Bipolar disorder: recent clinical trials and emerging therapies for depressive episodes and maintenance treatment

Ricardo P. Garay[1,2], Pierre-Michel Llorca[3], Allan H. Young[4], Ahcène Hameg[2] and Ludovic Samalin[3]

[1] INSERM U999, Université Paris-Sud et Hôpital Marie Lannelongue, Le Plessis-Robinson, France
[2] Craven, Villemoisson-sur-Orge, France
[3] Psychiatry Service, CHU Clermont-Ferrand, EA 7280, Auvergne University, Clermont-Ferrand, France
[4] Centre for Affective Disorders, Institute of Psychiatry, Kings College London, De Crepisgny Park, London, UK

Bipolar disorder (BD) is one of the world's ten most disabling conditions. More options are urgently needed for treating bipolar depressive episodes and for safer, more tolerable long-term maintenance treatment. We reviewed 30 recent clinical trials in depressive episodes (eight tested compounds) and 14 clinical trials in maintenance treatment (ten tested compounds). Positive results in Phase III trials, regulatory approval and/or new therapeutic indications were obtained with some of the developing drugs, particularly for depressive episodes. The current BD pipeline is encouraging with promising new compounds, acting on novel pharmacological targets and on specific aspects of bipolar depression.

Introduction

Bipolar disorder (BD) is a chronic, severe and recurring illness (typically manic episodes alternate with episodes of depression), which affects 3% or more of the population and is associated with substantial morbidity and mortality [1]. The mortality rate of those with BD is two-to-three-times higher than the rate in the general population, owing particularly to suicide but also to accidents, medical illness and substance abuse [2]. Indeed, BD is one of the world's ten most disabling conditions and one of the greatest public health problems [3].

BD refers to a continuum of disorders [4], including: (i) the traditional bipolar I subtype (BD-I), which includes episodes of full-blown mania and major depression; (ii) BD type II (BD-II) depressive and hypomanic episodes; (iii) cyclothymic disorder (depressive and hypomanic symptoms); and (iv) BD not otherwise specified.

The cause of BD is unknown, but genetic and environmental risk factors are believed to have a role [5,6]. Treatment commonly includes mood-stabilizing medication and supportive and educational therapy [7–12]. The treatment of mania is provided for by the available treatments: (i) mood stabilizers including lithium and anticonvulsants (valproate, carbamazepine) that are effective in treating acute manic episodes and preventing relapses; and (ii) some atypical antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole) initially used to treat schizophrenia, which have also been found to be efficacious for managing mania.

Generally speaking, the periods of depression far exceed those of mania in terms of frequency and duration [13,14]. BD patients commit or attempt suicide mostly during severe depressive episodes, but very rarely during states of euphoric mania or euthymia [2]. Quetiapine and an olanzapine–fluoxetine combination (OFC; a single capsule containing the atypical antipsychotic olanzapine and the selective serotonin reuptake inhibitor fluoxetine) are used to treat bipolar depressive episodes [10], but they are not exempt from adverse effects in long-term treatment (e.g. weight gain, dyslipidaemia and/or sedation or somnolence). Because of discordant data concerning lithium and valproate, these two drugs are placed either as first- or as second-line treatment for bipolar depression [12,15]. Unmet treatment needs in the management of BD include more options for treating bipolar depressive episodes and safer, more-tolerable medications for long-term maintenance treatment [8,16]. This review summarizes a selected number of recent clinical trials in bipolar depressive episodes and in long-term maintenance treatment and also discusses important ongoing trials.

Corresponding author:. Garay, R.P. (ricardo.garay@orange.fr)

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.07.010

Selection criteria

Clinical trial eligibility

Clinical trials were selected on the basis of the following criteria.

- The primary outcome was at least one of the following:
- efficacy in bipolar depressive episodes;
- long-term efficacy for relapse prevention or residuals symptoms;
- status as a long-term safety trial.
- The clinical trial was recruiting or active (not recruiting), or completed in 2012 or later.
- It was a Phase II, III or IV trial.
- It was a randomized trial, or an open trial versus placebo and/or a comparative compound.
- Compound development was not discontinued.

Data sources and search

We identified clinical trials in bipolar depressive episodes and long-term BD maintenance treatment using the following main sources.

