

ARTIGO DE REVISÃO NARRATIVA/REVIEW ARTICLE

Lurasidona: Dez Anos de Utilização no Tratamento da Depressão Bipolar em Adultos

Lurasidone: Ten Years Treating Adults with Bipolar Depression

✉ MARGARIDA ALBUQUERQUE^{1*}, ✉ JOÃO FACUCHO-OLIVEIRA¹, ✉ DANIEL ESTEVES-SOUSA¹, ✉ NUNO MOURA², ✉ DANIEL NETO³, ✉ PEDRO CINTRA⁴

1. Departamento de Saúde Mental, Hospital de Cascais, Cascais, Portugal

2. Departamento de Saúde Mental, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

3. Casa de Saúde São João de Deus, Funchal, Portugal

4. Departamento de Saúde Mental, Hospital de Cascais, Cascais, Portugal

Resumo

A lurasidona é um antipsicótico atípico, aprovado em 2010 no Canadá e Estados Unidos da América para o tratamento de doentes com o diagnóstico de esquizofrenia ou doença bipolar tipo I. Em 2014 obteve autorização de comercialização na União Europeia (UE), para o tratamento de doentes com 13 anos ou mais, com o diagnóstico de esquizofrenia. É um antipsicótico com estrutura derivada de benzisotiazol, com um perfil de ligação singular, que faz deste um candidato a antidepressivo com pouco impacto metabólico. Em doentes com diagnóstico de doença bipolar, os episódios depressivos tendem a estar presentes a maioria do tempo e a ser difíceis de tratar, como revelam vários estudos que indicam que mais de três quartos de doentes com depressão bipolar experimentam pelo menos dois fármacos e mais de um terço, três ou mais. Em linhas orientadoras de tratamento internacionais, as indicações de primeira linha no tratamento de episódios depressivos de doença bipolar são variadas, sendo a lurasidona considerada uma opção. Considerando a dificuldade na prática clínica em tratar os episódios depressivos na doença bipolar, a autorização de comercialização na UE exclusiva para utilização em esquizofrenia e a expectável disponibilidade do fármaco em Portugal no decurso do ano 2021, pretendemos realizar uma revisão de literatura com enfoque na eficácia e vantagens da utilização de lurasidona em episódios depressivos de doença bipolar e discutir a utilidade da sua aprovação como alternativa de tratamento.

Abstract

Lurasidone is an atypical antipsychotic approved in 2010 in Canada and in the USA for the treatment of adults with schizophrenia or bipolar type I disorder. In 2014 it was approved in the European Union for the treatment of patients with 13 years-old or older, with schizophrenia. Lurasidone is a benzisothiazole derivative with a binding profile that makes it an antidepressant candidate with a low metabolic impact. In patients with bipolar disorder, depressive episodes tend to be present for the majority of the time and are difficult to treat, as shown in multiple surveys indicating that more than three quarters of patients with bipolar depression receive at least two pharmaceutical drugs and more than one third receive three or more. Some relevant international guidelines include different first-line options in the treatment of bipolar depression, among which is lurasidone. Considering the difficulties in treating depressive episodes in bipolar disorder, the EU marketing authorization limiting the use of lurasidone in schizophrenia only and the expectable commercialization in Portugal by 2021, we aim to review the literature regarding the efficacy and advantages of lurasidone for depressive episodes of bipolar disorder and to discuss the usefulness of approving this medication as an alternative treatment approach.

Recebido/Received: 05-02-2021

Aceite/Accepted: 14/03/2021

Publicado / Published: 2021-06-05

* Autor Correspondente/Corresponding Author: Margarida Albuquerque | Departamento de Saúde Mental, Hospital de Cascais. Avenida Brigadeiro Victor Novais Gonçalves, 2755-009 Alcabideche, Portugal | amcrs.albuquerque@gmail.com
© Author(s) (or their employer(s)) and SPPSM Journal 2021. Re-use permitted under CC BY-NC. No commercial re-use.
© Autor (es) (ou seu (s) empregador (es)) e Revista SPPSM 2021. Reutilização permitida de acordo com CC BY-NC.
Nenhuma reutilização comercial.

Keywords: Adult; Antipsychotic Agents/therapeutic use; Bipolar Disorder/drug therapy; Lurasidone Hydrochloride/therapeutic use

Palavras-chave: Adultos; Antipsicóticos/uso terapêutico; Cloridrato de Lurasidona/uso terapêutico; Perturbação Bipolar/tratamento farmacológico

INTRODUCTION

Lurasidone is a benzisothiazole derivative with high affinity for dopamine D_2 , serotonin $5-HT_{2A}$ and $5-HT_7$ receptors (antagonist activity); moderate affinity for serotonin $5-HT_{1A}$ (partial agonist); weak affinity for noradrenaline α_1 , α_2 and serotonin $5-HT_{2C}$ receptors and almost no affinity for histamine H_1 and muscarinic M_1 receptors.¹ Affinity for H_1 and $5-HT_{2C}$ receptors is a potential mechanism for weight gain associated with most of the currently available antipsychotics.^{2,3} Agonist activity at $5-HT_{1A}$ receptors has been associated with antidepressant-like activity in animals and humans studies⁴ and antagonist activity at $5-HT_7$ receptors may also have antidepressant-like effects.⁵ Accordingly, the binding profile of lurasidone makes it a unique antidepressant candidate with a low metabolic impact.

