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REVIEW

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Refractoriness in Bipolar Disorder: Definitions and Evidence-Based Treatment

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Aniconvulsants; Antidepressants; Antipsychotics; Bipolar disorder; Evidence-based guidelines; Lithium; Mania; Mood stabilizers; Treatment.

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SUMMARY

Defining refractoriness in bipolar disorder is complex and should concern and include either every phase and pole or the disorder as a whole. The data on the treatment of refractory bipolar patients are sparse. Combination and add-on studies suggest that in acutely manic patients partial responders to lithium, valproate, or carbamazepine, a good strategy would be to add haloperidol, risperidone, olanzapine, quetiapine, or aripiprazole. Adding oxcarbazepine to lithium is also a choice. There are no reliable data concerning the treatment of refractory bipolar depressives and also there is no compelling data for the maintenance treatment of refractory patients. It seems that patients stabilized on combination treatment might do worse if shifted from combination. Conclusively there are only limited and sometimes confusing data on the treatment of refractory bipolar patients. Further focused research is necessary on this group of patients.

Introduction

Hippocrates and Areteus were the first to describe manic-depressive illness but in modern time, bipolar disorder (BD) was first defined as an illness by Falret in 1851 ("folie circulaire"). BD type I and type II have a combined prevalence rate of up to 3.7% and both are disabling conditions. The first problem in the gathering of scientific proof concerning the treatment of affective disorders lies in the low reliability and validity of diagnosis. Judgment is often made retrospectively, and this is especially true for BD and carries the risk of memory distortions and biases. Another problem is that a specific and different treatment needs to be considered separately for manic, hypomanic, mixed, and bipolar depression episodes, as well as for unipolar depression. Drugs proven effective for the acute phase of either pole should be tested in the maintenance phase [1].

Thus, the treatment of bipolar illness is complex and full of caveats for the clinician [2–5]. Depression is considered to be the most problematic facet [6], and the most likely cause of chronicity and long-term disability. The presence of residual affective symptoms is associated with a greater risk of relapse [7] and poorer functional outcomes [8–10]. In this frame, remission is a more desirable treatment target, however a significant proportion of patients are rather refractory to treatment and their outcome is at best suboptimal.

Several older studies (most of them open trials) have defined treatment refractoriness on the basis of on an inadequate response to a therapeutic trial of lithium or an inability to tolerate lithium's side effects [11–16]. Some authors utilized only lithium nonresponse or intolerance [11,12], others included an alternate nonresponse/intolerance to carbamazepine [11,13] or valproate [16] while others required nonresponse to at least two or more mood-stabilizing medications including antipsychotics [12,16–21].

The current article attempts to perform a review of the definitions of response, remission, and refractoriness in BD and to critically review and evaluate the available data on the treatment of refractory bipolar patients [22,23]. Eventually this will lead to suggesting future directions for research and development of guidance on the basis of real-world clinical needs.

Definition of Refractoriness in Mental Disorders

In the psychiatric literature, the definitions of "response," "remission," "recovery," "relapse," and "recurrence" have been elaborated during the recent couple of decades, starting with unipolar major depression [24,25] and spreading to many other mental disorders [26–29]. The above definitions apply to patients that received an adequate amount for an effective agent for sufficient

Table 1 Issues to be addressed in order to label a patient as being "refractory"

1. Correct diagnosis
2. The disorder is not secondary to an organic disorder
3. The poor response to treatment is not due to somatic or mental comorbidity
4. Poor response to treatment is not due to a somatic condition which might not constitute a disorder by itself (e.g. genetic factors, smoking, alcohol use, gender, race etc.)
5. The failure of therapy is not due to nontolerability
6. The patient complies with the recommended treatment and poor response is not a consequence of lack of adherence

duration. Patients unable to tolerate an adequate dose for a sufficient time due to any reason as well as noncompliant patients are rather "pseudorefracotry" [30,31]. Lack of adherence is a particularly important issue and should be recognized correctly [32]. The basis issues that should be addressed before a patient is considered to be refractory are shown in Table 1.

Another term, "refractory" or "treatment resistant" is inversely linked to the term "response"; that is "refractory" are those patients who do not respond. However a wider definition relates it to "remission" and thus "refractory" patients are those who do not remit. In unipolar depression, refractory patients according to Thase and Rush are those who haven't responded to at least two treatment trials with drugs from different pharmacological classes, each used in an adequate dose for a sufficient period of time [33].

