodes of depression, mania and mixed states often complicated by residual symptoms once the main episode has resolved [1]. The great rates of comorbidity, the presence of a relevant suicide risk and the functional impairment in BD also confirm that it is a common cause of disability as well as financial and social burden [2]. The lifetime prevalence of BD-I is estimated at 1% of the adult population, and BD-II seems to affect about 0.4% of adults [3].

The gold standard of treatment is lithium, with its well-recognized and proven efficacy as well as its prophylactic effects, but also other mood stabilizers may be effective especially when combined with lithium [4]. However, the use of antipsychotics in the treatment of BD, alone or in combination with lithium or other mood stabilizers, has been showed to be effective and the use of such compounds are common in the everyday clinical practice [5]. This may be particularly true for Second Generation Antipsychotics (SGAs) such as olanzapine, quetiapine, risperidone, ziprasidone and aripiprazole [2,6,7].

Recently the introduction of Second Generation Long-Acting Antipsychotics (SGA-LAIs) in the treatment of schizophrenia has been addressed several problems in the administration of SGAs such as the patients' adherence to the treatment [8]. The adherence has been described 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" [9,10]. The aim of this commentary was to provide an overview of the use of SGA-LAIs in the treatment of BD.

Some critical challenges in the contemporary clinical interventions in the treatment of BD

The challenges of the contemporary prevailing clinical approaches and clinical interventions in the treatment of BD often limit the possibility to effectively control the symptoms of the disorders or to prevent recurrence. One of the important challenges in the treatment of BD (and, in opinion of who is writing this commentary, the most important challenge) is the problem of non-adherence to oral medications.

Even if the adherence to the treatment in patients with schizophrenia is relatively low especially at the onset of the disorder and in the long term, the problem of non-adherence is relatively

common also in patients with BD [11]. It is obvious and understandable that most patients with BD seek help and treatment during depressive episodes (often preferring the prescription of the only antidepressant without a mood stabilizer or an antipsychotic), but they often refuse the treatment with mood stabilizers or antipsychotic for hypomanic, manic or mixed episodes or may discontinue the treatment during these phases of illness [12]. Several studies and reviews had concluded that about 40% to 50% of patients with BD (range 9%-66%) do not take their medications regularly as prescribed and rates are basically the same irrespective of whether patients are taking mood stabilizers or antipsychotics [13]. Moreover, the non-adherence in DB seems unchanged or even increased over the years even with the introduction of numerous new drugs and often clinicians appear to be mostly likely to underestimate non-adherence in their patients with BD [14]. The consequence of non-adherence in BD is very dangerous and comprises higher suicide risk and rates, rapid cycling, treatment refractoriness etc. [15]. Increased risk of non-adherence may be associated with new oral antipsychotic starts, poor insight into the need for medication, younger patients, concomitant substance abuse diagnosis, taking an antidepressant, concern about adverse effects and several psychiatric hospitalizations [16]. The use of SGA-LAIs in the treatment of such condition and to overcome non-adherence may play a key role in providing an effective and safe therapeutic option to these subjects.

Another important challenge is that personality disorders (PD) and BD may often coexist [17]. Some studies have suggested that around 66% of individuals with borderline personality disorder may have an affective diagnosis such as BD [18,19]. It is true that several affective symptoms may be part of the borderline personality disorder spectrum (i.e., sense of emptiness, mood lability, irritability, dysphoria, affective instability, anger, suicidal ideation, self-harm), and borderline characteristics may be associated with rapid cycling BD or mixed episode [20]. Several studies have indicated an improvement in borderline symptoms in response to conventional mood stabilizers but some reports have pointed out the efficacy of SGAs (such as olanzapine, risperidone, paliperidone, aripiprazole etc.) in the control of some symptoms (i.e., psychotic symptoms, dissociation episodes, impulsive behavioral dyscontrol) that do not adequately respond to conventional mood stabilizers (including lithium) [21-24]. Despite this, it is worthy to note that the PD-BD comorbidity may further decrease treatment adherence and, therefore, the use of a SGA-LAI may improve the compliance and the overall outcomes in such cases [25-28].