The first episode of a bipolar disorder is usually depressive, and for most people with either bipolar I or bipolar II disorder, depressive episodes last considerably longer than manic or hypomanic episodes, leading frequently to a misdiagnose of major depressive disorder.⁶ Depressive components of bipolar disorders are strongly associated with disability, cognitive impairment, and excess mortality associated with suicide and other violent behavior in youth and intercurrent medical disorders in older years. The high proportion of unresolved long-term depressive morbidity in bipolar disorders anticipates that treatment-resistance represents a major clinical challenge for these illnesses.⁷

As such, management of these patients requires acute phase treatment followed by maintenance therapy, aiming to prevent depressive and/or manic episodes. Treatment involves mostly pharmacological interventions and/or electroconvulsive therapy. Medications used for depressive episodes include lithium, sodium valproate (VPA), carbamazepine, lamotrigine, antidepressants and antipsychotics.⁸ Treatment of depressive symptoms most frequently requires polypharmacy with multiple large scale surveys of prescribing practices indicating that more than three quarters of patients with bipolar depression receive at least two pharmaceutical drugs and more than one third receive three or more.⁹ Lurasidone has been shown to be relevant for bipolar I disorder being specifically approved for depressive episodes both in monotherapy or as adjunctive to lithium or VPA in 2010 in Canada and the USA.^{10,11} In the European Union (EU), marketing authorization was released in 2014 but the treatment with lurasidone was only approved for schizophrenia patients older than 13 years of age.¹² Relevant international guidelines include different options concerning the treatment of bipolar depression. Canadian Network for Mood and

Anxiety Treatments and International Society for Bipolar Disorders guidelines (2018) consider lurasidone, quetiapine, lithium, lamotrigine and combination of lurasidone with lithium/valproic acid.¹³ The British Association for Psychopharmacology Guidelines (2016) considers lurasidone as a first-line option along with quetiapine and olanzapine in the acute treatment.¹⁴ Lurasidone is also an option in prevention of relapse along with lithium, lamotrigine and quetiapine.¹⁴ In the long-term, lurasidone can be used in monotherapy.¹⁴ The Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines (2015) classify quetiapine, lurasidone, olanzapine (in this order), lithium, lamotrigine and valproate as first-line.¹⁵ Other guidelines do not include lurasidone: the National Institute for Health and Care Excellence Guidelines (2018) recommends olanzapine+fluoxetine or quetiapine¹⁶; the World Federation of Societies of Biological Psychiatry (2010)¹⁷ and German S3 Guidelines¹⁸ only include quetiapine as first-line agent for the acute treatment of bipolar depression and the Swiss Society for Bipolar Disorder (2015) recommends monotherapy with lithium, quetiapine and lamotrigine.¹⁹

We aim to review the currently available literature regarding the potential benefits of lurasidone for the treatment of depressive episodes in bipolar disorder, in order to obtain a broad overview of the topic. This is particularly relevant as lurasidone is expected to be available in Portugal during the current year of 2021 and the limitation of marketing authorization in the EU to treat schizophrenia will most likely delay more effective and beneficial treatment approaches for patients with bipolar disorder. The article selection process that was followed during the prosecution of this literature revision consisted in PubMed search with the keywords “lurasidone” and “bipolar depression”, articles published between 2010-2020 in English, Portuguese or Spanish, focusing in adult population. The database search identified 39 articles. After a careful evaluation of title and abstracts, we selected 15 articles which we considered relevant to expose the state of art on the topic and to the clinical practice. The remaining articles were excluded due to title considered not relevant, duplicates or after abstract screening. The articles selected include case reports, clinical trials, observational studies and randomized controlled trials. The characteristics of the selected studies are presented in Table 1.

Table 1. Study characteristics

Author (Date), Country of study	Study design (method)	Duration	Participants	Measures	Outcome
Loebel <i>et al</i> (2014) ²² Multicentric	Randomized, double-blind, placebo-controlled	6-weeks	505 adults, 18- -75 years-old, with bipolar I disorder, currently in a depressive episode	MADRS, CGI- -BP, QIDS, HAM-A, SDS, Q-LES-Q-SF	Lurasidone improved depressive symptoms in patients with bipolar depression
Chapel <i>et al</i> (2016) ²³ Multicentric	Dose-response analysis	6-weeks	825 adults, 18- -75 years-old, with bipolar I disorder currently in a depressive episode	MADRS	Higher doses of lurasidone are associated with greater improvement in depressive symptoms.
Suppes <i>et al</i> (2016) ²⁴ Multicentric	Randomized, double-blind, placebo-controlled	6-weeks	211 adults, 18- -75 years-old, with major depressive disorder with mixed features	MADRS, CGI- -S, YMRS, HAM-A, SDS	Lurasidone significantly improved depressive symptoms.
Sajatovic <i>et al</i> (2016) ²⁵ Multicentric	Post hoc analysis from two randomized, double- -blind, placebo- -controlled	6-weeks	136 adults, > 55 years-old, with bipolar I disorder currently in a depressive episode	MADRS, CGI- -BP-S, QIDS, HAM-A, Q-LES-Q-SF, SDS.	Monotherapy with lurasidone improved depressive symptoms, while improvement on lurasidone adjunctive was not significant.
Nagpal <i>et al</i> (2017) ²⁶ India	Case report	2-weeks	♀ 62 years- -old, bipolar IV disorder, currently in a depressive episode	MADRS	Within 2 weeks of lurasidone plus lithium, the patient showed improvement, with MADRS declining to zero.
Loebel <i>et al</i> (2014) ²⁷ Multicentric	Randomized, double-blind, placebo-controlled	6-weeks	348 adults, 18- -75 years-old, with bipolar I disorder, currently in a depressive episode	MADRS, CGI- -BP, QIDS, HAM-A, SDS, Q-LES-Q-SF	Lurasidone was effective and well tolerated in patients with bipolar depression when added to stable lithium or valproate.
Suppes <i>et al</i> (2016) ²⁸ Multicentric	Randomized, double-blind, placebo-controlled	6-weeks	356 adults, 18- -75 years-old, with bipolar I disorder, currently in a depressive episode	MADRS, CGI- -BP, QIDS, HAM-A, SDS, Q-LES-Q-SF	Significant improvement was not demonstrated for lurasidone adjunctive with lithium or valproate, compared with placebo.
Tohen <i>et al</i> (2017) ²⁹ Multicentric	Database, retrospective cohort study	14-months	3329 adults with bipolar disorder, with at least one prescription of atypical antipsychotic	Characteristics of the patients treated with lurasidone	Patients had highest rates of cardiovascular and metabolic risk factors, more likely to have been initiated in a depressive episode.
Taylor <i>et al</i> (2014) ³⁰	Meta-analysis of randomized, double- -blind, controlled comparisons	Studies with 4-16 weeks duration	Studies including adults with bipolar depression	Studies reporting continuous outcomes in MADRS and HAM-D	Lurasidone was most likely to be ranked second (behind olanzapine+fluoxetine) for efficacy.

