

Enhancing stability in bipolar disorder

Il valore della stabilizzazione nel disturbo bipolare

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Summary

Objectives

Bipolar disorder (BD) is usually diagnosed after a delay of at least 10 years; during this period, bipolar subjects often take inappropriate treatments. The purpose of this overview of the current literature is to provide a specific point of view regarding several critical issues such as diagnosis, management and treatment of this complex illness.

Methods

A detailed search of the literature was conducted in Pubmed/Medline, Scopus, Science Direct, PsycLit and PsycInfo databases to identify all publications in English language from January 1980 to January 2013. The study used the following terms: "Stabilization" and "Management" and "Bipolar Disorder" OR "BD" and "acute treatment" and "maintenance treatment".

Results

Mood stabilizers are the first-line treatment during manic, hypomanic and mixed episodes of BD. Lithium still represents

the gold standard among all the currently available treatments of BD. Most of the available evidence suggests that mood stabilizers are effective in the acute treatment, maintenance and prophylaxis of BD. Quetiapine is the only one among the available second-generation antipsychotics to have an indication in the acute depressive episodes of BD, whereas both quetiapine and lamotrigine are indicated for the prophylaxis of depressive bipolar episodes. These agents can be used as monotherapy but also, more frequently, in combination.

Conclusions

Treatment of BD should be focused on maintenance therapy through the use of mood stabilizers. Antidepressant drugs should be avoided due to the possible induction of rapid cycling and the long-term instability.

Key words

Bipolar disorder • Mood stability • Maintenance treatment • Antidepressant medications • Mood stabilizers

Introduction

Misdiagnosis in psychiatry is quite common, but it is also frequent to get unexpected findings using the available psychoactive treatments. None of the clinical histories of individuals with bipolar disorder (BD) may be considered similar to another, and each case must be considered a unique clinical experience.

In most cases, diagnosis of BD is performed with a mean delay of about 10 years, and during this period bipolar subjects usually take inappropriate treatments that are active on aspecific symptoms¹⁻³. Specifically, over 60% of patients with BD reported having received at least 1-4 previous diagnoses: the diagnostic delay is more pronounced in women with BD type II than in men². One of the most important reasons concerning the mean diagnostic delay in BD is typically related to the various clinical presenta-

tions of the disease⁴ and, in particular, to the fact that only a part of the clinical history is referred by bipolar patients who frequently deny their illness.

More generally, affective disorders are associated with a higher risk of suicide compared to the general population⁵⁻⁹, and suicide is widely recognized as one of the leading causes of death in patients with BD¹⁰. In fact, suicide rates in patients diagnosed with BD (especially with BD type I) or severe recurrent depression are at least 20 times higher than those in the general population, and substantially higher than those in other psychiatric disorders. In BD suicide risk is on average 390/100,000/year (0.39%/year), which is 28 times higher than that of the general population. It is important to highlight that the early and timely diagnosis is also associated with a lower prevalence of suicide attempts and a less severity of the illness¹.

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Depressed mood is, no doubt, one of the most frequent symptoms during depressive bipolar episodes, although insomnia/hypersomnia, anorexia/hyperphagia, slow-down/psychomotor agitation are also very common¹¹. In addition, DSM-IV-TR includes in the same diagnostic category patients with very different clinical features such as those with mania or mixed states (characterized by the presence of both depressive and manic symptoms). Subjects with a mixed episode frequently show heterogeneous clinical features: Kraepelin identified, within what we currently mention as bipolar spectrum¹²⁻¹³, the following opposite psychopathological states “pure mania” and “pure depression” as well as many clinical variants including agitated depression, mania with poverty ideation, manic stupor, depression with flight of ideas and inhibited mania¹⁴.

The current diagnostic criteria also suggest the existence of a relevant heterogeneity within the different bipolar subtypes. The prevalence of mood disorders generally varies according to the different diagnostic criteria that were used. There is evidence that the same subject has a likelihood of 11.1% of receiving a diagnosis of BD according to DSM-IV-TR, 33.3% with Zurich “hard” criteria and 50% using Zurich “soft” criteria¹⁵.

By using hyperactivity and duration of manic/hypomanic episode as criteria for the diagnostic evaluation, it is usually not possible to distinguish if patients with major depressive disorder have a bipolar or unipolar disorder. The present overview of the literature aimed to provide a critical and detailed point of view concerning several crucial issues such as diagnosis, management and treatment of bipolar illness, and to analyze the real value of stabilization in the long-term outcome of BD.