The general concept starts with "response" defined as significant reduction of the index scale score after treatment with an agent of known efficacy for a specific duration. The magnitude of change is arbitrary defined (usually 30–50%) and depends on the disorder. A more complex approach has been proposed recently with grading the response (25%, 50%, 75%, and 100%) after taking into consideration the history of the patients [34]. In the same frame, "remission" is defined as drop of the index scale score below a certain level (e.g., HDRS below 8) and this should be sustained for at least a specific period of time. Currently a more pragmatic approach does not require complete absence of symptoms but rather minimal symptoms with mild disability [35–37]. Recently, the definition of remission gained status as a more stringent, reliable, and valid standard than response [25,38,39]. Recent discussion have resulted in the expansion of the remission concept to encompass "sustained symptom remission" during the maintenance phase with the use of specific time frames [26], leading eventually to the definition of "recovery" which requires sustained symptom remission along with return of function to near-normal levels [27]. The relationship of the definition of remission to functional outcome is unstable and unclear and improves as multiple clinical domains are included in this definition [40–43] while the relationship between remission status and quality of life is unclear [44].

The problem is that these general concepts are very good for diseases with a more or less linear course, with exacerbations and remissions of a single factor or constellation of symptoms (e.g., unipolar melancholic depression) and are fair for diseases like schizophrenia who, in spite of the multiplicity of the clinical picture, their treatment is more or less unimodal (antipsychotics) and the course of the disease is monotonous. For example, there are several papers defining response, remission and refractoriness in schizophrenia [21,34,37,40–43,45–55] with definitions being rather narrow and vague. However, when it comes to a disorder like BD, the reliability and validity of this approach is questionable because both the clinical picture and the treatment are complex and interrelated, and the course is not monotonous but instead manifests unpredictable increases and decreases of function with complex relation to clinical symptoms. This complexity puts forward a number of methodological problems from precision of definitions to global psychometric assessment to critical judgment of functional status. After all, BD is maybe the only mental (or even medical) disorder where high functioning could be a sign of illness. For example, if one uses only the MADRS scale (or even in combination with a general global scale like the CGI) to assess response to treatment with a tricyclic of a severely depressive bipolar patient, in case the patient becomes mixed or rapid cycling, it is highly likely that the assessment will classify him as being a "responder." Whether this constitutes true response or destabilization of the illness with a long-term negative impact on the outcome, is a matter of scientific debate. It is important to have in mind that simple approaches like the one in this example, cannot serve as solutions.

Definition of Refractoriness in Bipolar Disorder

In principle, BD has two distinct poles (manic and depressive although in clinical practice there could be several intermediate or mixed conditions) and two phases (acute and maintenance). The clinical characteristics of BD and the types of BD cases the therapist faces are shown in Tables 2 and 3. While "acute" treatment is easy to define, "continuation" overlaps with "maintenance" with the former concerning prophylaxis against relapses while the latter against recurrence [24,56]. By definition relapses are of the same polarity with the index episode, and they tend to occur within the first months of improvement. Thus, an early emergence of an episode of the opposite polarity cannot be considered as being a relapse. In this frame, mixed episodes constitute a conceptual problem, although it seems that patients with an index manic or hypomanic and not depressed episode tend to relapse into a mixed [57].

Table 2 Bipolar illness basic clinical characteristics

1. Manic episodes
2. Depressive episodes
3. Mixed episodes
4. Subthreshold manic symptoms
5. Subthreshold depressive symptoms
6. Predominant polarity
7. Frequency of episodes
8. Neurocognitive disorder
9. Functional deficit
10. Drug/alcohol abuse
11. Comorbid anxiety and other mental disorders

Table 3 Types of BD cases to treat

(a) Acute
1. Classic mania
2. Classic bipolar depression
3. Mixed episodes (DSM definition)
4. Mixed episodes (beyond the DSM definition)
5. Psychotic symptoms
6. Alcohol and/or substance abuse
7. Comorbidity
(b) Maintenance
1. With predominant manic polarity
2. With predominant depressive polarity
3. With tendency for mixed episodes
4. Without a predominant polarity
5. Rapid cycling
6. With subthreshold manic symptoms
7. With subthreshold depressive symptoms
8. With subthreshold mixed symptoms
9. With subthreshold psychotic symptoms
10. With functional impairment
11. With alcohol and/or substance abuse
12. Comorbidity

Therefore, the first problem when defining response, remission, and refractoriness in BD is whether the definitions will narrowly concern each phase and pole (e.g., refractory acute mania or refractory recurrent mania) or the disorder as a whole. The first approach will be easier to operationalize, but the second is more clinically oriented and meaningful. However it does not seem possible to arrive at the second approach without first passing through the first one, and subsequently synthesizing the results.

