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ScienceDirect

Comprehensive Psychiatry 66 (2016) 146–156

COMPREHENSIVE PSYCHIATRY

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Clinical correlates of sustained response to individual drugs used in naturalistic treatment of patients with bipolar disorder

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Abstract

Objective: To report use and treatment success rates of medications for bipolar disorder as a function of patients' clinical characteristics.
Method: Outpatients with bipolar illness diagnosed by SCID were rated by research assistants on the NIMH-LCM and those who had an good response for at least 6 months (much or very much improved on the CGI-BP) were considered responders (treatment "success"). Clinical characteristics associated with treatment response in the literature were examined for how often a drug was in a successful regimen when a given characteristic was either present or absent.
Results: Lithium was less successful in those with histories of rapid cycling, substance abuse, or (surprisingly) a positive parental history of mood disorders. Valproate was less successful in those with ≥20 prior episodes. Lamotrigine (LTG) was less successful in those with a parental history of mood disorders or in BP-I compared to BP-II disorder. Antidepressants (ADs) had low success rates, especially in those with a history of anxiety disorders. Benzodiazepines had low success rates in those with child abuse, substance use, or ≥20 episodes. Atypical antipsychotics were less successful in the presence of rapid cycling, ≥20 prior episodes, or a greater number of poor prognosis factors.
Conclusion: Success rates reflect medications used in combination with an average of two other drugs during naturalistic treatment and thus should be considered exploratory. However, the low long-term success rates of drugs (even when used in combination with others) that occurred in the presence of many very common clinical characteristics of bipolar illness speak to the need for the development of alternative treatment strategies.

1. Introduction

Many naturalistic follow up studies indicate a relatively low rate of response and remission and their persistence in the treatment of patients with bipolar disorder [1–5]. We have previously reported on the long-term prospective outcome in 525 outpatients with bipolar disorder studied in our international network from 1996 to 2002 [6–8]. We characterized good long term responders (n = 195) (37.1%) who showed either much improvement or very much improvement on the CGI-BP [9] for at least six months and compared them with 234 (49.6%) poor responders who

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http://dx.doi.org/10.1016/j.comppsych.2016.01.009
0010-440X/

did not achieve this degree of improvement [10,11]. 96 subjects (18.3%) who were essentially "Well on Entry" into the network and maintained their improvement.

In the 429 patients who were ill on Network entry, the good responders were on an average of three drugs at the time of their clinical improvement. Similarly, the non-responders were on an average of 3 drugs or at any time during their treatment in the Network [10,11]. It took an average of 1.5 years in the Network before those who were ill on entry began to have their good response for 6 months. This time included unsuccessful clinical trials with an average of two drugs, which were initiated and discontinued prior to the patient achieving the good response. The poor responders we exposed to an average of 7.3 drugs over the course of their time in the Network, which averaged 36.0 months of follow up [10,11].

We found that lithium had the highest overall "success rate" of 49.3%, i.e. lithium was involved in the treatment regimen of the good responders and those who were Well on Entry compared to its use in the non-responders [10,11]. The next drugs with the best overall success rate were carbamazepine at 39.9%, followed by valproate (34.8%), any atypical (20.7%), any antidepressant (17.8%), and any typical antipsychotic (11.8%).

In the current analysis, we examine how often drugs were used and their success rate as a function of clinical characteristics that had previously been associated with a poor long term treatment outcome in the literature, what have been characterized as a poor prognosis factors (PPFs) [5,10–14]. These PPFs included the presence of a prior history of: 1) rapid cycling, 2) more than 20 prior episodes, 3) a comorbid anxiety disorder, 4) a substance abuse disorder, 5) physical or sexual abuse, and 6) an early onset of bipolar illness (prior to age 19). A positive parental history of bipolar or unipolar disorder was also examined. In this manuscript, we only focus on the 429 patients who were ill on admission to Network in order to assess the differential utilization and success rates of drugs when they were used in the Network in an attempt to stabilize patients during prospectively assessed naturalistic treatment.

2. Methods

Clinical characteristics of the entire outpatient cohort are described in detail elsewhere [8,11,15]. Briefly, all patients gave informed consent for participation and follow up in the Network. They were diagnosed by SCID interview by trained clinical research assistants, and diagnoses were re-confirmed in the prospective clinician ratings of the NIMH-Life Chart Method which assessed the frequency and severity of manic and depressive fluctuations. Patients also give separate consent as appropriate for entry into any individual clinical trials [16]. The majority of these trials were of a design paralleling, as closely as possible, naturalistic treatment. This included acutely depressed patients who were randomized blindly to one of three different antidepressant drugs [16], or in those who were overweight or obese, randomized openly to drugs associated with weight loss (sibutramine versus topiramate) [17]. There was one placebo controlled add on study of omega-3-fatty-acids (EPA, 6 g) which was followed by an open 8 month continuation phase for responders [18]. EPA effects did not exceed those of placebo, such that patients remained essentially in naturalistic treatment during the entire duration of the study.

Patients were studied over the duration of time the network was funded, from 1996 to 2002. It should be emphasized that the individual drugs or classes of drugs utilized and classified for their success rates according to whether patients had or did not have a given clinical characteristic, were almost never used in monotherapy [10]. The percentage of "utilization" of a drug represented any time the drug was administered (in addition to an average of 2 other drugs) either in the presence or absence of a given clinical characteristic. The "success rate" for a drug in patients with or without a given characteristic or comorbidity was examined in those who were initially ill on entry and showed a sustained response (N = 195) involving that drug for 6 months compared with non-responders (N = 234) and those who had discontinued the drug for lack of effectiveness. For the drug to be considered involved with sustained improvement it had to be started with two weeks of the improvement period and maintained during at least 75% of the improvement period. The response was considered in those who achieved a rating of 1) very much or 2) much improved on the CGI-BP Improvement scale [9] when a rater examined the entire length of the NIMH-Life Chart Method (LCM) clinician ratings. A rating of 1) reflects a virtual remission of all dysfunctional symptoms, while a 2) reflects considerable improvement, but some residual remaining symptoms of mania and/or depression. It should be noted that 3) mild degrees of improvement were not considered as a clinical response and were included in the non-responder category.

The LCM rating was performed by a research assistant at each visit of the patient which typically ranged from every 2 weeks to once a month. This rater was not blind to treatment, but the rater did not know about the primary use of these assessments in relationship to the presence or absence of a given illness characteristic that is the focus of this manuscript. If the patient had been able to complete their own daily LCM self ratings, these were utilized by the clinician (usually with relatively minor revisions for the severity of mania which was sometimes underestimated by the patient). If the patient ratings were not completed, the clinician rated the severity of mania and depression based on the degree of impairment experienced by the patient in their usual family, educational, or employment roles (ranging from mild to low moderate to high moderate to severe). As these ratings were based on functional impairment, the patient was able to give a good daily history of mood fluctuations over the interval between visits, as previously