Methods

We conducted a detailed search of the current literature using Pubmed/Medline, Scopus, Science Direct, PsycLit and PsycInfo databases in order to identify all English-language full-text publications from January 1980 to January 2013.

The search used the following terms: “Stabilization” and “Management” and “Bipolar disorder” OR “BD” and “Acute treatment” and “Maintenance treatment”. One researcher (GS) independently conducted the search, and any discrepancies regarding the inclusion of potentially eligible studies was performed by consulting the second senior author (PG).

The reference lists of all included studies were also manually consulted to include additional eligible studies. We included all English-language studies with original data about the main topic of the research. Approximately 150 studies were recognized as eligible, and 90 were included in this literature overview.

The use of antidepressants in the treatment of BD

To date, there is no study showing that antidepressant drugs add stabilizing effects to the long-term treatment of BD. According to the stress-diathesis model¹⁶⁻¹⁸, we may imagine that BD is divided into 3 general stages. 1) An early phase that can be defined by the presence of a biological predisposition (vulnerability), which is necessary but not sufficient for the development of bipolar illness. The beginning of this phase is usually represented by the onset of a reactive depression; in these cases, if the subject is not treated with antidepressant drugs, only a cyclothymic disorder characterized by mood fluctuations without significant psychosocial impairment may emerge. 2) A hypomanic/manic-depression-free interval as a result of the worsening of any mood cycle that is characterized by pathological mood fluctuations (here, a psychiatric disorder is usually emerging). 3) A cycle of hypomanic/manic-depressive-free interval that has usually a negative outcome since it is characterized by higher clinical severity than other subtypes.

Importantly, it is more difficult to (retrospectively) evaluate euphoria rather than hyperactivity in clinical practice, and similarly the distinction between hypomania and mania is not always straightforward¹⁹. Clinicians should be able to diagnose BD even after depressive episodes, during hyperactivity: BD is a mood disorder that leads to several impairments in the biological rhythms. When hypomania occurs, patients do not refer to psychiatrists for several reasons. Firstly, they do not realize the “fluctuations” of their mood (it is possible that symptoms such as delusions, hallucinations or impaired insight occurred). Second, our society tends to judge individuals based on their levels of performance, and hypomania is not generally considered pathological by most subjects. Hypomania or mania last few days and generally represent the egosyntonic part of the disease whereas depressive episodes usually represent the egodystonic part that was largely declared by patients, being experienced as painful and disabling. Moreover, studies clearly indicated that depression is a cyclic and also recurrent disease (consisting of phasic phenomena)²⁰⁻²². If antidepressant medications that are usually associated with a reduction of the perceived depressive pain are prescribed, as mentioned, patients are forced to believe that antidepressant medications can really “heal”, and that his/her psychiatrist was able to intervene in a very effective and timely manner, without considering that a new hypomanic/manic episode could be induced.

Antidepressant medications should be considered, in our opinion, as drugs with strong stimulant properties that may induce mood instability. These are molecules that act by reducing the free intervals of the illness up to determining their suppression over time: under antidepressants, the

disorder may acquire the specific features of continuous cyclicity²³⁻²⁷. Currently, there are no studies demonstrating that antidepressant drugs are actually useful in the treatment of BD, and some researchers²⁸⁻³⁰ have suggested that this is related to the fact that most mood disorders diagnosed as “unipolar” are actually bipolar types.

Rapid cycling BD was, up to 30-40 years ago, a rather uncommon diagnostic subtype that was mainly observed as a long-term complication of BD. Rapid cycling BD seems to be increasing due to the fact that patients are currently much more sensitive to stimulants than in the past; patients continuously sought stimulants as a valid form of emotional support^{25 31-33}. These are individuals having a strong tendency towards consumption of stimulants such as alcohol, caffeine and cocaine, and often exhibit altered behaviours determining insomnia, which enhances the tendency to mania. The use of stimulants causes the secretion of dopamine, catecholamines and endorphins²⁴⁻³⁶ leading to increased resistance to fasting, a “doping” effect on the body and resulting in clinical hyperactivity and marked alteration of the sleep/wake and activity/rest biorhythms.

According to Koukopoulos and Ghaemi²⁰, the “*primum movens*” underlying mood disorders is mania. The treatment of BD cannot, therefore, be effective without treating manic episodes. Even in some depressive/mixed episodes, the key element of the illness is represented by mania because thoughts are accelerated, and there is a disabling hyperactivity in addition to motor slowing. Moreover, subjects with BD may have few thoughts, they do not want to do anything and they are agitated, but mania is usually present. The outcome of subjects suffering from BD is variable and largely depends on the episode for which bipolar individuals are treated. Whether a stabilizing treatment is prescribed in a timely manner (this should not include the use of antidepressant drugs), subjects can heal, and even interrupt pharmacotherapy for a long period of time. In most cases, however, people suffering from such diseases are forced to continue treatment due to the recurrence of the “self-doping” tendency and the frantic search of stimulants as a form of emotional support.

