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Pharmacological Treatment of Refractory Bipolar Disorder: What Does the Evidence Say?

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Abstract

Bipolar disorder constitutes a therapeutical challenge. In spite of intense reseach on its treatment during the last decades, the data on the treatment of refractory bipolar patients are sparse. For acutely manic patients who are 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. The treatment of refractory bipolar depressives remains terra incognita and also there is no compelling data for the maintenance treatment of refractory patients. 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

The treatment of Bipolar Disorder (BD) is complex and full of caveats for the clinician [1-4]. The presence of residual affective symptoms is associated with a greater risk of relapse and poorer functional outcomes. 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 [5-10]. Some authors utilized only lithium non-response or intolerance [5,6], others included an alternate nonresponse/intolerance to carbamazepine [5,7] or valproate [10] while others required nonresponse to at least two or more mood-stabilizing medications including antipsychotics [6,10-15]. The current article attempts to perform a review of the treatment of refractory bipolar patients [16,17].

Definition of Refractoriness in Bipolar Disorder

Currently, the International Society on Bipolar Disorder (ISBD) definitions is the most comprehensive and updated. They 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). 'Recovery' is defined as sustained remission after at least 8 weeks [18], which is similar to the approach of the AMA [19]. 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 [18]. It is interesting that the ISBD definitions do not include functioning in their criteria while other authors do include it [20].

A dilema 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 disease as a whole. The first approach will be easier to operationalize, but the second is more clinically oriented and meaningful.

Another 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.

The third problem concerns trial duration. It is necessary to wait for sufficient time for the agent to act. Taken the data altogether it seems that at least 10-12 weeks of duration should be the minimum of a therapeutic acute phase trial before the patient should be considered as non-responder. During the maintenance phase it is reasonable to consider response and refractoriness in the frame of 1 year (52 weeks) duration, remission should require at least 2-3 years and recovery 3-5, because of the episodic nature of the illness.

In table 1, a summary of practical criteria for response, remission and recovery, developed by the author [21] and based on the ISBD definitions [18] are shown.

Treatment Modalities with Proven Efficacy in BD

The author has already published several reviews on the evidence concerning the pharmacological treatment of bipolar disorder [1,3,4,16,17,21-41]. The current paper is based on these previous studies and the reader is encouraged to utilize them for details. The review of the data was updated through May 1st 2013. A list of agents with proven efficacy against the various facets of BD is shown in table 2.

Treatment of Refractory Cases

Refractory mania

Combination studies do not support the proposal that combination

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	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 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

Table 1: Practical definitions of response, remission, recovery and refractoriness, based mainly on the ISBD criteria.

treatment is first line treatment for all patients [42-48]. In partial responders under lithium, valproate or carbamazepine at therapeutic levels, adding 1-6 mg risperidone improved the outcome [49]. In incomplete responders to lithium adding carbamazepine or oxcarbazepine (600-1200 mg daily) during maintenance treatment improved the result especially concering adding oxcarbazepine. Although this trial was on patients in the 'maintenance' phase the design and the results are more relevant to the acute manic phase [50]. In partially responsive manic patients already receiving valproate or lithium, adding olanzapine 5-20 [51,52] aripiprazole [53], quetiapine (up to 800 mg daily) [54,55] or asenapine [56] improves the outcome. However, a more recent 6-week RCT does not support adding quetiapine to lithium or valproate in partial responders [57]. One study reported that adding valproate to neuroleptics improves the outcome [58]. One unpublished [59] and one published [60] add-on studies of ziprasidone vs. placebo on top of lithium or a mood stabilizer were negative. Data as an adjunctive therapy are negative for topiramate, in spite of some positive reports [61]. The unpublished NCT00309686 was negative for paliperidone 3-12 mg daily as adjunctive therapy to lithium or valproate. 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