- The clinical trials databases of the NIH (National Institutes of Health; http://www.clinicaltrials.gov/), the European Medicines Agency (EMA; EU Clinical Trials Register; https://www.clinicaltrialsregister.eu/ctr-search/search;jsessionid=sa0a1Jq2IuPPzCa-QoIpaEOkYugzkgm_2UA9T_Bmp3ks9p4LXbe5D!-895578838) and WHO (World Health Organization International Clinical Registry Platform; http://apps.who.int/trialsearch/).
- Records from the EMA (http://www.ema.europa.eu/ema/) and FDA (http://www.fda.gov/).
- Medical journals, using PubMed, Science Direct and Google Scholar.
- Conferences and meetings on psychiatry.
- Websites of pharmaceutical and biotech companies active in the field of BD-targeted therapies.

Identification of clinical trials and compounds

Clinical trials are given with their proper name or a literature reference, or the ClinicalTrial.gov identifier, in decreasing order of priority. Compounds are given with their generic name and the biotech or pharmaceutical company in charge of development. Trade name is indicated when available.

Compound classification

Compounds reviewed here are divided into FDA- and/or EMA-approved compounds (for the bipolar depressive episodes, for BD maintenance treatment or for other psychiatric disorders) and new investigational compounds (for the treatment of bipolar depressive episodes and/or for maintenance treatment). Finally, the phase of development is indicated together with its status.

- With results.
- Completed.
- Ongoing, with the estimated study completion date.

Recent clinical trials in bipolar depressive episodes

Our search identified 30 eligible clinical trials in bipolar depressive episodes (accessed between 19th February and 7th May 2014) corresponding to eight developing compounds.

- The olanzapine–fluoxetine combination (OFC, Symbyax®, Eli Lilly) – for review of previous studies see [17].
- Quetiapine extended-release (XR) (quetiapine XR, Seroquel XR®, AstraZeneca) [18].
- Asenapine (Saphris®, Forest, USA; Sycrest®, Lundbeck, EU) [19].
- Lurasidone (Latuda®, Sunovion) [20].
- Armodafinil (Nuvigil®, TEVA) [21].
- Ramelteon (Rozerem®, Takeda Pharmaceuticals, Japan) [22].
- Lisdexamfetamine dimesylate (Vyvanse®, Shire Pharmaceuticals, UK) [23].
- Cariprazine (Forest Laboratories, USA) [24].

TABLE 1

Investigational compounds for bipolar depressive episodes and maintenance treatment of bipolar disorder (BD) reviewed in this article.

Family	Compound	Main receptor actions	Main medication uses[f]	Refs
Atypical antipsychotics(±antidepressant)	Quetiapine	D2 and 5-HT2A antagonist[b]	BD and schizophrenia	[18]
	Olanzapine	D2 and 5-HT2A antagonist[b]	BD and schizophrenia	[33]
	Paliperidone	D2 and 5-HT2A antagonist[b]	BD and schizophrenia	[35]
	Lurasidone	D2 and 5-HT2A antagonist[b]	BD and schizophrenia	[20]
	Asenapine	D2 and 5-HT2A antagonist[b]	BD and schizophrenia	[19]
	Aripiprazole	D2 and D3 partial agonist[c]	BD and schizophrenia	[34]
	OFC[a]	D2 and 5-HT2A antagonist[b] + SSRI[d]	Bipolar depression and TRD[g]	[17]
Anticonvulsants	Lamotrigine	Sodium channel blocker	BD, epilepsy and seizures	[32]
New investigational compounds	Armodafinil	Unknown (dopamine suspected)	Sleep disorders	[21]
	Ramelteon	Melatonin MT1/MT2 agonist	Insomnia	[22]
	Lisdexamfetamine	TAAR1[i] activator	ADHD[j] disorder	[23]
	Cariprazine	D2 and D3 partial agonist[c]	Under investigation[h]	[24]
	Scyllo-inositol	Amyloid antiaggregation agent	Under investigation[h]	[36]
	Mifepristone	Progesterone and glucocorticoid[e]	Abortifacient and contraceptive	[38]

[a] Olanzapine–fluoxetine combination.
[b] Dopamine D2 and serotonin 5-HT2A antagonist (see ref. for other actions on neurotransmitter receptors).
[c] Dopamine D2 and D3 partial antagonist (see ref. for other actions on neurotransmitter receptors).
[d] Selective serotonin reuptake inhibitor.
[e] Progesterone and glucocorticoid receptor antagonist.
[f] FDA and/or EMA approval status before 2012 is given in Figs 1,2.
[g] Treatment-resistant depression.
[h] Cariprazine is currently under investigation for the treatment of BD and schizophrenia and scyllo-inositol is under investigation for the treatment of Alzheimer's disease.
[i] Trace-amine-associated receptor 1.
[j] Attention deficit hyperactivity disorder.