These are individuals with a chronic tendency to self-induce mania, they are generally depressed and have a tendency to fail in the achievement of long-term stability as they are biologically and psychologically dependent by the manic episode. To help these people heal, mania and hypomania must be adequately diagnosed even if diagnosis of the latter is very difficult being usually retrospective^{19 37}.

Overall, BD is a disease that severely impairs biorhythms and typically needs the use of mood stabilizers which, however, may exert different effects depending on the episode for which bipolar patients were treated.

Currently available medications with mood stabilizing properties

Mood stabilizers are the first-line treatment during manic, hypomanic or mixed episodes of BD³⁸. Most evidence suggests that mood stabilizers are effective both in the acute treatment of manic/hypomanic episodes as well as in the maintenance treatment focused on the prevention of relapses of BD³⁸⁻³⁹. To date, none of the second-generation antipsychotics has been recognized in the acute treatment of depressive episodes of BD with the exception of quetiapine⁴⁰.

Mood stabilizers can be used as monotherapy but also, more frequently, they may be combined in those illness subtypes that are characterized by elevated aggressiveness or impulsiveness. The association of a mood stabilizer with first- or second-generation antipsychotics is frequent and may offer some advantages particularly related to the lower latency of response⁴¹ in the treatment of acute episodes.

The first-line treatment of BD is, undoubtedly, represented by lithium⁴¹. Being a drug with a low therapeutic index, lithium levels should be regularly checked in serum. The use of lithium requires special caution such as the frequent monitoring of renal, thyroid and cardiovascular functioning. When administered in the elderly, lithium may frequently induce accumulation associated with decreased renal clearance.

Lithium can also frequently cause tremor, nausea, vomiting, polyuria and polydipsia. Hyperreflexia, confusion, convulsions, tremor, dysarthria, profuse diarrhea, neurological signs and finally coma are clear signs of toxicity⁴². In case of serious contraindications related to the utilization of lithium (e.g. severe renal failure), the use of other mood stabilizers is highly recommended.

Sodium valproate is one of the most widely used drugs among all mood stabilizers: this medication, however, can often lead to weight gain, abnormal liver functioning, thrombocytopenia, gastrointestinal disorders, neurological disorders and sedation⁴³. Carbamazepine should be prescribed with extreme caution due to the frequent interactions with other drugs and possible hepatotoxic effects⁴³.

Among all drugs which are commonly used to treat BD, antiepileptic drugs that have not yet been recognized as having mood stabilizing properties are also used. First, topiramate may induce adverse effects such as sedation, anorexia, nephrolithiasis, neurological and gastroenterological disorders; oxcarbazepine is associated with hyponatraemia to a greater degree than carbamazepine; lamotrigine is frequently associated with sedation, dizziness, neurological disorders (diplopia, ataxia, blurred vision), gastrointestinal disturbances (nausea and vomiting) and skin rash (Stevens Johnson Syndrome)⁴³.

In addition, atypical antipsychotics may be used in the treatment of BD: olanzapine, quetiapine, risperidone, paliperidone, aripiprazole, ziprasidone and asenapine⁴⁴⁻⁴⁸. However, based on the current literature, among all atypical antipsychotics, quetiapine is the only medication that is indicated in the treatment of depressive, manic and mixed episodes of BD. It therefore represents an effective pharmacological option in both the short- and long-term treatment of BD⁴⁹.

Quetiapine monotherapy and combination with additional mood stabilizers may be useful in the prophylaxis of depressive episodes⁵⁰. All the most recent guidelines for the treatment of acute bipolar depression recommend quetiapine as a first-line option, and suggest that it may also be useful for continuation and maintenance treatment of BD⁵⁰⁻⁵³. The antidepressive effects of quetiapine in bipolar and unipolar depression with a special focus on its early onset of action and sleep improving effects have recently been reviewed by Rihmer⁵⁴.

In the context of BD, quetiapine has shown efficacy when used as monotherapy or adjunctive therapy for acute manic/mixed episodes in adults⁵⁵. Maintenance treatment with quetiapine combined with lithium/divalproate significantly increased the time to recurrence of any event (mania, depression, or mixed episode) regardless of the polarity of the index episode compared with placebo and lithium/divalproate⁵⁶.