Unfortunately the options for the treatment of refractory bipolar depression are limited. Most studies are negative. Older add on studies with imipramine as adjunctive therapy on lithium in bipolar depression were negative [62-64]. More recently one study used imipramine or paroxetine vs. placebo as add on to lithium and reported that antidepressants were beneficial for patients with low but not for high levels of lithium [65]. Adding venlafaxine, sertraline or buproprione on a mood stabilizer increases the response rate [66-68]. Similar findings were reported for citalopram [69], paroxetine and amitriptyline [70]. The problem is that the above studies are not placebo-controlled, and unfortunately, a recent double-blind, placebo-controlled study, of adding an antidepressant on a mood stabilizer in 179 bipolar depressed patients was negative [71]. On the contrary another earlier one supported the usefulness of paroxetine as add on therapy [72]. A more recent study reported that adding lamotrigine to lithium was better than placebo in patients with bipolar depression under long term lithium treatment [73] 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 [50]. Recently one add- on 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 only few 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

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	ACUTE MANIA						ACUTE BIPOLAR DEPRESSION						MAINTENANCE TREATMENT						
Agent/modality (alphabetical order)	**FLM**	**Combination in refractory cases**					**FLM**	**Combination in refractory cases**					**Index episode**	**FLM**	**Combination in refractory cases**				
		MS	**Cbz**	**Lam**	**Li**	**Val**		**MS**	**Cbz**	**Lam**	**Li**	**Val**			**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	-	-	-	-

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

Table 2: Therapy data
+++: 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

combination) [74]. Clozapine is superior to treatment as usual in the prevention of mania in refractory patients [75]. One study reports that adding lamotrigine to lithium was better than placebo in patients with bipolar depression under long term lithium treatment [73].

A 40 week placebo controlled extension study of the safety and efficacy of Asenapine when added to lithium or valproate was inconclusive because of high drop out rate [56] and a 40 week extension study of asenapine vs. olanzapine (Ares 7501007) is 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. Data are positive for cognitive therapy [76,77], intensive psychotherapy with family-focused therapy, interpersonal and social rhythm therapy, [77] and psychoeducation [78-84].

The gradings of data concerning each treatment modality for the different phases of BD are shown in Table 2.

Other agents and therapeutic modalities

A number of medications outside the usual groups and classes might be useful especially in the treatment of complex and resistant cases. 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 anti-anxiety and sedative properties. Their major problem is addiction and tolerance as well as many interactions with other medications.

Recent placebo-controlled RCTs support the efficacy of the purinergic agents' allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania [85], of celecoxib as an adjunct in the treatment of mixed episodes with a rapid action [86] and of folic acid as an adjunct to valproate [87]. Dopaminergic agents and especially pramipexole could be useful in the treatment of bipolar depression either as monotherapy or as add on therapy [88,89]. Inositol could also be used as an augmenting agent in refractory depressive patients [90] and N-acetyl cysteine for maintenance [91]. Recently a placebo-controlled study of adjunctive modafinil has been shown to improve the outcome of bipolar depression without switching to mania or hypomania [92], however subclinical swithes could be present [93]. Data are also positive for ketamine [94,95].

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 [96-102], 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 bi-frontally is reported to be effective. However data are still insufficient and no conclusions can be drawn [103-106].

Sleep deprivation and other noninvasive circadian-related interventions could be useful add-on treatment in order to accelerate and sustain antidepressant response [107].

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 3.

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

Table 3: List of agents studied for augmentation strategies.

Discussion

The current study reviews the issue of treatment of refractory bipolar patietns. It is obvious that the data are limited 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 or asenapine is recommended. Some reports 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.

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.

Conflict of interest

Dr Fountoulakis is/was member of the International Consultation Board of Wyeth for desvenlafaxine, BMS for aripiprazole in bipolar disorder and Servier for agomelatine and has received honoraria for lectures from AstraZeneca, Janssen-Cilag, Eli-Lilly and research grants from AstraZeneca and Pfizer Foundation.

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