The second problem is that not all agents and therapeutic modalities traditionally used in the treatment of BD have proven efficacy against the specific facets of the disorder they are used against, and even more important, there is little "class effect" in the treatment of BD. For example, it has been proposed that refractory bipolar depression can be defined on the basis no remission despite two adequate trials of standard classes of antidepressant agents (6 weeks each) with or without augmentation strategies [58]. Another proposal was to consider lithium treatment at serum levels of 0.8 mmol/L and above for 6 weeks [59]. However today we know that only the quetiapine and the olanzapine–fluoxetine combination have proven efficacy against bipolar depression. Lithium has negative data [60], although some earlier studies are positive [61] and some authors consider the overall conclusion to be equivocal.

The third problem concerns trial duration. It is necessary to wait for sufficient time for the agent to act. In an early article the authors suggested that an adequate trial of lithium for acute mania should be of 3–4 weeks at plasma concentrations of 1.2 mmol/L; consequently a patient could be considered nonresponsive if symptoms persisted following such a trial [62]. It is essential to take into consideration that the time course of onset of response to any mood stabilizer (lithium, carbamazepine, or valproate) might be directly related to the time to therapeutic plasma concentration [63], that more recent studies suggest the antimanic effect of antipsychotics could be already present at days 2–4 even with aripiprazole which needs weeks to achieve therapeutic levels [64–68], and that unfortunately lithium and anticonvulsants might need 1–2 weeks for response [69]. On the other hand we know that both aripiprazole [70] and ziprasidone (unpublished NCT00141271) failed at week 8 while their data until week 6 were favorable, therefore at least 8 weeks are necessary as the minimum trial duration. Also, the commonly observed fluctuation in the clinical picture of BD makes necessary for the improvement to be present for at least 2–4 weeks before the therapist is sure that it constitutes a stable change of the condition [71]. Thus at least 10–12 weeks of duration should be the minimum of a therapeutic trial before the patient should be considered as nonresponder.

A fourth problem is more methodological and practical and it concerns the application of these definitions to the maintenance phase. Since only a minority of patients achieve complete remission, and only a minority is free or recurrence in the long term, response is defined on the basis of lower frequency and milder symptoms. Practically this is very difficult to say this for the individual patient since it demands long term follow-up and detailed registration of the longitudinal course, which is often complicated by the high comorbitidy, which especially characterizes BD-II. A general guide could derive from the natural history literature (especially based on the pretreatment era) which indicates that if untreated, bipolar depressive episodes last about 3–6 months, classic manic episodes 2–4 months and mixed episodes last about 6 months or longer [71]. However the relevance of this literature to contemporary real-world patients is questionable [72]. Maybe it is reasonable to consider response and refractoriness in the frame of 1-year (52 weeks) duration, since most maintenance RCTs use the 6–12 months duration. Remission should require at least 2–3 years and recovery 3–5, because of the episodic nature of the illness.

To date, the ISBD definitions are the most comprehensive and updated, and utilize both a syndromal (on the basis of DSM criteria) and symptomatic (on the basis of rating scales) approach. These definitions recommend the use of incremental steps for symptom improvement (<25%; 25–49%; 50–74%; 75–100%) in order to define response. They propose multiple cut-off points for the definition of remission with the most stringened being <6 for HDRS-17 and MADRS and <5 for the YMRS in the cases of depression and mania, respectively. These stringened criteria made possible the consideration of subsyndromal states, which are very important in BD (7–14 in HDRS or MADRS and 8–14 in YMRS). In essence the definition of subsyndromal states is utilized also for the definition of treatment-emergent-affective-switch. These authors defined "recovery" as sustained remission after at least 8 weeks [71], which is similar to the approach of the AMA [73]. However with only a minority of patients in RCTs achieving complete remission, the use of definitions (relapse vs. recurrence and continuation vs. maintenance) becomes even more problematic with more frequent use of the terms "relapse" and "maintenance." The continuation treatment phase covers up to 12 months, and theoretically the duration depends on an estimate of when the episode would have remitted spontaneously. Maintenance treatment covers several years and starts after remission. The FDA policy is to accept evidence based on patients in remission for less than 2 months, thus adding to the "continuation" versus "maintenance" confusion of definitions [74].