Atypical antipsychotics differ in terms of safety and tolerability. These drugs should be prescribed with caution in the elderly due to the increased susceptibility to adverse effects such as sedation, extrapyramidal and hypotension. In the elderly, it is also necessary to slowly increase the dose of atypical antipsychotics; the daily therapeutic dosages should be lower than in younger patients. They may also induce anticholinergic and extrapyramidal adverse effects.

Quetiapine is usually, considered a safe medication; it may be transiently associated with sedation and hypotension particularly in the early phases of treatment⁴⁹. The most common adverse effects that may be induced by other atypical antipsychotics are: hyperprolactinaemia with risperidone; leukopenia and agranulocytosis, seizures, tachycardia, orthostatic hypotension, myocarditis, increased risk of pulmonary embolism and severe constipation with clozapine; weight gain and metabolic syndrome, sedation and orthostatic hypotension with olanzapine; lengthening of the QTc interval and eventual induction of arrhythmias with ziprasidone; headache, insomnia, dyspepsia, nausea, vomiting and constipation associated with the use of aripiprazole; sedation, akathisia and oral hypoesthesia with asenapine⁴⁴⁻⁴⁵.

There are also some medications that have demonstrated promising properties in the treatment of BD: allopurinol (600 mg per day)⁵⁷, memantine (10-30 mg per

day)⁵⁸, tamoxifen (80 mg per day)⁵⁹⁻⁶¹ in manic episodes; modafinil (200 mg per day)⁶², N-acetylcysteine (2000 mg per day)⁶³⁻⁶⁴, pramipexole (1-2.5 mg per day)⁶⁵⁻⁶⁶, riluzole (50-200 mg per day)⁶⁷⁻⁶⁸ in depressive episodes; memantine (10-30 mg per day)⁵⁸ in mixed episodes. Tables I and II summarized the most important clinical characteristics of medications with mood stabilizer properties.

Management of BD using mood stabilizers

The discovery of mood stabilizers occurred for “serendipity”⁶⁹⁻⁷⁰. Mood stabilizers may be defined as those drugs that are active in the treatment of mood episodes as well as in the prevention of bipolar recurrences enhancing stability over time. Since 1949 when John Cade published his article “Lithium in the treatment of psychotic agitation”⁷¹, lithium has never ceased to be used in psychiatry. The Australian researcher had suggested the lethargy that lithium may induce in rodents, and he had administered lithium to patients with a history of manic disorder obtaining successful results.

However, in the late 1940s, lithium was also used as sodium chloride in patients with cardiovascular disorders leading to cases of severe poisoning and death. These deaths postponed for more than 20 years the clinical use of lithium for the treatment of mania. Only at the end of 1960, after a series of controlled clinical studies focused on the efficacy and tolerability of this drug, lithium was regularly introduced by Gershon⁷²⁻⁷³ in the United States as a short-term treatment and prophylaxis of BD.

In addition, the clinical use of certain drugs mainly used as antiepileptic medications (carbamazepine, oxcarbazepine, sodium valproate, lamotrigine, gabapentin, topiramate) significantly contributed to the pharmacotherapy of major psychopathological disorders, and in particular, of those included within the affective spectrum.

Drugs with mood stabilizing properties can be divided into the following categories: 1) dibenzodiazepines, 2) atypical antipsychotics, 3) antiepileptic drugs, 4) lithium. One of the most important failures in the history of psychiatry occurred when it has been postulated that BD was the sum of two diseases: mania that may be successfully treated with anti-manic drugs and depression that may be successfully treated with antidepressant medications; this assumption largely contributed to suicidality among patients with BD.

The indiscriminate use of psychoactive compounds having antidepressant properties in subjects with BD increased, in our opinion, the instability over time, and the global severity of the illness. During the last centuries, some prejudices concerning the uncertain tolerability and inadequate efficacy of mood-stabilizing drugs have limited the use of these compounds. Negative attitudes include painting all mental patients as incompetent and

TABELLA I.Major currently available mood stabilizing medications. *Principali farmaci stabilizzanti del tono dell'umore attualmente in commercio.*