Author (Date), Country of study	Study design (method)	Duration	Participants	Measures	Outcome
Yatham <i>et al</i> (2017) ³² Canada	Randomized, open-label	6-weeks	34 adults, 19-65 years-old, with bipolar I disorder, currently euthymic with reduced cognitive function	International Society for Bipolar Disorders Battery Assessment of Neurocognition (ISBD-BANC)	Significant improvement in the lurasidone group compared with the treatment as usual group
Rajagopalan <i>et al</i> (2016) ³³ Multicentric	Secondary analysis from two randomized 6-week, multicenter, double-blind, placebo-controlled studies	6-weeks	825 adults with bipolar I disorder, currently in a depressive episode	Q-LES-Q-SF	Lurasidone performed significantly better in comparison to placebo, similarly as monotherapy and adjunctive therapy in improving self-reported health-related quality of life in patients with bipolar depression
Ketter <i>et al</i> (2016) ³⁴ Multicentric	Open-label, uncontrolled extension study	24-weeks	817 adults, 18-75 years-old, with bipolar I disorder	MADRS, CGI-BP-S, QIDS, HAM-A, Q-LES-Q-SF, SDS.	Sustained improvement in depressive symptoms in patients treated with lurasidone.
Forester <i>et al</i> (2018) ³⁵ Multicentric	Post hoc analysis of a multicenter, 6-months, open-label extension study	24-weeks	141 adults, 55-75 years-old, with bipolar I disorder	MADRS	The antidepressant effect of lurasidone were maintained over 6 months.
Calabrese <i>et al</i> (2017) ³⁶ Multicentric	Randomized, double-blind, placebo-controlled	28-weeks	496 adults with bipolar I disorder, with ≥ 1 manic, mixed manic or depressive episode in the past 2 years, previously stabilized with lurasidone plus lithium/VPA	Time to recurrence as defined by YMRS or MADRS total score ≥ 18 or the CGI-BP score ≥ 4 . QIDS, Q-LES-Q-SF, SDS	Continued treatment with lurasidone was associated with a non-significant reduction in the probability of recurrence of any mood episode compared with placebo.
Miller <i>et al</i> (2018) ³⁷ United States of America	Open, naturalistic, retrospective study	18-weeks	61 adults with bipolar disorder, during a depressive episode or euthymia already under treatment with psychotropic.	Rates of discontinuation of lurasidone; mood state at baseline and at final; CGI-BP at baseline and at final	Discontinuation of lurasidone was related to akathisia, sedation/somnolence, nausea and weight gain. Lurasidone tended to relieve depressive symptoms and to maintain euthymia.
Schaffer <i>et al</i> (2016) ³⁸ Japan	Open, naturalistic, retrospective study	34-months	49 adults with bipolar disorder, treatment-resistant with multiple previous standard medications.	CGI-BP	Adjunctive lurasidone can be effective for maintenance treatment of bipolar disorder, up to 25 months, with a favorable benefit-risk both in acute and maintenance phase of bipolar disorder.

Table 2. Studies of therapeutic efficacy of lurasidone in the short term as measured by MADRS.

Study	N° of patients	Medication	Duration	Mean Change in MADRS	Comparator	Mean Change in MADRS	Significant difference
Loebel <i>et al</i> (2014) ²²	166	Lurasidone monotherapy (20-60 mg/day)	6 weeks	-10.4	Placebo	-6.9	Yes
Loebel <i>et al</i> (2014) ²²	169	Lurasidone monotherapy (80-120 mg/day)	6 weeks	-10.4	Placebo	-6.9	Yes
Loebel <i>et al</i> (2014) ²⁷	348	Lurasidone (20-120 mg/day) adjunctive Lithium/ valproate	6 weeks	-17.1	Placebo adjunctive Lithium/ valproate	-13.5	Yes
Suppes <i>et al</i> (2016) ²⁴	211	Lurasidone monotherapy (20-60 mg/day)	6 weeks	-20.5	Placebo	-13.0	Yes
Suppes <i>et al</i> (2016) ²⁸	356	Lurasidone adjunctive Lithium/ valproate	6 weeks	-11.8	Placebo adjunctive Lithium/ valproate	-10.4	No
Sajatovic <i>et al</i> (2016) ²⁵	84	Lurasidone monotherapy pooled dose (20-60 mg/day or 80-120 mg/day)	6 weeks	-14.8	Placebo	-7.1	Yes
Sajatovic <i>et al</i> (2016) ²⁵	53	Lurasidone adjunctive Lithium/ valproate	6 weeks	-13.9	Placebo adjunctive Lithium/ valproate	-11.1	No

THERAPEUTIC EFFICACY OF LURASIDONE IN SHORT-TERM

Acute-phase treatment of depressive episodes in bipolar I disorder is a key component of management of the disorder, however there is controversy regarding drug selection.^{8,20} Ideal treatment would rapidly and completely ameliorate depressive symptoms without increasing the risk of mania or other adverse effects. Clinical practice shows that the drugs used are not uniformly effective, especially in monotherapy.⁸ Besides, most therapeutic approaches are frequently associated with adverse effects including weight gain and other metabolic disturbances, extrapyramidal symptoms, sexual dysfunction and anticholinergic effects. Other less frequently but highly relevant side effects include QT prolongation in the electrocardiogram, skin rash or central nervous system symptoms such as ataxia or seizures.¹³