The use of the SGA-LAIs in the treatment of BD

The majority of studies have focused on Risperidone Long-Acting (RLAI) which was the first SGA-LAI introduced in the market [29,30]. RLAI has demonstrated similar effectiveness, safety and tolerability compared to oral antipsychotics in a 6 month pilot trial [31]. As well, RLAI may be beneficial in the maintenance therapy of stable bipolar patients with a reduction of relapses of manic and mixed states [32,33], in an observational long-term study, showed that RLAI was effective for the maintenance treatment of mania, also improving treatment adherence, reducing relapses and re-hospitalization rates. The efficacy of RLAI to prevent elevated mood episodes in BD was also confirmed in a more recent study of the same group [34].

The observations of effectiveness of RLAI were also confirmed by several long term, retrospective and randomized trials [35]. For example, MacFadden et al. [36] conducted a randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive RLAI therapy in patients with BD-I who relapsed frequently and observed that adjunctive RLAI significantly delayed time to relapse in such problematic patients. Interestingly also RLAI monotherapy significantly delayed the time to recurrence of mood episodes, versus placebo, in a controlled, randomized study in patients with BD-I [37]. Bobo et al. [38] conducted a trial rapid cycling BD (that is the most difficult to treat condition in such disorder) to compare adjunctive RLAI plus treatment as usual (TAU) versus TAU alone for relapse, rehospitalization, and urgent care events in rapid cycling BD patients in routine care settings. They found that the rates of any-cause relapse did not differ considerably between RLAI+TAU and TAU alone, but RLAI significantly reduced the need for urgent care referrals or the frequency of medication adjustments to prevent relapses. Moreover adjunctive RLAI can be considered as a useful treatment option also in patients with BD and psychotic features [39]. Recently, Wu et al. [40] compared the treatment effectiveness between RLAI and long-acting injectable first-generation antipsychotics (FGA-LAIs) among patients with BD and found RLAI was superior to first-generation antipsychotics in the rate of psychiatric hospitalization. In fact, it has been demonstrated BD patients had lower inpatient and emergency room (ER) utilization, and non-medication costs after using RLAI, also decreasing the number of change-in-mood episode.

On May 2009, the US Food and Drug Administration (FDA) have approved RLAI for use alone or with lithium or valproate in the treatment of bipolar I disorder. However, it is worthy to note that RLAI may be associated with several adverse effects (especially at higher dosages) that may be particularly bothering for some patients such as weight gain, elevation in prolactin levels and the possibility of developing rigidity or tardive dyskinesia [41-43].

Recently has been evaluated the aripiprazole long-acting injection in the treatment of DB-I [25]. Aripiprazole may be a potential favorable option in the treatment of patients with BD due to its clinical efficacy and the relative lacking of metabolic, endocrine and extrapyramidal effects. There is one large study, some case reports and several reviews that have investigated the efficacy of the once-monthly long-acting aripiprazole formulation (AOM) in the treatment of BD [44-46].

Calabrese et al. [47] conducted a double-blind, placebo-controlled, 52-week randomized withdrawal study on 266 patients with BP-I currently experiencing a manic episode stabilized sequentially on oral aripiprazole and AOM 400 mg and then randomized to AOM 400 mg or placebo. AOM 400 treatment considerably delayed the time to recurrence of any mood episode and significantly fewer patients showed recurrence of any mood episode with AOM 400 compared with placebo, with the effects observed mainly on manic episodes. On the basis of this only study, in July 2017, the FDA approved AOM for maintenance monotherapy of bipolar I disorder in adults. However, in the registration study of Calabrese et al. [47] some treatment-emergent adverse events were noted even if, for the most part, mild to moderate. Akathisia was the most common adverse event, which, combined with restlessness, was experienced by 23% of the sample. No effects of AOM on weight gain or hearth conduction were observed. More recently, Calabrese et al. [48] further demonstrated that patients with BP-I experiencing an acute manic episode achieved symptomatic and functional improvements during stabilization with oral aripiprazole and AOM 400 that were maintained with continued AOM 400 treatment but not placebo.