Drug	Main clinical uses	Pharmacokinetics	Mechanism of action
Lithium	Short and long-term prophylactic treatment of BD I	Peak concentration after 1-1.5 hours; lithium does not bind to plasma proteins and is excreted by the kidney; half-life 19-24 hours	Currently unknown; presumable block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Carbamazepine	Treatment of acute mania and prophylactic treatment of BD I; treatment of epilepsy	Limited water solubility; active metabolites through the system oxidative hepatic; slow absorption; half-life 12-17 hours; self-induction of its own metabolism	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Sodium valproate	Treatment of acute mania and prophylactic treatment of BD I; treatment of epilepsy	Half-life 5-20 hours; 70-95% plasma protein binding	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Oxcarbazepine	Treatment of epilepsy	High lipophilicity, volume of distribution of 49 L, serum protein binding 40%	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Lamotrigine	Prophylaxis of depressive relapses in bipolar depression; treatment of epilepsy	Bioavailability 98%, peak plasma levels 1-3 hours, half-life 33 hours; binding serum protein: 55%	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Gabapentin	Treatment of epilepsy	Bioavailability 60%; peak plasma levels 2-3 hours; it does not bind to plasma proteins; volume of distribution: 58 L; half-life 5-7 hours	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Topiramate	Treatment of epilepsy	Bioavailability 81%; peak plasma levels 2-3 hours; half-life 21 hours; 13-17% is bound to plasma proteins; 81% eliminated through the kidney	Block of voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate

Main adverse effects	Dosage	Plasma levels	Recommendations
Weight gain, polyuria, polydipsia, tremor, hypothyroidism, flattening-T-wave inversion, motor incoordination, weakness, seizures, peripheral neuropathy, benign intracranial hypertension, diarrhoea, nausea, decreased appetite, alopecia, acne, psoriasis	900-1200 mg	0.4-1 mEq/l	The onset and severity of side effects are generally related to plasma levels. The determination of lithium in the serum should be carried out once a week for 1-2 months, once a month for 6-8 months and every 2-3 months later
Hyponatraemia, elevated liver enzymes, liver toxicity, blurred vision, diplopia, ataxia, dizziness, motor incoordination, confusion, rash, leukopenia, aplastic anemia, Stevens-Johnson syndrome, pancreatitis, conduction disturbances	800-1600 mg/day	-12 mg/ml	Absolute contraindications to the use: blood disorders by bone marrow suppression, narrow-angle glaucoma, first trimester pregnancy, concomitant clozapine administration
Weight gain, increased liver enzymes, reversible thrombocytopenia, epistaxis, bruising, nausea, vomiting, anorexia and dyspepsia, ataxia, dysarthria, tremor, leukopenia, altered cognitive functioning, encephalopathy and hemorrhagic pancreatitis	1200-1500 mg/day	50-100 µg/ml	In the elderly, the free fraction of the drug may increase up to 70%. Elevated free fraction of the drug (about two times higher) in diabetes mellitus and renal failure may be found
Skin eruptions (Stevens-Johnson), asthenia, dizziness, memory impairment, headache, tremors, sleep disorders, numbness, affective lability, tinnitus, ataxia, depression, diplopia, anxiety, weight loss, postural hypotension	600-1200 mg/die (max 3000 mg/day)	0-4 µg/ml	Monitor patients with frequent visits. In case of overdose, possible cardiac conduction disorders, respiratory and electrolyte abnormalities
Rash (Stevens-Johnson syndrome, Lyell's syndrome), fever, arthralgia, lymphadenopathy, eosinophilia, teratogenicity. Because of possible cross-reactions, it should be given with caution in patients with known hypersensitivity to carbamazepine and phenytoin	50-200 mg	3-14 mg/L	Monitor patients with frequent visits. Carbamazepine reduces the time of elimination of lamotrigine by 50% (14 hours) whereas sodium valproate, by inhibiting its metabolism, increases its half-life to 70 hours
Cases of suicidal ideation and suicidal behavior. Drowsiness, dizziness, fatigue, ataxia, tremors, palpitations, hypertension, skin rashes (Stevens-Johnson), leukopenia, impotence, increased liver enzymes, nausea, vomiting, diarrhoea, anorexia, joint pain, diplopia, ear infections, dizziness	900-1800 mg/day (max 3600 mg/day)	4.5-5 µg/ml	Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, childhood
Nasopharyngitis, anaemia, anorexia, altered cognitive functioning, blurred vision, diplopia, visual disturbances, dizziness, tinnitus, ear pain, dyspnea, epistaxis, vomiting, constipation, upper abdominal pain, dyspepsia, abdominal pain, alopecia, rash, pruritus, arthralgia, nephrolithiasis	100-200 mg/day	3-20 µg/ml	Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, children. It inhibits CYP2C19 (may interfere with the metabolism of diazepam, imipramine, moclobemide, proguanil, omeprazole)

TABELLA II.Major atypical antipsychotic drugs that may be used in management of BD. *Principali farmaci antipsicotici atipici che possono*