According to the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guidelines, first-line treatment in the acute management of bipolar-depression includes lithium, lamotrigine, quetiapine or lurasidone monotherapy. Importantly, the same international guidelines define that these can be combined and any first-line treatment monotherapy can be augmented with any other drug of the list. All

first-line options should be tried in adequate doses for an adequate duration of time before considering second-line options either as an add-on or switch strategy. Second-line treatments comprise monotherapy with VPA or adjunctive treatment with antidepressants (VPA/lithium plus selective serotonin reuptake inhibitor (SSRI) or bupropion), cariprazine (although there is less clinical experience supporting its use) and olanzapine/fluoxetine. For patients with psychotic depression, catatonia, elevated risk of suicide, treatment-refractory depression or with certain medical complications, electroconvulsivotherapy should be considered. In general, medications that have been found to be effective in the acute phase, should be continued during the maintenance phase.¹³ The British Association Pharmacology declares quetiapine to have the most convincing short-term efficacy and relapse prevention profile for bipolar depression. Olanzapine (in combination with fluoxetine or to a lesser extent in monotherapy), lurasidone and lamotrigine also have data supporting efficacy.¹ Antidepressants approved for unipolar depression may be effective but require co-prescription with an agent that reduces the risk of mania, like lithium, VPA or antipsychotics. Poor evidence supports monotherapy with lithium, VPA or carbamazepine for acute treatment of bipolar depression.²¹

a. Efficacy on depressive symptoms

i. Acute treatment with lurasidone as monotherapy

In a 6-week randomized, double-blind, placebo-controlled study with 505 patients (18-75 years-old), named PREVAIL 2, lurasidone 20-120 mg showed efficacy as monotherapy. Patients had the diagnosis of bipolar I disorder and were experiencing a depressive episode (according to Diagnostic Statistical Manual of Mental Disorders DSM-IV-TR, with or without rapid cycling and without psychotic features). They were randomly assigned to placebo or lurasidone groups. Lurasidone significantly reduced mean Montgomery-Asberg Depression Rating Scale (MADRS) total scores at week 6 for both the 20-60 mg/day group and the 80-120 mg/day group compared to placebo. Moreover, lurasidone treatment also resulted in a significantly greater endpoint reduction in Clinical Global Impression – Bipolar Illness (CGI-BP) depression severity scores for both the 20-60 mg/day group and the 80-120 mg/day group compared to placebo. This study suggests that treatment should be started at 20 mg/day and increased as needed over the 20-120 mg/day range.²²

A dose-response analysis evaluating exposure to 20-120 mg/day of lurasidone and subsequent clinical efficacy was made in order to inform clinical dosing decisions and identify subgroups of patients with bipolar depression who might need dose adjustments. The mean net drug effect at week 6 end point was estimated to be a 6.0-point decrease in MADRS score per 100 mg of lurasidone. A linear dose-dependent effect has been demonstrated: higher doses of lurasidone in monotherapy are associated with greater improvement in depressive symptoms in a sample of 485 bipolar I patients, based on MADRS score.²³

In a randomized double-blind placebo-controlled clinical trial including 211 adult patients diagnosed with major depressive disorder associated with subthreshold hypomanic symptoms, lurasidone (20-60 mg/day) greatly improved the depressive symptoms from week 1 to week 6 on the MADRS assessment, and from weeks 2 to 6 on CGI-S (Clinical Global Impressions Severity Subscale Score).²⁴

The efficacy and safety of lurasidone in patients aged 55 years or older with bipolar depression was evaluated in a post-hoc analysis derived from two multiregional double-blind, placebo-controlled, parallel-group trials of lurasidone in the acute treatment of adult bipolar depression. Patients were assigned to a monotherapy arm study, divided in two groups in fixed flexible dose ranges of either 20-60 mg or 80-120 mg of lurasidone daily. The results suggest that monotherapy with lurasidone is an effective treatment for bipolar depression with efficacy shown by mean changes from baseline to week 6 in the MADRS, CGI-BP-S and Quick Inventory of Depressive Symptomatology- Self Report (QIDS-SR₁₆) being significantly greater for lurasidone versus placebo.²⁵

Finally, an off-label use of lurasidone, concerning a case of a moderate depressive episode in a 62-year-old lady diagnosed with bipolar type IV disorder, pointed out the probable utility of lurasidone in the bipolar spectrum, beyond type I.²⁶

ii. Acute treatment with lurasidone as adjunctive therapy

In patients with bipolar I disorder who had insufficient response to monotherapy with mood-stabilizing agents after 28 days of treatment, the association of lurasidone with lithium or VPA was shown to be clinically relevant (in a study named PREVAIL 1). For the adjunctive treatment with lithium or VPA, the sample consisted of 348 patients receiving at least one dose of 20-120 mg/day of lurasidone. Importantly, lurasidone adjunctive treatment significantly reduced mean MADRS and CGI-BP total score at week 6 compared with the placebo group.²⁷

Also clinically relevant, a linear dose-dependent effect has been demonstrated in a sample of 340 bipolar I patients. Treatment with lurasidone (20-120 mg/day) as adjunctive therapy to lithium or VPA resulted in greater improvement of depressive symptoms based on MADRS assessments.²³ Despite the above mentioned results, other authors have not found clinical benefits of lurasidone in acute treatment of bipolar depression. In the post-hoc analysis of Sajatovic *et al*, the efficacy and safety of lurasidone adjunctive to lithium or valproate in bipolar depression patients during acute treatment was evaluated. Patients were assigned to the adjunctive therapy arm study (patients on treatment with lithium or VPA to either adjunctive lurasidone 20-120 mg or placebo), with efficacy shown by mean changes from baseline to week 6 in the MADRS, CGI-BP-S and Quick Inventory of Depressive Symptomatology- Self Report (QIDS-SR₁₆). The mean change in the scores at week 6 was not significantly different from placebo.²⁵