Recently, Augusto et al. [49] evaluated the cost-effectiveness of AOM in maintenance monotherapy treatment of BD-I and found it

cost-effective in the maintenance monotherapy treatment when compared to RLAI, paliperidone palmitate (PLAI), oral cariprazine and best supportive care.

Concluding remarks and recommendations

All considered, the use of SGA-LAIs such as RLAI and AOM may have an important impact on the maintenance treatment of BD both in monotherapy or in association with mood stabilizers.

The best mood stabilizer to be chosen as the first choice in addition to a SGA-LAI is obviously lithium due to its well established clinical effectiveness [50-52]. Furthermore, it can be hypothesized that if patients decide to drop lithium treatment that is more than a remote possibility, especially in the long-term [53], the concomitant administration of a SGA-LAI may be their lifeline and may permit psychiatrist to re-evaluate its reintroduction or using patient-centred strategies (such as individual or group psychoeducation) in order to improve compliance when the patients come to our facilities to receive the injections [54-56].

In our opinion, the treatment with a SGA-LAI should be initiated as early as possible as suggested for schizophrenia, especially when non-adherence is suspected [57,58]. The real-world studies suggest that patients with schizophrenia or BD who began receiving LAIs had better medication adherence and lower discontinuation risk than those who changed to a different oral antipsychotic monotherapy [57]. In 2018, Lahteenvuo et al. [59] evaluated the real-world effectiveness of pharmacologic treatments for the prevention of re-hospitalization in a finish cohort of subjects with BD and found that both lithium long-acting injections were the most effective drugs in preventing hospitalization due to mental or physical illness.

Overall, on the basis of literature, we believe that all LAIs were associated with a substantially lower risk of re-hospitalizations in BD than their identical oral formulations, mainly due to better treatment adherence. This observation was corroborated also from a Swedish nationwide cohort of patients with schizophrenia, which indicated that inadequate treatment adherence is a similar problem in bipolar disorder and schizophrenia [60].

Moreover, as PD and BD may often coexist, it is worthy to note that the PD-BD comorbidity may further decrease treatment adherence and, therefore, we believe that the early use of a SGA-LAI both in monotherapy or in association with mood stabilizers may dramatically improve the compliance and the overall outcomes in such cases.

However, we firmly believe that the safety profile should be always kept in mind and the right choice of the SGA-LAI is crucial for the optimal treatment and AOM should be preferred to RLAI due to its better adverse effects profile especially on metabolic and cardiovascular parameters [8].

Unluckily, to date, we have no data on the clinical efficacy of PLAI and olanzapine pamoate (OLAI) that may further add something to the BD therapy armamentarium. Therefore, further studies on PLAI and OLAI are undoubtedly needed.