Drug	Main clinical uses	Pharmacokinetics	Mechanism of action
Risperidone	Treatment of acute mania	Peak plasmatic levels 1-2 hours; 70% bioavailability, plasma protein binding 90%; half-life of about 20 hours, renal elimination	Activity on the following receptor systems: 5HT ₂ , D ₂ , alpha ₁ and alpha ₂ , H ₁ . 5H- risperidone is the active metabolite of the drug
Quetiapine	Treatment of acute mania and acute bipolar depression; prophylactic treatment of BD	Binding of quetiapine to plasmatic proteins is approximately 83%; half-life 7-12 hours	Activity on the following receptor systems: D ₁ , D ₂ , 5HT ₂ . Norquetiapine, the active metabolite, has a high affinity for the norepinephrine transporter, histaminergic, alpha ₁ and alpha ₂ adrenergic, serotonergic 5HT _{1A} receptors
Olanzapine	Treatment of acute mania and prevention of relapse of manic episodes in BD	Peak plasmatic levels 5-8 hours; linear pharmacokinetics, bioavailability not affected by food intake; half-life 10-16 hours	Activity on the following receptor systems: D ₁ , D ₂ , D ₄ , 5HT _{2A} , 5HT _{2C} , 5HT ₃ , M ₁ , alpha ₁ , H ₁
Aripiprazole	Treatment of acute mania and prevention of relapse of manic episodes in BD	Peak plasmatic levels 3-5 hours; bioavailability 87%; plasmatic protein binding by more than 99% half-life 75-146 hours (depending on the activity of CYP2D6)	Activity on the following receptor systems: D ₂ , D ₃ , D ₄ , 5HT _{1A} , 5HT _{2A} , 5HT _{2C} , 5HT ₇ , alpha ₁ , adrenergic and H ₁
Ziprasidone	Treatment of acute mania	Peak plasmatic levels 6-8 hours; bioavailability 60%; plasmatic protein binding of more than 99%; half-life 6.6 hours	Activity on the following receptor systems: D ₂ , 5HT _{2A} , 5HT _{2C} , 5HT _{1D} , 5HT _{1A} , H ₁ , alpha ₁ , M ₁
Asenapine	Treatment of acute mania	Peak plasmatic concentrations within 0.5 to 1.5 hours; bioavailability 35%; plasma protein binding 95%; half-life 24 hours	Activity on the following receptor systems: D ₂ , 5HT _{2A} , 5HT _{1A} , 5HT _{1B} , 5HT _{2C} , 5HT ₆ , 5HT ₇ , D ₃ and alpha ₂

essere attualmente utilizzati nella gestione del BD.

Main adverse effects	Dosage	Recommendations
Anxiety, insomnia, agitation, headache, tachycardia, rhinitis, rash, drowsiness, fatigue, difficulty concentrating, dizziness, nausea, vomiting, abdominal pain, constipation, urinary incontinence, blurred vision, as well as sexual dysfunction, orthostatic hypotension, hyperprolactinaemia, hyperglycaemia, orthostatic hypotension, palpitations, weight gain, decreased libido and erection difficulties, tremor, rigidity, bradykinesia, malignant syndrome, thrombocytopenic purpura and priapism	4-6 mg die (max 16 mg day)	It should be administered with caution in patients with cardiovascular diseases. The association with phenytoin or SSRIs can cause extrapyramidal effects. The association with opioids can cause abstinence related to opioid withdrawal. The association with clozapine increases plasma concentrations. It may antagonize the effect of levodopa and other dopamine agonist agents
Leukopenia, hyperprolactinaemia, decreased free and total T4 and T3, increased TSH, nightmares, dizziness, drowsiness, headache, tachycardia, palpitations, blurred vision, orthostatic hypotension, rhinitis, dyspnoea, metabolic syndrome	25-800 mg die (max 1500 day)	Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, childhood
Drowsiness and weight gain, dry mouth, confusion, sedation, insomnia, orthostatic hypotension, tardive dyskinesia, neuroleptic malignant syndrome, diabetes and diabetic ketoacidosis with acute onset, increased levels of triglycerides and metabolic syndrome	2.5-20 mg die (max 30 mg day)	Use caution in patients receiving drugs that can cause depression of the central nervous system. Smoking and carbamazepine may lead to a reduction of concentrations. Fluvoxamine inhibits the metabolism of olanzapine. It may antagonize the effects of direct and indirect dopamine agonists
Headache, dyspepsia, vomiting, nausea, constipation, salivary hypersecretion, feeling light-headed or empty, insomnia or drowsiness, restlessness, blurred vision, fever, sweating, dysregulation of blood pressure and heart rate, muscle aches, allergic reactions, extrapyramidal symptoms, akathisia, tremor	2.5-30 mg day	The co-administration with CYP3A4 inhibitors of P450 enzymes, such as ketoconazole and erythromycin increases serum concentrations. Quinidine increases aripiprazole levels but reduces those of its metabolite, dehydro-aripiprazole. Carbamazepine reduces the levels of both medications. Valproate reduces serum levels of aripiprazole by 25%. The co-administration of lamotrigine may increase the risk of Stevens-Johnson syndrome
Restlessness, dystonia, akathisia, extrapyramidal disorders, parkinsonism (including cogwheel rigidity, bradykinesia, hypokinesia), tremor, dizziness, sedation, drowsiness, headache, blurred vision, nausea, vomiting, constipation, dyspepsia, dry mouth, salivary hypersecretion, musculoskeletal stiffness, weakness, fatigue	80-160 mg day	Monitor patients with frequent visits. It can induce QT prolongation. Contraindications: hypersensitivity, lactation, children
Hyperglycaemia, elevated levels of total cholesterol, triglycerides, significant prolongation of the QTc interval, somnolence, akathisia and oral hypoaesthesia, weight gain and appetite, dystonia, akathisia, dyskinesia, parkinsonism, sedation, dizziness, dysgeusia, increased liver enzymes, muscle stiffness, fatigue	5-20 mg day	Not approved in the elderly, dementia-related psychosis for the higher risk of death. Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, childhood