One other study evaluated 365 adult outpatients diagnosed with bipolar I depression with a history of at least one manic or mixed manic episode without psychotic features, that were treated for at least 28 days with lithium and VPA. Patients were randomized, based on treatment with lithium or VPA, to either adjunctive lurasidone 20-120 mg/day or placebo in 1:1 ratio and assessed on MADRS and on CGI-BP-S from baseline to week 6. Statistical superiority for lurasidone versus placebo was observed from weeks 2 to 5 for changes in MADRS and from 3 to 5 in CGI-BP-S. At week 6, however, no significant improvement was demonstrated. Nevertheless, a previous adjunctive study of lurasidone (PREVAIL 1)²⁷ regarding treatment of bipolar depression successfully demonstrated efficacy at 6 weeks on both MADRS and CGI-BP-S. A possible reason for this small effect size may be the median duration of treatment with lithium or VPA (4.4 and 7.5 months respectively) which was notably longer than in PREVAIL 1.²⁸

iii. Lurasidone compared to other antipsychotics

A retrospective cohort study (including 3329 patients) compared and described background characteristics, comorbidities, prior health care utilization, and costs for patients with bipolar disorder who initiated lurasidone versus other antipsychotics. The study provided insight on how the medications are used in real-world contexts, showing that lurasidone-treated patients with bipolar disorder tended to have a more complex clinical profile, highest rates

of prior cardiovascular and metabolic risk factors (which may be in line with its favorable metabolic tolerability profile) and increased probability (than those treated with quetiapine or risperidone) of prior antidepressant treatment (which may be related to a previous diagnosis of unipolar depression).²⁹

A multiple-treatment meta-analysis of randomized, double-blind, controlled comparisons of 4-16 weeks in adults with bipolar depression using validated psychometric scales (MADRS or HAM-D) showed that: olanzapine plus fluoxetine was most likely to be ranked first for efficacy with respect to response. Remarkably, lurasidone was ranked as second in the same study assessing efficacy. However, concerns about metabolic side effects of olanzapine discourage its usage. Selective inhibitors of MAO (iMAO), ziprasidone, aripiprazole and risperidone showed limited or no therapeutic benefits in bipolar depression.³⁰ In The National Institute for Health and Care Excellence 2014 guidelines quetiapine is considered to have a unique combination of pharmacological actions, meriting the first line status in bipolar depression. Olanzapine and lurasidone also merit this first line status, with lurasidone having the best metabolic profile. Aripiprazole trials failed in proving efficacy in bipolar depression. Cariprazine showed efficacy.¹⁶

iv. Lurasidone adjunctive to other antipsychotics

As stated before, lurasidone has a high affinity to 5-HT₇. These receptors are involved in cognitive function, such as learning and memory.³¹ Yatham *et al* evaluated the efficacy of lurasidone as adjunctive therapy in improving cognitive function in bipolar I disorder in a 6-week, randomized, trial with 34 patients to evaluate treatment as usual or “add-on” therapy of lurasidone (20-80 mg). Assessment with clinical rating scale (International Society for Bipolar Disorders Battery for Assessment of Neurocognition ISBD-BANC) at week 3 and week 6 showed that the adjunctive lurasidone group had better results than treatment as usual in improving ISBD-BANC global cognition score (mainly visual and working memory), which is noteworthy once patients with bipolar disorder often complain of cognitive difficulties.³²

v. Efficacy on anxiety symptoms, illness severity and health-related quality of life and disability

Treatment in monotherapy with lurasidone (study PREVAIL2) was associated with significant improvement compared with placebo in anxiety symptoms, as measured by the clinician-rated Hamilton Anxiety Rating Scale (HAM-A), the patient-rated Quick Inventory of Depressive Symptomatology, the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) and the Sheehan Disability Scale (SDS).²² Similarly, in the PREVAIL1, a significantly great improvement in anxiety symptoms and in patient-reported measures of quality of life and functional impairment was registered based on the analysis of HARS, QIDS-SR₁₆, Q-LES-Q-SF and SDS.²⁶ A secondary

analysis of these two previous placebo-controlled trials (PREVAIL 1/2)^{22,27} was made to assess the direct and indirect effects of lurasidone on health-related quality of life (HRQoL). This analysis showed that lurasidone performed significantly better in comparison to placebo in improving self-reported HRQoL in patients with bipolar depression, similarly as a monotherapy and as an adjunctive therapy. These changes were largely mediated by improvement in depressive symptoms.³³

Sajatovic *et al* conducted a post-hoc analysis derived from double-blind, placebo-controlled trials of lurasidone in the acute treatment of patients older than 55 years-old with bipolar depression. Besides the already reported analysis of efficacy in MADRS, CGI-BP-S and QIDS-SR₁₆, it was also evaluated for efficacy in HAM-A, Q-LES-Q-SF and SDS scores. However, both in the monotherapy and adjunctive therapy arm groups, the mean changes in the scores were significant, compared to placebo.²⁵ Suppes *et al* demonstrated significant improvement in anxiety and quality of life both in monotherapy and adjunctive to lithium/valproate groups^{24,28} as measured by HAM-A and Q-LES-Q.