References

1. Han KM, De Berardis D, Fornaro M, Kim YK (2018) Differentiating between bipolar and unipolar depression in functional and structural MRI studies. Prog Neuropsychopharmacol Biol Psychiatry S0278-5846: 30051-30054.
2. Fornaro M, De Berardis D, Koshy AS, Perna G, Valchera A, et al. (2016) Prevalence and clinical features associated with bipolar disorder polypharmacy: a systematic review. Neuropsychiatr Dis Treat 12: 719-735.
3. Pavlova B, Perlis RH, Alda M, Uher R (2015) Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 2: 710-717.
4. Fornaro M, Iasevoli F, Novello S, Fusco A, Anastasia A, et al. (2018) Predictors of hospitalization length of stay among re-admitted treatment-resistant Bipolar Disorder inpatients. J Affect Disord 228:118-124.
5. Fornaro M, Nardi AE, De Berardis D, Carta MG (2016) Experimental drugs for bipolar psychosis. Expert Opin Investig Drugs 25: 1371-1375.
6. Fornaro M, Stubbs B, De Berardis D, Perna G, Valchera A, et al. (2016) Atypical Antipsychotics in the Treatment of Acute Bipolar Depression with Mixed Features: A Systematic Review and Exploratory Meta-Analysis of Placebo-Controlled Clinical Trials. Int J Mol Sci 17: 241.
7. Orsolini L, Tomasetti C, Valchera A, Vecchiotti R, Matarazzo I, et al. (2016) An update of safety of clinically used atypical antipsychotics. Expert Opin Drug Saf 15(10): 1329-1347.
8. De Berardis D, Marini S, Carano A, Lang AP, Cavuto M, et al (2013) Efficacy and safety of long acting injectable atypical antipsychotics: a review. Curr Clin Pharmacol 8: 256-264.
9. Burkhart PV, Sabate E (2003) Adherence to long-term therapies: evidence for action. J Nurs Scholarsh 35: 207.
10. Chakrabarti S (2016) Treatment-adherence in bipolar disorder: A patient-centred approach. World J Psychiatry 6: 399-409.
11. Murru A, Pacchiarotti I, Amann BL, Nivoli AM, Vieta E, et al. (2013) Treatment adherence in bipolar I and schizoaffective disorder, bipolar type. J Affect Disord 151: 1003-1008.
12. Thase ME (2012) Strategies for increasing treatment adherence in bipolar disorder. J Clin Psychiatry 73: e08.
13. Levin JB, Krivenko A, Howland M, Schlachet R, Sajatovic M (2016) Medication Adherence in Patients with Bipolar Disorder: A Comprehensive Review. CNS Drugs 30: 819-835.
14. Leclerc E, Mansur RB, Brietzke E (2013) Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J Affect Disord 149: 247-252.
15. Jackson WC (2008) The importance of facilitating adherence in maintenance therapy for bipolar disorder. J Clin Psychiatry 69: e3.
16. Lang K, Korn J, Muser E, Choi JC, Abouzaid S, et al. (2011) Predictors of medication nonadherence and hospitalization in Medicaid patients with bipolar I disorder given long-acting or oral antipsychotics. J Med Econ 14: 217-226.
17. Perugi G, Fornaro M, Akiskal HS (2011) Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a common cyclothymic diathesis? World Psychiatry 10: 45-51.
18. di Giacomo E, Colmegna F, Aspesi F, Dakanalis A, Clerici M (2018) Distinguishing Between Borderline Personality Disorder and Bipolar Disorder. J Clin Psychiatry 79: 880-886.
19. Fornaro M, Orsolini L, Marini S, De Berardis D, Perna G, et al. (2016) The prevalence and predictors of bipolar and borderline personality disorders comorbidity: Systematic review and meta-analysis. J Affect Disord 195: 105-118.
20. di Giacomo E, Aspesi F, Fotiadou M, Arntz A, Aguglia E, et al. (2017) Unblending Borderline Personality and Bipolar Disorders. J Psychiatr Res 91: 90-97.
21. Zimmerman M (2016) Improving the Recognition of Borderline Personality Disorder in a Bipolar World. J Pers Disord 30: 320-335.
22. Swartz HA, Pilkonis PA, Frank E, Proietti JM, Scott J (2005) Acute treatment outcomes in patients with bipolar I disorder and co-morbid borderline personality disorder receiving medication and psychotherapy. Bipolar Disord 7: 192-197.