Table 4 Practical definitions of response, remission, recovery, and refractoriness, based mainly on the ISBD criteria

	Phase	Scale scores	Trial duration
Response	Acute mania	<25%, 25–49%, 50–74%, 75–100% reduction in YMRS or MRS scores. No significant increase in MADRS or HDRS scores and MADRS and HDRS scores stay below 6.	8–10 weeks
	Acute Bipolar depression	<25%, 25–49%, 50–74%, 75–100% reduction in MADRS or HDRS scores. No significant increase in YMRS or MRS scores and YMRS and MRS scores stay below 5.	10–12 weeks
	Maintenance	Significant change in the frequency of episodes.	1 year
Remission	Acute mania	YMRS and MRS scores stay below 5. No significant increase in MADRS or HDRS scores and MADRS and HDRS scores stay below 6	?
	Acute Bipolar depression	MADRS and HDRS scores stay below 6. No significant increase in YMRS or MRS scores and YMRS and MRS scores stay below 5.	?
	Maintenance	Very rare new episodes, and MADRS/HDRS scores < 6 and YMRS/MRS scores < 7 between episodes.	2–3 years?
Recovery	Acute mania	YMRS and MRS scores stay below 5 No significant increase in MADRS or HDRS scores and MADRS and HDRS scores stay below 6.	8 weeks
	Acute Bipolar depression	MADRS and HDRS scores stay below 6. No significant increase in YMRS or MRS scores and YMRS and MRS scores stay below 5.	8 weeks
	Maintenance	No new mood episodes and MADRS/HDRS scores < 6 and YMRS/MRS scores <7 between episodes.	3–5 years?
Refractoriness	Acute mania	No significant reduction in YMRS or MRS scores, or significant increase in MADRS or HDRS scores or MADRS and HDRS scores exceed 6.	8–10 weeks
	Acute Bipolar depression	No significant reduction in MADRS or HDRS scores or significant increase in YMRS or MRS scores or YMRS and MRS scores exceed 5.	10–12 weeks
	Maintenance	No change in the frequency of episodes, or MADRS/HDRS scores > 6 or YMRS/MRS scores > 7 between episodes.	1 year

The ISBD definitions suggest that noncriterion symptoms that are commonly associated with BD (usually during the depressive phase) such as anxiety, panic attacks, irritability, hopelessness, avoidance, or cognitive dysfunction should not be included in the definitions [71].

In Table 4, a summary of practical criteria for response, remission, and recovery, mainly based on the ISBD definitions [71] are shown.

Treatment Modalities with Proven Efficacy in BD

Reviewing the evidence is not the aim of this study and such an analysis can be found elsewhere [22,23]. A list of agents with proven efficacy against the various facets of BD is shown in Table 3.

What are impressive are the rates of response and remission. Even concerning acute mania, these rates are surprisingly low and they suggest that almost 50% of patients in an acute manic episode do not respond while the respective nonresponse to placebo is around 75% [66–68,75–84]. It is not clear how this fact should be interpreted since it implies that half or more of patients could suffer from chronic mania even after treatment in contrast to naturalistic data which suggest this percentage is no more than 5% [85] and such a diagnostic condition is not recognized by the DSM-IV-TR. What is even more impressive is the fact that in these RCTs the vast majority of patients were receiving the higher dosage permitted by the design of the study.

Bipolar depression is a rather difficult to treat condition. Only quetiapine and the olanzapine–fluoxetine combination have solid ways. A comparison of lithium versus quetiapine in acute bipolar depression was negative for lithium [86]. Again the response rate is around 50% with placebo close to 25% [87–90].