b. Therapeutic efficacy of lurasidone in long-term

A 6-month, open-label, uncontrolled study enrolling 817 patients who had completed one of three 6-week double-blind trials^{22,27,28} evaluating the efficacy of lurasidone compared to placebo for treatment of bipolar I depression, either as monotherapy or adjunctive therapy with lithium or VPA showed a sustained improvement in depressive symptoms, based on MADRS score, in patients taking 20-120 mg of lurasidone daily. The mean maintenance dose was similar to that used in acute study: about 65 mg. In the extension group who switched from acute-phase placebo to lurasidone monotherapy, the mean change in MADRS at month 6 was 10.8; in the group maintaining lurasidone in monotherapy, the mean change was 5.0. Additional improvement was also observed for the adjunctive therapy group that continued to receive lurasidone (mean change of 4.9) and for the adjunctive therapy group that switched from placebo to lurasidone (mean change of 8.2). At baseline, the proportion of patients who met response criteria was 56.3% in monotherapy and 51.1% in adjunctive therapy and the proportion of patients who met remission criteria was 44.9% and 45.7% respectively. The responder and remitter criteria were analyzed at month 6 and the proportion of responders and remitters increased both in the monotherapy and in the adjunctive therapy. Among the nonresponders at baseline, the majority had converted to responder status both in the monotherapy (83%) and adjunctive therapy (73%). The proportion of relapse was about 10% in both groups.³⁴

A parent 6-month open-label extension post-hoc analysis from the same three 6-week, double-blind, acute treatment studies was also carried out. The 141 patients (older adults, 80% aged 55-65 years-old) who have completed 6 weeks of double-blind, placebo-controlled treatment either with lurasidone monotherapy or adjunctive therapy (with lithium or VPA) were enrolled in the analysis.

Antidepressant effectiveness was again accessed using MADRS. There was a significant decrease in MADRS score in both the monotherapy and adjunctive therapy group. Among older adults who switched from acute-phase placebo to lurasidone, the mean score change at month 6 was 12.0-points. Among those who were kept on lurasidone, the mean change in MADRS score was 3.3-points. At month 6 of this extension, the proportion of older adults receiving lurasidone who met response criteria was 76.9% in monotherapy and 77.8% in adjunctive therapy and the proportion of ones who met remission criteria was 64.1% in monotherapy and 71.4% in adjunctive therapy. Regarding patients who did not meet response criteria at baseline of the current extension study, 85.3% became responders during 6 months of treatment with lurasidone.³⁵

In a multiregional, randomized, double-blind, placebo-controlled study with patients who had completed a 12-20 week open-label treatment with lurasidone combined with lithium or VPA (stabilization phase), 465 patients were randomized to continue on lurasidone (dose range 20-80 mg) or switch to placebo for 28 weeks (in combination with lithium or valproate). Treatment with lurasidone reduced the probability of recurrence of mood episodes, compared to placebo plus lithium or valproate (without statistical significance). Despite lurasidone being found to be particularly beneficial in the reduction in time to recurrence of a depressive episode, this reduction also did not achieve statistical significance. Different factors may have contributed to this result: the short period of randomization (6-month compared to 12-24 months) may have limited the recurrence rate in the placebo group, which may mean that the sample size was insufficient.³⁶ Nevertheless, the decreasing time to recurrence of depressive episodes is likely to be clinically very meaningful considering the long-term suffering of bipolar patients.

Additionally, a retrospective, open, naturalistic study of 61 patients with bipolar disorder who received adjunctive treatment with lurasidone (starting at 20 mg/day with a weakly based increase to reach 80 mg/day) during a depressive or euthymic episode, showed that, despite a high rate of discontinuation, lurasidone appeared to be very relevant at improving depressive symptoms and maintaining euthymia. The discontinuation was associated with adverse effects (54%), inefficacy (16%) and other reasons (6%) including hypomania. The open naturalistic design of the study is an important limitation of this study as stated by the authors.³⁷

c. Therapeutic efficacy of lurasidone in treatment-resistant bipolar disorder

A retrospective, naturalistic, open-trial of lurasidone for 2-month (acute) followed by a 34-month (maintenance) adjunctive therapy in 49 patients with treatment-resistant bipolar disorder (both non responders or partial but inadequate responders to numerous previous trials of standard medication for bipolar disorder) showed that lurasidone is effective in the short-term and up to 25 months. The only exclusion criteria were pregnancy, active substance abuse and age (<18 years-old). The severity of symptoms was

accessed before treatment with CGI-BP score. The most common causes for discontinuation in the acute phase (27 patients) were: unacceptable adverse effects (59%) and lack of efficacy (41%). At the end of the maintenance phase, 64% of the patients (14) were still taking lurasidone. The average dose of lurasidone was 21mg and they were taking an average of other 3 psychiatric drugs.³⁸

d. Tolerability of lurasidone

Acute treatment with lurasidone was associated with a small dose-related effect on prolactin and minimal changes in weight, blood lipid profile and measures of glycemic control.^{22,24,25,27,34} The most frequent adverse events associated with lurasidone were mild to moderate nausea^{22,24-28}, diarrhea,²⁸ headache,^{22,24-27} akathisia,^{22,24-28} extrapyramidal symptoms²⁸ and somnolence^{22,24,28} or insomnia.^{25,27}

Similarly, among the 6-month extension post-hoc study including younger patients, the most reported adverse events were parkinsonism, akathisia, somnolence, headache, nausea, insomnia and anxiety, mild to moderate.³⁴ Among the 6-month extension post-hoc study including older patients, the most reported adverse events were headache, insomnia and nasopharyngitis. Up to 7.5 months of lurasidone treatment in older adults (55-65 years-old) was associated with no increase in mean weight or glycemic indices, no meaningful changes in vital signs, electrocardiogram parameters or blood chemistry.³⁵

In the randomized, double-blind, placebo-controlled study with patients who had completed a 12-20 week open-label treatment with lurasidone combined with lithium or VPA (stabilization phase), no difference between lurasidone and placebo at end-point in body weight or body mass index (BMI) was shown.³⁶

e. Lurasidone and risk of mania and suicide ideation

There were no differences observed between lurasidone and placebo-groups, both in monotherapy and adjunctive studies, concerning the incidence of emergent mania^{22,27,28,38} or suicidal ideation,^{22,27,28,38} in the acute studies. In the extension studies, the treatment emergent mania incidence was low (3.8% in adjunctive therapy and 1.3% in monotherapy).³⁴ These rates are consistent with the incidence reported in the 6-month study of older population³⁵ and with the incidence in the treatment-resistant group, where none of the patients experienced suicidal thoughts or behaviours.³⁸

CONCLUSION

The above data suggests that lurasidone offers potential to control depressive symptoms when used as monotherapy or as an adjunct to lithium or VPA in patients with a depressive episode in the context of bipolar type I disorder, in the acute phase. In table 2 (Appendix) we summarize the reported results of the short-term studies included in this revision, as measured by MADRS.