23. Belli H, Ural C, Akbudak M (2012) Borderline personality disorder: bipolarity, mood stabilizers and atypical antipsychotics in treatment. J Clin Med Res 4: 301-308.
24. Ingenhoven TJ, Duivenvoorden HJ (2011) Differential effectiveness of antipsychotics in borderline personality disorder: meta-analyses of placebo-controlled, randomized clinical trials on symptomatic outcome domains. J Clin Psychopharmacol 31: 489-496.
25. Martinez JS, Caballero AR (2017) Long-Acting Aripiprazole in Comorbid Bipolar Disorder and Borderline Personality Disorder and Substance Abuse. J Clin Psychopharmacol 37: 266-267.
26. Palomares N, Montes A, Diaz-Marsa M, Carrasco JL (2015) Effectiveness of long-acting paliperidone palmitate in borderline personality disorder. Int Clin Psychopharmacol 30: 338-341.
27. Carrasco JL, Palomares N, Marsa MD (2012) Effectiveness and tolerability of long-acting intramuscular risperidone as adjuvant treatment in refractory borderline personality disorder. Psychopharmacology (Berl) 224: 347-348.
28. Diaz-Marsa M, Galian M, Montes A, Fernandez R, Arza R, Lopez-Ibor J, et al. (2008) Long-acting injectable risperidone in treatment resistant borderline personality disorder. A small series report. Actas Esp Psiquiatr 36: 70-4.
29. Savas HA, Yumru M, Ozen ME (2006) Use of long-acting risperidone in the treatment of bipolar patients. J Clin Psychopharmacol 26: 530-531.
30. Braunig P, Sacchetti E, Medori R (2008) Risperidone long-acting injectable for maintenance therapy in bipolar disorder: An open-label pilot study. Int J Psychiatry Clin Pract 12: 74-77.
31. Yatham LN, Fallu A, Binder CE (2007) A 6-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. Acta Psychiatr Scand Suppl 434: 50-56.
32. Han C, Lee MS, Pae CU, Ko YH, Patkar AA, et al. (2007) Usefulness of long-acting injectable risperidone during 12-month maintenance therapy of bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 31: 1219-1223.
33. Vieta E, Nieto E, Autet A, Rosa AR, Goikolea JM, et al. (2008) A long-term prospective study on the outcome of bipolar patients treated with long-acting injectable risperidone. World J Biol Psychiatry 9: 219-224.
34. Vieta E, Montgomery S, Sulaiman AH, Cordoba R, Huberlant B, et al. (2012) A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. Eur Neuropsychopharmacol 22: 825-835.
35. Chan HW, Huang CY, Feng WJ, Yen YC (2016) Clinical outcomes of long-acting injectable risperidone in patients with bipolar I disorder: A 1-year retrospective cohort study. J Affect Disord 205: 360-364.
36. Macfadden W, Alphs L, Haskins JT, Turner N, Turkoz I, et al. (2009) A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. Bipolar Disord 11: 827-839.
37. Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner S, et al. (2010) Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry 68: 156-162.
38. Bobo WV, Epstein RA, Lynch A, Patton TD, Bossaller NA, et al. (2011) A randomized open comparison of long-acting injectable risperidone and treatment as usual for prevention of relapse, rehospitalization, and urgent care referral in community-treated patients with rapid cycling bipolar disorder. Clin Neuropharmacol 34: 224-233.
39. Malempati RN, Bond DJ, Kunz M, Malemati C, Cheng A, et al. (2011) Long-term efficacy of risperidone long-acting injectable in bipolar disorder with psychotic features: a prospective study of 3-year outcomes. Int Clin Psychopharmacol 26: 146-150.
40. Wu CS, Hsieh MH, Tang CH, Chang CJ (2016) Comparative effectiveness of long-acting injectable risperidone vs. long-acting injectable first-generation antipsychotics in bipolar disorder. J Affect Disord 197: 189-195.
41. Chung AK (2012) Atypical presentation of tardive dyskinesia associated with risperidone long-acting injection as maintenance treatment in bipolar affective disorder: a case report. Curr Drug Saf 7: 21-23.