incurable; as a result, even though effective pharmacological medications are currently available, most patients neither seek nor receive appropriate treatments.

BD is usually a disease with a duration of at least two years, and the treatment with mood stabilizers must take into account a sufficient period of treatment of at least two years at adequate dosages⁴. The characteristics of mood stabilizers should be: absence of depressive effects and efficacy on manic symptoms, good safety and tolerability, thus allowing a good adaptation among bipolar subjects^{4 72 73}. The aim of mood stabilizers is also to restore biorhythms⁷⁴⁻⁷⁷.

Lithium is, no doubt, widely recognized by several guidelines as the gold standard for the treatment of both acute episodes as well as maintenance therapy of BD^{52 78}. In Italy, in contrast to other countries, the slow-release lithium formulation is not available. This formulation is clinically associated with lower dropout rates than the quick-release lithium (although there are not currently, to our knowledge, controlled studies that compare the long-term outcome of patients using these different formulations) probably due to the possible induction of a kidney damage related to the quick-release of lithium. The quick-release of lithium is also able to overcome the threshold of renal re-absorption; it may not adequately act during the entire duration of a manic episode.

These manic episodes usually occur, in our experience, in the late afternoon or in the early evening, when fatigue appears as dysphoria, and usually occurs together with the need to perform an appropriate response to environmental stressors and recall residual resources. Mood stabilizers must be able, as mentioned, to restore the sleep-wake biorhythm^{69 79}. Sleep is, among all biological functions, one of the most fascinating and embarrassing mysteries in the field of neuroscience⁸⁰⁻⁸². It is not only a quantitative phenomenon as sleep essentially plays the function of "anti-stress", able to antagonize the negative effects of the free radicals that have been accumulated throughout the day. At a molecular level, the effects of stress on neurons are clearly evident at the end of a manic episode. Neurons remain without tigroid substance, appear as hypotrophic and have few dendritic arborizations and/or connections with other neurons^{83 84}.

Sleep would be the price that individuals have to pay to allow the daily neuroplasticity and neurogenesis processes⁸¹. The most useful hours of sleep are those ranging from the sunset to those immediately following the midnight: sleep at this stage largely depends by the release of cortisol⁸⁵. Mood stabilizers should be able to restore these useful (crucial) hours of sleep; depressed subjects usually feel better in the evening, but this often coincides with the onset of hypomania (not adequately reported by patients). When subjects perceive a state of

well-being, they really experience a moment of discomfort and should be treated with reasonable dosages of mood stabilizers⁸⁶. Mood stabilizers should also be able to restore a reliable activity/rest biorhythm, in particular for what concerns the most significant life activities of subjects, such as occupational functioning. Mood stabilizers should be able to restore biorhythms that patients are not be able to restore, thereby giving subjects a new type of balance^{69 79}.

Another critical aspect must be mentioned. BD is frequently associated with high mortality rates as it is associated with a high rate of metabolic syndrome: it may be clearly defined as "the disease of exaggeration". BD is associated with many cardiovascular disorders such as arterial hypertension and heart failure. Whenever insomnia, abnormal activity/rest rhythm, metabolic syndrome and medical diseases occur, clinicians have to consider the diagnosis of bipolar illness, and therefore adequately treat patients taking into account the existence of comorbidities.