Because many authors consider all or almost all antidepressants to exert a similar or near similar effect against bipolar depression, carrying the experience of unipolar depression also to bipolar depression, failures with paroxetine were generalized and antidepressants in general are considered by many authors as ineffective in acute bipolar depression and this is argued to have been replicated, in the largest and best designed studies [91]. However, paroxetine failed not only during the STEP-BD trial [92], but also in two RCTs [93,94]. Data for other antidepressants are also sparse and incomplete, but in contrast, at least fluoxetine in combination with olanzapine has sufficient data to support its effectiveness against acute bipolar depression [87].

Concerning the maintenance phase, the evidence suggests that lithium, olanzapine, aripiprazole, and quetiapine are rather selectively protective against manic episodes while lamotrigine and fluoxetine protect against depressive episodes [95,96]. Surprisingly the data for valproate are insufficient but so far negative and insufficient also for carbamazepine. The effectiveness of psychosocial interventions during the maintenance phase is supported by a number of studies and it seems these interventions add to the overall pharmacological efficacy (64.4% vs. 51.5%) [97–104].

A problem with agents that preferentially act against the one pole of the illness is the possibility of inducing the opposite pole. However switching to depression (even at a subclinical level) is documented only concerning haloperidol and perphenazine [105,106]. A similar problem with antidepressants is the potential risk to induce mania, mixed episodes, and rapid cycling. Adjunctive studies report that around 14% of bipolar depressed patients under both an antidepressant and a mood stabilizer switch to mania or hypomania [107,108]. The metaanalysis suggests a higher switch rate for venlafaxine [109] and maybe absent for fluoxetine [110,111]. It seems that without the concomitant use of an antimanic agent the average switch rate is around 25% [112]. However the overall picture suggest the switch rate was not different in the prepharmacologic era compared to nowadays [113] and only a subgroup of patients is at risk of switching under antidepressants [114].

Evidence for the Treatment of Refractory Cases

Refractory Mania

Several combination therapies give equivocal results and do not support combination treatment as first line treatment for all patients [115–121].

However, in partial responders under lithium, valproate, or carbamazepine at therapeutic levels, adding 1–6 mg risperidone improved the outcome (response rate: 48% vs. 31% at week 1; 61% vs. 43% at week 3) [122]. An 8-week trial on 52 incomplete responders to lithium utilized adding carbamazepine or oxcarbazepine (600–1200 mg daily) during maintenance treatment. Although this trial was on patients in the "maintenance" phase the design and the results are more relevant to the acute manic phase. The study sample constituted of manic, mixed, and depressed patients. Both groups improved with the addition of either drug but those receiving oxcarbazepine improved significantly more concerning their YMRS score [123]. In partially responsive manic patients already receiving valproate or lithium, adding olanzapine 5–20 mg daily improves the outcome after 6 weeks (response rate 67.7% vs. 44.7% with placebo) with a robust effect on mixed-depressive symptoms [124] and on suicidality [125]. In a 3-weeks combination treatment placebo-controlled study, quetiapine (up to 800 mg daily) was added to patients under lithium (0.7–1.0 mEq/L) or valproate (50–100 μg/mL) the response rate was higher for the quetiapine group (54.3% vs. 32.6%) [126]. Adding up to 800 mg of quetiapine daily on lithium or valproate in partial responders, improved the response rate at week 3 (55.7% vs. 41.6% with placebo) [127]. However a more recent 6-week RCT does not support adding quetiapine to lithium or valproate in partial responders [128]. Adding aripiprazole on lithium (0.6–1.0 mmol/L) or valproate (50–125 μg/mL) in partial responders produced higher response rate at week 6 (62.8% vs. 48.5% concerning both lithium and valproate groups) [129]. One study reported that adding valproate to neuroleptics improves the outcome (70% vs. 46%) [130].

An unpublished study of 80–120 mg ziprasidone daily versus placebo on top of lithium was negative concerning the primary outcome, which was the YMRS [131]. Data as an adjunctive therapy are negative for topiramate, in spite of some positive reports [132]. The unpublished NCT00309686 was negative for palimperidone 3–12 mg daily as adjunctive therapy to lithium or valproate.

The results of a 12-week placebo controlled study on the safety and efficacy of asenapine when added to lithium or valproate (NCT00145470 and NCT00145509) was positive. Recent trials with licarbazepine reported negative results.

Thus, combination and add-on studies suggest that in acutely manic patients partial responders to lithium, valproate, or carbamazepine, a good strategy would be to add haloperidol, risperidone, olanzapine, quetiapine, or aripiprazole. Adding oxcarbazepine to lithium is also a choice.