42. Gwynette MF, Evangelidis N (2013) Treating symptomatic hyperprolactinemia secondary to a long-acting injectable atypical antipsychotic in a patient with bipolar disorder due to an anoxic brain injury. Prim Care Companion CNS Disord 15.
43. Kishi T, Oya K, Iwata N (2016) Long-Acting Injectable Antipsychotics for Prevention of Relapse in Bipolar Disorder: A Systematic Review and Meta-Analyses of Randomized Controlled Trials. Int J Neuropsychopharmacol 19.
44. Aggarwal A, Schrimpf L, Lauriello J (2018) Aripiprazole Long-Acting Injectable for Maintenance Treatment of Bipolar I Disorder in Adults. Clin Schizophr Relat Psychoses 11: 221-223.
45. Torres-Llenza V, Lakshmin P, Lieberman DZ (2018) Spotlight on once-monthly long-acting injectable aripiprazole and its potential as maintenance treatment for bipolar I disorder in adult patients. Neuropsychiatr Dis Treat 14: 285-292.
46. Suzuki H, Hibino H, Inoue Y, Mikami K (2018) The advantages of introducing aripiprazole once-monthly 300mg in the bipolar disorder-II maintenance treatment regime for 2 patients. Asian J Psychiatr 34:11.
47. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, et al. (2017) Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study. J Clin Psychiatry 78: 324-331.
48. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, et al. (2018) Symptoms and functioning with aripiprazole once-monthly injection as maintenance treatment for bipolar I disorder. J Affect Disord 227: 649-656.
49. Augusto M, Greene M, Touya M, Sweeney SM, Waters H (2018) Cost-effectiveness of long-acting injectable aripiprazole once-monthly 400 mg in bipolar I disorder in the USA. J Comp Eff Res.
50. Won E, Kim YK (2017) An Oldie but Goodie: Lithium in the Treatment of Bipolar Disorder through Neuroprotective and Neurotrophic Mechanisms. Int J Mol Sci 18: 2679.
51. Sani G, Perugi G, Tondo L (2017) Treatment of Bipolar Disorder in a Lifetime Perspective: Is Lithium Still the Best Choice? Clin Drug Investig 37: 713-727.
52. Girardi P, Brugnoli R, Manfredi G, Sani G (2016) Lithium in Bipolar Disorder: Optimizing Therapy Using Prolonged-Release Formulations. Drugs R D 16: 293-302.
53. Fornaro M, Stubbs B, De Berardis D, Iasevoli F, Solmi M, et al. (2016) Does the "Silver Bullet" Lose its Shine Over the Time? Assessment of Loss of Lithium Response in a Preliminary Sample of Bipolar Disorder Outpatients. Clin Pract Epidemiol Ment Health 12: 142-157.
54. Azadforouz S, Shabani A, Nohesara S, Ahmadzad-Asl M (2016) Non-Compliance and Related Factors in Patients With Bipolar I Disorder: A Six Month Follow-Up Study. Iran J Psychiatry Behav Sci. 10: e2448.
55. Etain B, Scott J, Cochet B, Bellivier F, Boudebesse C, et al. (2018) A study of the real-world effectiveness of group psychoeducation for bipolar disorders: Is change in illness perception a key mediator of benefit? J Affect Disord 227: 713-720.
56. Bond K, Anderson IM (2015) Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. Bipolar Disord 17: 349-362.
57. Greene M, Yan T, Chang E, Hartry A, Touya M, et al. (2018) Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. J Med Econ 21: 127-134.
58. El-Mallakh RS (2007) Medication adherence and the use of long-acting antipsychotics in bipolar disorder. J Psychiatr Pract 13: 79-85.
59. Lahteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, et al. (2018) Real-world Effectiveness of Pharmacologic Treatments for the Prevention of Rehospitalization in a Finnish Nationwide Cohort of Patients With Bipolar Disorder. JAMA Psychiatry 75: 347-55.

60. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtala J, Hoti F, et al. (2017) Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29823 Patients With Schizophrenia. JAMA Psychiatry 74: 686-693.