Although lithium represents, as mentioned, the gold standard in the treatment of BD⁴, there are limitations in the prescription of this medication as monotherapy especially in terms of tolerability and uncertain compliance (lithium should never be interrupted even after a long-term period). Moreover, it should be not rapidly discontinued due to the increased risk of suicide^{87 89} and the rebound of mania/hypomania that can be induced with rapid discontinuation^{89 90}.

Mania/hypomania induced by the rapid interruption of lithium can last up to 18 months and may be dramatically characterized by an increased risk of suicide^{87 88 91}. Whether clinical conditions do not allow the administration of lithium or there are serious issues concerning the utilization of lithium, mood stabilizers as similar as possible to lithium should be administered.

Nonetheless, the perfect mood stabilizer does not exist. Mood stabilizers should: 1) exert anti-manic properties and should not induce depression, 2) have not antipsychotic properties (especially with high-affinity for D₂ receptors), 3) be medications that do not block the transport of catecholamines, 4) be associated with a good clinical profile in terms of safety and tolerability; 5) be associated with a good compliance; 6) be able to act as long-term agents associated with stable plasma levels (and thus it would be preferable to use slow-release formulations).

The importance of stability: conclusive remarks

The best treatment of BD is maintenance and continuation therapy, that should not include antidepressant or anti-manic medications that tend to act according to a cross-sectional limited perspective^{92 93}. However, most

subjects with BD are examined during the acute manic or depressive episodes, and diagnosed as having of psychosis/schizophrenia or major depression; therefore they are treated with high-dosages antipsychotics or antidepressants, respectively, according to an approach focused on crisis intervention.

If antipsychotics (especially those with high-affinity for D₂ receptors), were used, considering the cyclical nature of the disorder, they can lead to depression that will be treated using antidepressant medications. Conversely, if antidepressants were used, they may induce mania/hypomania and subsequently, over time, long-term instability and rapid cycling forms⁹⁴. In order to enhance stability in BD, it is necessary to emphasize long-term strategies and highlight the relevance of a terminological mistake that has been proposed for a long time: the care of BD should not be based on the use of those drugs having “anti-” properties (anti-manic, anti-depressant), but upon the use of “pro-” strategies (pro-health, pro-brain function, etc.). A typical manic-depressive cycle usually includes the following pattern: mania/hypomania-depression-free interval and, more occasionally, the alternative pattern mania/hypomania-depression-free interval. This latter alternative cycle of BD is usually associated with a lower response to treatment and less favourable outcome than other subtypes⁹⁵; in addition, this cycle is clinically prevalent when mania/hypomania is not appropriately diagnosed^{19,37}. Clinicians need to be completely aware of the increased severity associated with this illness cycle compared to others.

The most useful treatments of BD are also those that tend to not impair insight/awareness into illness as well as the proper activation of the frontal and prefrontal brain areas. BD requires adherence to treatment since subjects must be able to realize the implications related to the illness according to the use of psycho-educational strategies⁹⁶. Finally, in order to correctly restore individual lifestyles as well as to promote a rehabilitative perspective, it is necessary to promote the most adequate care focused on socio-cultural integration. This cannot ignore patients' motivation to care that can be enhanced through the use of mood-stabilizing medications able to satisfy the following characteristics: efficacy, safety and tolerability, and should not result in significant life changes (that can be perceived as invasive by patients).

Such medications should be dimensionally designed to control emotional reactivity together with restoring biorhythms. Historically, the first treatment in BD were: lithium and haloperidol; lithium and antiepileptics; lithium, antiepileptic drugs and second-generation antipsychotics. Quetiapine is currently, among all atypical antipsychotic drugs, a good option in the treatment of depressive, manic and mixed episodes of bipolar illness. Considering its early onset of action and its ability to stabilize

the biorhythm awake/asleep, quetiapine represents an interesting therapeutic option in BD^{97,98}. However, the current scenario of mood stabilizing agents may provide alternative or adjunctive strategies to strongly improve the quality of life of patients suffering from BD.

Conflict of interest

Prof. Girardi has served as a consultant to, or has engaged in research collaborations Organon, Eli Lilly, Janssen, Merck, Bristol-Myers Squibb, Pfizer, AstraZeneca Corporations e Innova Pharma. Dr Serafini has served as a consultant to, or engaged in research collaborations with Bristol-Myers Squibb, Janssen-Cilag, Eli Lilly, Glaxo Smith Kline and AstraZeneca, Innova Pharma, Lundbeck, Servier.

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