Refractory Bipolar Depression

Older add on studies with imipramine as adjunctive therapy on lithium in bipolar depression were negative [133–135]. More recently one study used imipramine or paroxetine versus placebo as add on to lithium and reported that antidepressants were beneficial for patients with low but not for high levels of lithium [93]. Adding venlafaxine, sertraline, or buproprione on a mood stabilizer increases the response rate [107,108,136]. Similar findings were reported for citalopram [137] and paroxetine and amitriptyline [138].

However in a recent negative double-blind, placebo-controlled study, adding an antidepressant on a mood stabilizer in 179 bipolar depressed patients was not significant better than placebo after 26 weeks of treatment and the recovery rates (23.5% in the antidepressant group vs. 27.3% in the placebo group) and switch rates were similar [92], while on the contrary another earlier one supported the usefulness of paroxetine as add on therapy [139]. A more recent study reported that adding lamotrigine to lithium was better than placebo in patients with bipolar depression under long-term lithium treatment [140] and another recent 8 week trial on 52 incomplete responders utilized adding carbamazepine or oxcarbazepine (600–1200 mg daily) during maintenance treatment (results are more relevant to the acute depressive phase) with lithium was positive [123]. Recently one add on unpublished study with ziprasidone (NCT00483548) was negative.

Strictly speaking, there are no reliable data concerning the treatment of refractory bipolar depressives. Since only quetiapine and the OFC are the only treatment options with proven efficacy against this condition, RCTs with patients who fail under them are necessary. Until today, such studies do not exist and existing data cannot be considered to concern refractory patients.

Refractory Maintenance

There are several combination therapies on nonrefractory study samples. Two combination studies with lithium plus imipramine, carbamazepine or perphenazine and carbamazepine or valproate plus perphenazine were negative [106,135], the OFC was superior to lamotrigine in the prevention of bipolar depression [141], quetiapine plus mood stabilizer was superior to placebo plus mood stabilizer in the prevention of manic and depressive recurrences [142,143], adding olanzapine on lithium or valproate is better

than monotherapy with lithium or valproate [144], ziprasidone plus a mood is better than mood stabilizer [145]. Adding olanzapine to lithium or valproate improves outcome [144] and may reduce suicidality [125], valproate is more effective than lithium when added on antidepressants for the prevention of bipolar depression [146], and a recent double blind study suggested that adding an antidepressant (buproprion, sertraline, or venlafaxine) on a mood stabilizer improved both the acute phase outcome and after 1 year follow up without inducing mania [136]. There is also one positive add on study on long acting injectable risperidone [147]. The recently published BALANCE could neither reliably confirm nor refute a benefit of combination therapy compared with lithium monotherapy [148] at least partially because of methodological flaws [149].

Overall, there is no compelling data that combination treatment does better than monotherapy in nonselected patients. However patients stabilized on combination treatment might do worse if shifted to combination.

There are only three RCTs utilizing refractory patients. In a three phase crossover and eventually combination treatment of lithium plus carbamazepine, the results suggested that there was no further improvement for patients although rapid cycling patients do better under combination than under monotherapy (28.0% responded to lithium; 19.0% responded to carbamazepine, and 56.3% to their combination) [150]. Clozapine is superior to treatment as usual in the prevention of mania in refractory patients [151]. One study reports that adding lamotrigine to lithium was better than placebo in patients with bipolar depression under long-term lithium treatment [140].

A 40-week placebo controlled study of the safety and efficacy of Asenapine when added to lithium or valproate (NCT00145509) and a 40-week extension study of asenapine versus olanzapine (Ares 7501007) are expected to be announced.

Psychological Treatments

Adding a psychological treatment to pharmacotherapy, especially in refractory patients, is a standard in psychiatry although hard data are limited.

A recent randomized controlled trial of cognitive therapy (CT) in 52 bipolar patients for 6 months reported that at the end of the study the CT group had lower depression scores and less dysfunctional attitudes. A number of positive trends towards better overall outcome even at 12 months were also reported [97]. Another randomized controlled study on 293 patients concerning the effectiveness of family-focused therapy, interpersonal and social rhythm therapy, and cognitive behavior therapy on bipolar depression suggested that patients receiving intensive psychotherapy had significantly higher year-end recovery rates (64.4% vs. 51.5%) and shorter times to recovery than patients in collaborative care. No statistically significant differences were observed in the outcomes of the three intensive psychotherapies [98]. More positive data are available concerning psychoeducation [99–104].