The extension studies (longer than 12 weeks) give important information, in spite of the fact that all of them present

relevant limitations due to its open-label, uncontrolled design and lack of an active comparator, which compromises the reliability of the conclusions.

Similarly, lurasidone is associated with significant improvement, compared to placebo, in anxiety symptoms and quality of life.

Both as monotherapy and as adjunctive therapy, in the short and long-term, lurasidone shows a favorable tolerability profile, carrying a relatively low risk of weight gain, metabolic disturbances and cardiac arrhythmias and a favorable profile of risk of emergent mania or suicide ideation.

Nevertheless, it is important to refer that the studies included in this revision present some limitations: the majority of short-term studies utilize placebo as comparator, which difficult the generalization of the results to the real world patients; one of the studies was a case report, which is also a limitation when we try to extrapolate the results; the duration of the studies was far from real-world needs in the treatment of these patients; the selection biases was evident in almost all studies (except the «treatment-resistant patients» study) because patients with significant medical and neurological comorbidities were excluded. Besides, these results are based on a scientific review of the literature which aims at documenting the state of art with respect to the utilization of lurasidone in bipolar depression. It consists of a critical analysis of the literature, providing the reader

with actualized knowledge on the topic. However, it lacks the methodological approach of a systematic review, that would allow the access to many more articles and studies, reducing the risk of bias in our conclusions. In the topic «Lurasidone compared to other antipsychotics», a systematic review would probably be very relevant, since it may have given practice-oriented conclusions and guidelines on the comparison with other second and third generation antipsychotics.

The «real-world» studies^{29,37,38} showed us that lurasidone-treated patients tended to have a more complex clinical profile, medical comorbidities and prior treatment history when compared to patients who are initiated other medication, which may reflect the role perceived by clinical practitioners for lurasidone in clinical use. It also indicates that lurasidone is safe and an effective adjunctive treatment in treatment-resistant patients diagnosed with bipolar disorder, both in acute and long-term.³⁷

In conclusion, these exploratory studies should promote more research in order to fully assess clinical utility of lurasidone in depressive episodes of bipolar disorder in real-world patients, to better clarify the role of this drug. Regardless, considering the hardship in the treatment of depressive episodes in bipolar disorder, we emphasize the importance of considering lurasidone as a therapeutic option.

Acknowledgments/Agradecimentos: To Maria Reis, Molecular Biology Researcher at Ophiomic®, Lisbon, Portugal, for the scientific and linguistic revision of the manuscript.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.

Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

References

- Ishibashi T, Horisawa T, Tokuda K, Ishiyama T, Ogasawa M, Tagashira R, et al. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. *J Pharmacol Exp Ther.* 2010;334:171-81. doi:10.1124/jpet.110.167346.
- Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology.* 2003; 28:519-26. doi:10.1038/sj.npp.1300027
- Reynolds GP, Hill MJ, Kirk SL. The 5-HT2C receptor and antipsychotic induced weight gain - mechanisms and genetics. *J Psychopharmacol.* 2006; 20:15-8. doi:10.1177/1359786806066040.
- Millan MJ. Improving the treatment of schizophrenia: focus on serotonin (5-HT)(1A) receptors. *J Pharmacol Exp Ther.* 2000; 295:853-61.
- Hedlund PB, Huitron-Resendiz S, Henriksen SJ, Sutcliffe JG. 5-HT7 receptor inhibition and inactivation induce antidepressant-like behavior and sleep pattern. *Biol Psychiatry.* 2005; 58:831-7. doi:10.1016/j.biopsych.2005.05.012.
- Carvalho AF, Firth J, Vieta E. Bipolar Disorder. *N Engl J Med.* 2020; 383:58-66. doi: 10.1056/NEJMra1906193.

