



Ockham Technical Synopsis is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

BIPOLAR DISORDER (ACUTE MANIA)

OPERATIONAL OVERVIEW

Although the large number of anticonvulsants and atypical antipsychotic agents in the pharmacopeia has greatly enhanced the ability to treat patients with Bipolar Disorder (BD)¹, a clear need remains to develop truly novel agents that adequately treat this devastating illness and modify the long-term outcome for millions of sufferers.

The 1-year prevalence of any BD in adults in the Epidemiological Catchment Area (ECA) study was 1.2%.¹ The National Co-morbidity Survey (NCS) found the 1-year prevalence of a manic episode to be 1.3%.

Despite the remarkable increase in medications validated as effective in treating BD, treatment is still plagued by inadequate response in acute manic episodes or in long-term preventive maintenance treatment. Established first-line treatments include lithium, valproate, and second-generation antipsychotics (SGA), as well as extended release carbamazepine in acute mania. Combining multiple agents is considered optimal treatment in acute mania (lithium or valproate plus an SGA). Toxicity, metabolic and neurologic side effects often limit compliance in these agents. The ideal anti-manic agent will have a more rapid onset of action and, therefore, may be more effective initially, specially in severely manic or agitated patients, and will have a more benign side effect profile.

For over a decade calcium channel antagonists (CCA) have been considered to have possible use in the treatment of BD due to some overlap in physiological activities of CCAs with those of lithium, and a possible association between BD and calcium dysregulation.

STUDY DESIGN

Typically, in acute mania 3- and 4-week placebo-controlled studies have been used to demonstrate safety and efficacy. These trials included patients with

¹ also known as manic-depressive illness

or without psychotic features and with or without a rapid-cycling course.

Primary rating instruments used for assessing manic symptoms in these trials are the Young Mania Rating Scale or the Mania Rating Scale (derived from the Schedule for Affective Disorders and Schizophrenia-Change Version), and the Clinical Global Impression - Severity of Illness Scale (CGI-S), used to assess the clinical significance of treatment response.

CHALLENGES: SITE SELECTION, PATIENT SELECTION

STEP BD, a long-term study of current treatments (including medications and psychosocial therapies) is the largest treatment study conducted for BD. STEP-BD completed its data collection on 30 September 2005 with a total enrollment of 4,361 participants and is no longer enrolling. Competition for enrollment may come for Investigator-initiated studies and Phase III and IV studies.

A growth in interest in BD has led to a substantial increase in the number of clinical trials conducted over the past few years, and has begun to magnify some of the very important methodological, regulatory and ethical difficulties now being faced.

U.S. Food and Drug Administration (FDA) guidelines for BD studies tend to be dated, and there is much discussion in the research world regarding the need for novel study designs. In particular, use of placebo is being questioned by clinicians and Investigators.

Dropout rates in these studies are typically very high. In one trial, only 21% of placebo and 42% of study drug-treated patients had data beyond two weeks. However, there is literature indicating that by Day 11 meaningful conclusions can be drawn from the rate of dropouts.

An acute mania program will have to take into consideration these challenges before selecting both the study design and the sites.

There is some difficulty in recruiting appropriate patients for clinical studies. At least two separate issues have converged to create this problem:

- The prototypical clinical trial subject makes for a very atypical BD patient. The best trial patients are compliant and have clear, well-delineated psychopathology (e.g., classic elated mania) uncomplicated by complex features (e.g., rapid cycling, mixed states) or co-morbidity (e.g., alcohol and substance abuse). This profile does not capture the typical BD patient.
- There has been an exponential increase in the number of studies currently underway to test the efficacy in BD of the newest generation of anticonvulsants, antipsychotics, and

antidepressants, many of which are competing for the same patient pool. This pressure to recruit patients doubtless exacerbates the problem of placebo response, which is also driven by other poorly understood factors.

ENROLLMENT

To facilitate enrollment, Ockham recommends:

- Developing the protocol in conjunction with both thought leaders and representatives from patient and advocacy groups, to ensure that the design is both scientifically meaningful and at the cutting edge of ethical concerns.
- A site recruitment plan with each site to ensure a proactive approach to patient enrollment and recruitment-enhancing activities such as physician-to-physician letters, and posting the study with local support groups (support group Web sites).
- Encouraging sites to use a “large net” approach by advertising early with local emergency rooms and clinicians, and by having frequent interactions with referral sources.
- Selecting a variety of sites, favoring those clinical practice sites not affiliated with academic institutions, which are more likely to treat a more severe, more chronically ill population, with higher co-morbidity.
- Implementation of a competitive site start-up process where a higher number of sites is selected to yield a number of active sites. Sites are initiated in the order of contract and regulatory approval until site capacity is reached. Sites not meeting cut-off will complete the study start-up process and will be held in the queue and initiated should the enrollment rate be lower than expected.

COMPETING STUDIES

Phase	Treatment	Number of Studies	Number of Patients	Number of Sites
II	Lamotrigine	1	36	2
	MCN36	1	40	5
	Mifepristone	1	110	10
	Talwin Nx	1	10	1
	Tamoxifen	2	110	2
	Taurine	1	30	1
	Tryptophan	1	40	1

III	Abilify	1	150	1
	Aripiprazole	4	1905	304
	Asenapine	6	3376	0
	Divalproex	3	355	20
	Licarbazepine	2	830	21
	Lithium	2	630	6
	Olanzapine	1	280	18
	Paliperidone	1	464	17
	Quetiapine	5	1850	366
	Valnoctamide	1	80	3
	Ziprasidone	2	452	5
IV	Aripiprazole	2	1335	167
	Carbamazepine	1	20	1
	Divalproex	1	20	1
	Lamotrigine	1	20	1
	Lithium	1	258	6
	Olanzapine	2	893	52
	Quetiapine	2	320	13
	Risperidone	2	168	2