The gradings of data concerning each treatment modality for the different phases of BD are shown in Table 5.

Other Agents and Therapeutic Modalities

Benzodiazepines can be used as adjunctive medication. They are not considered effective against the core symptoms of bipolar illness; however they could be useful because of their antianxiety and sedative properties. Their major problem is addiction and tolerance as well as many interactions with other medications.

A recent placebo-controlled 4-week RCT supported the efficacy and safety of the purinergic agents' allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania [152]. Also another placebo controlled RCT supported the usefulness of celecoxib as an adjunct in the treatment of mixed episodes with a rapid action [153]. Folic acid was also found to be useful as an adjunct to valproate [154].

Dopaminergic agents and especially pramipexole could be useful in the treatment of bipolar depression either as monotherapy or as add on therapy [155]. Inositol could also be used as an augmenting agent in refractory depressive patients [156] and N-acetyl cysteine for maintenance [157]. Recently a placebo-controlled study of adjunctive modafinil has been shown to improve the outcome of bipolar depression without switching to mania or hypomania [158], however subclinical swithes could be present [159].

Older clinical observations and some more recent clinical trials support the efficacy of electroconvulsive therapy (ECT) in acute mania, and in treatment resistant bipolar depression [160–164], although there are no definite data. Transcranial magnetic stimulation (rTMS) of the brain at 20 Hz over the right but not left frontal cortex or 1 Hz bifrontally is reported to be effective. However data are still insufficient and no conclusions can be drawn [165–168].

Sleep deprivation and other noninvasive circadian-related interventions could be useful add-on treatment in order to accelerate and sustain antidepressant response [169].

However augmentation strategies have not been tested adequately and most of them cannot be considered to have proven efficacy beyond doubt. Augmentation strategies are summarized in Table 6.

Discussion

This study tackles the issue of refractoriness in BD. Although a complete search of the literature has been done, the most significant limitation is that data are incomplete and do not always permit an evidence-based approach. Our knowledge concerning the treatment of BD has changed radically during the last couple of decades. Although the earlier studies suggested a high effectiveness for older agents and a high prevalence of switching with antidepressants, these were not confirmed by newer studies. The collapse of the "class effect" approach to BD treatment raises important questions as to which patients are truly refractory and which were simply treated in a suboptimal way.

The data are few and might provide with insight only in the case of acute mania. Ironically, acute mania is the least problematic phase in comparison to acute bipolar depression or the maintenance phase.

For refractory manic patients, the combination of Li or valproate with aripiprazole, olanzapine, risperidone, and maybe quetiapine

Table 5 Therapy data

Agent/modality (alphabetical order)	ACUTE MANIA						ACUTE BIPOLAR DEPRESSION						MAINTENANCE TREATMENT						
		Combination in refractory cases						Combination in refractory cases						Combination in refractory cases					
	FLM	MS	Cbz	Lam	Li	Val	FLM	MS	Cbz	Lam	Li	Val	Index episode	FLM	UT	MS	Lam	Li	Val
Amis	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Arip	+++	–	–	–	++	++	neg	–	–	–	–	–	m	m	–	–	–	–	–
Asen	+++	–	–	–	+++*	+++*	–	–	–	–	–	–	–	–	–	–	–	–	–
Bupr	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cbz	+++	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	neg	–
Chrp	++	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cloz	+	–	–	–	–	–	–	–	–	–	–	–	m	m*	–	–	–	–	–
ECT	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Flu	–	–	–	–	–	–	+++	–	–	–	–	–	–	–	–	–	–	–	–
Gab	neg	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hal	+++	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Lam	neg	–	–	–	–	–	neg	–	–	–	–	–	m/d	d	–	–	–	–	–
Li	+++	–	++	–	–	–	neg	–	–	+++	–	–	m/d	m	–	neg	d	–	–
Olz	+++	–	–	–	+++	+++	E	–	–	–	–	–	m	m/d	–	–	–	–	–
OFC	–	–	–	–	–	–	+++	–	–	–	–	–	–	–	–	–	–	–	–
Oxcbz	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pal	+++	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Parx	–	–	–	–	–	–	neg	–	–	–	–	–	–	–	–	–	–	–	–
Perph	–	–	–	–	–	–	–	–	–	–	–	–	m	–	–	–	–	–	–
Quet	+++	–	–	–	E	E	+++	–	–	–	–	–	m/d	–	–	–	–	–	–
Ris	+++	–	+++	–	+++	+++	–	–	–	–	–	–	–	–	–	–	–	–	–
LIR	–	–	–	–	–	–	–	–	–	–	–	–	m	–	–	–	–	–	–
SP	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Tam	+++	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
TMS	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Top	neg	neg	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Val	+++	–	–	–	–	–	E	–	–	–	–	–	–	–	–	–	–	–	–
Zip	+++	–	–	–	neg	–	neg	–	–	–	–	–	m	–	–	–	–	–	–
CBT	–	–	–	–	–	–	–	–	–	–	–	–	d	–	d	–	–	–	–
Psy-Ed	–	–	–	–	–	–	–	–	–	–	–	–	m/d	–	m/d	–	–	–	–