7. Tondo L, Vázquez GH, Baldessarini RJ. Options for pharmacological treatment of refractory bipolar depression. *Curr Psychiatry Rep.* 2014;16:431. doi:10.1007/s11920-013-0431-y.
8. Vieta E, Valentí M. Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. *CNS Drugs.* 2013; 27:515-29. doi:10.1007/s40263-013-0073-y.
9. Greil W, Häberle A, Haueis P, Grohmann R, Russman S. Pharmacotherapeutic trends in 2231 psychiatric inpatients with bipolar depression from the International AMSP Project between 1994 and 2009. *J Affect Disord.* 2012; 136:534-42. doi:10.1016/j.jad.2011.10.033.
10. Latuda (lurasidone hydrochloride) [Internet]. 2020 [cited 2020 Dez 10]. Available from: <https://www.sunovion.ca/monographs/latuda.pdf>
11. FDA [Internet]. 2013 [cited 2020 Dez 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/200603lbls10s11.pdf
12. European Medicines Agency [Internet]. 2014 [cited 2020 Dez 10]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/latuda>
13. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20:97-170. doi:10.1111/bdi.12609
14. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. Full guideline. 2016[cited 2021 mar 5]. Available from: <https://www.bap.org.uk/docdetails.php?docID=6>
15. Malhi GS, Bassett Darryl, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry.* 2015;49:1087-206. doi:10.1177/0004867415617657.
16. National Institute for Health and Care Excellence. Clinical Guideline Number 185 (CG185); Bipolar disorder: assessment and management [cited 2021 mar 9]. Available from: <https://www.nice.org.uk/guidance/cg185/resources/bipolar-disorder-assessment-and-management-pdf-35109814379461>.
17. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry.* 2010;11:81-109. doi:10.3109/15622970903555881
18. Pfennig A, Bschor T, Baghai T, Bräunig P, Brieger P, Falkai P, et al. S3-Leitlinie zur Diagnostik und Therapie bipolarer Störungen: Entwicklungsprozess und wesentliche Empfehlungen. *Nervenarzt.* 2012; 83:568-86. doi: 10.1007/s00115-011-3415-3.
19. Hasler G, Preisig M, Müller T. Bipolare Störungen: update 2015. *Schweizerisches Med Forum.* 2015; 15:486-94.
20. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry.* 2013; 170:1249-62. doi:10.1176/appi.ajp.2013.13020185.
21. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorders: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol.* 2016; 30:495-553.
22. Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2014; 171:160-8. doi:10.1176/appi.ajp.2013.13070984
23. Chapel S, Chiu Y, Hsu J, Cucchiaro J, Loebel A. Lurasidone Dose Response in Bipolar Depression: A Population Dose-response Analysis. *Clin Ther.* 2016;38:4-15. doi:10.1016/j.clinthera.2015.11.013.
24. Suppes T, Silva R, Cucchiaro J, Mao Y, Targum S, Streicher C, et al. Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study. *Am J Psychiatry.* 2016;173:400-7. doi:10.1176/appi.ajp.2015.15060770.
25. Sajatovic M, Forester BP, Tsai J, Kroger H, Pikalov A, Cucchiaro J, et al. Efficacy of Lurasidone in Adults Aged 55 Years and Older With Bipolar Depression: Post Hoc Analysis of 2 Double-Blind, Placebo-Controlled Studies. *J Clin Psychiatry.* 2016;77:e1324-e1331. doi:10.4088/JCP.15m10261.
26. Nagpal K, Kumar M, Kumar R. Utility of lurasidone in bipolar disorder type IV patient-A case report. *Asian J Psychiatry.* 2017;29:164-5. doi:10.1016/j.ajp.2017.05.020.
27. Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2013;171:169-77. doi:10.1176/appi.ajp.2013.13070985.
28. Suppes T, Kroger A, Pikalov A, Loebel A. Lurasidone adjunctive with lithium or valproate for bipolar depression: A placebo-controlled trial utilizing prospective and retrospective enrolment cohorts. *J Psychiatr Res.* 2016;78:86-93. doi:10.1016/j.jpsychires.2016.03.012.
29. Tohen M, Ng-Mak D, Rajagopalan K, Halpern R, Chuang CC, Loebel A. Patient Characteristics Associated with Use of Lurasidone Versus Other Atypical Antipsychotics in Patients With Bipolar Disorder: Analysis From a Claims Database in the United States. *Prim Care Companion CNS Disord.* 2017;19. doi:10.4088/PCC.16m02066

30. Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*. 2014; 130:452-69. doi:10.1111/acps.12343.
31. Cifariello A, Pompili A, Gasbarri A. 5-HT7 receptors in the modulation of cognitive processes. *Behav Brain Res*. 2008; 195: 171-9. doi: 10.1016/j.bbr.2007.12.012.
32. Yatham LN, Mackala S, Basivireddy J, Ahn S, Walji N, Hu C, et al. Lurasidone versus treatment as usual for cognitive impairment in euthymic patients with bipolar I disorder: a randomised, open-label, pilot study. *Lancet Psychiatry*. 2017; 4:208-17. doi:10.1016/S2215-0366(17)30046-9.
33. Rajagopalan K, Bacci ED, Ng-Mak D, Wyrwich K, Pikalov A, Loebel A. Effects on health-related quality of life in patients treated with lurasidone for bipolar depression: results from two placebo controlled bipolar depression trials. *BMC Psychiatry*. 2016;16:157. doi:10.1186/s12888-016-0865-y.
34. Ketter TA, Sarma K, Silva R, Kroger H, Cucchiaro J, Loebel A. Lurasidone in the long-term treatment of patients with bipolar disorder: a 24-week open-label extension study. *Depress Anxiety*. 2016; 33:424-34. doi:10.1002/da.22479.
35. Forester BP, Sajatovic M, Tsai J, Pikalov A, Cucchiaro J, Loebel A. Safety and Effectiveness of Long-Term Treatment with Lurasidone in Older Adults with Bipolar Depression: Post-Hoc Analysis of a 6-Month, Open-Label Study. *Am J Geriatr Psychiatry*. 2018; 26:150-9. doi:10.1016/j.jagp.2017.08.013.
36. Calabrese JR, Pikalov A, Streicher C, Cucchiaro J, Mao Y, Loebel A. Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder. *Eur Neuropsychopharmacol*. 2017; 27:865-76. doi:10.1016/j.euroneuro.2017.06.013.
37. Miller S, Do D, Gershon A, Wang PW, Hooshmand F, Chang LS, et al. Longer-Term Effectiveness and Tolerability of Adjunctive Open Lurasidone in Patients With Bipolar Disorder. *J Clin Psychopharmacol*. 2018;38:207-211. doi:10.1097/JCP.0000000000000867.
38. Schaffer CB, Schaffer LC, Nordhal TE, Stark NM, Gohring CE. An Open Trial of Lurasidone as an Acute and Maintenance Adjunctive Treatment for Outpatients With Treatment-Resistant Bipolar Disorder. *J Clin Psychopharmacol*. 2016; 36:88-9. doi:10.1097/jcp.0000000000000450.