Amis, Amisulpride; Arip, Aripiprazole; Asen, Asenapine; Bupr, Bupropione; Cbz, Carbamazepine; Chrp, Chlorpromazine; Cloz, Clozapine; d, Depressive episode; ECT, Electro-Cunvulsive Therapy; FLM, First line monotherapy; Flu, Fluoxetine; Gab, Gabapentin; Hal, Haloperidol; Lam, Lamotrigine; Li, Lithium; m, Manic/mixed episode; MS, Mood Stabilizer; Olz, Olanzapine; OFC, Olanzapine-Fluoxetine combination; Oxcbz, Oxcarbazepine; Parx, Paroxetine; Pal, Paliperidone; Perph, Perphenazine; Quet, Quetiapine; Ris, Risperidone, oral; LIR, Risperidone, Long-acting Injectable; SP, Sleep deprivation; Tam, Tamoxifen; TMS, Transcranial Magnetic Stimulation; Top, Topiramate; Val, Valproate; Zip, Ziprasidone; CBT, Cognitive-behavioral therapy; Psy-Ed, Psychoeducation; UT, Usual Treatment.

+++: strong positive evidence on the basis of placebo-controlled RCTs.

+++*: unpublished data; suggested with reservation.

++: evidence on the basis of RCTs but without placebo arm or with small study sample.

+: positive evidence on the basis of open studies.

neg: strong negative data on the basis of RCTs.

E: equivocal data.

m: manic/mixed episode.

d: depressive episode.

m/d: either manic/mixed or depressive episode.

m*: with proven efficacy in the prevention of mania only in refractory patients.

Table 6 List of agents studied for augmentation strategies

Agent/modality	Indication for augmentation
Celecoxib	Mania/mixed
Dopaminergic agents (pramipexole)	Bipolar depression
ECT	Bipolar depression or mania/mixed
Folic acid	Mania/mixed
Inositol	Bipolar depression
Modafinil	Bipolar depression
N-acetyl cysteine	Bipolar depression
Purinergic agents	Mania/mixed
Sleep deprivation	Bipolar depression
TMS	Bipolar depression or mania/mixed

or asenapine is recommended. Anecdotal data suggest the use of ECT or higher dosages of neuroleptics, but the data are insufficient. Unfortunately there are even fewer data to support a valid strategy to cope with refractory bipolar depressive cases and with maintenance treatment. By utilizing the results of a single study [140] on Li plus lamotrigine, the conclusion could be that this combination is effective during both the acute bipolar phase as well as during the maintenance treatment for the prevention of depressive episodes in refractory patients.

Thus the paucity of data leaves the clinician with the heavy burden to decide on the basis of clinical experience and wisdom. In this frame, existing treatment guidelines cannot be considered to rely on hard data after their first step recommendations. Future research is essential and necessary to test possible treatment approaches for refractory patients of all kinds.

This research should utilize operationalized definitions on the basis of treatments with proven efficacy against the respected condition. Add-on studies or combination studies might give some kind of information; however the interpretation is complex and so far failed to provide reliable ground for decision-making. The "superiority design" concept of these studies with the use of non-refractory patients might reflect a specific logic in the approach of the problem but so far has been proven to be inadequate.

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