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Preliminary communication

Superior chronic tolerability of adjunctive modafinil compared to pramipexole in treatment-resistant bipolar disorder

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ABSTRACT

Background: Suboptimal outcomes are common in bipolar disorder (BD) pharmacotherapy, and may be mitigated with novel adjunctive agents such as modafinil (a low-affinity dopamine transport inhibitor) and pramipexole (a dopamine D2/D3 receptor agonist). While uncontrolled long-term effectiveness data have been reported for these treatments, reports specifically assessing their comparative acute versus chronic tolerability in BD are lacking. Such information, particularly in relation to discontinuation causes, has substantial relevance, providing initial indications to clinicians which treatment may be better tolerated, and to researchers which agent ought to be assessed in longer-term controlled trials.
Methods: BD outpatients assessed with the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation, and followed with the STEP-BD Clinical Monitoring Form, were naturalistically prescribed adjunctive modafinil or pramipexole, and somatic/psychiatric intolerability discontinuation rates were compared.
Results: Among 63 BD outpatients (mean ± SD age 43.5 ± 14.3 years, 60.3% female, 42.9% type I, 44.4% type II, 12.7% type not otherwise specified), taking 3.5 ± 1.5 (median 3) concurrent prescription psychotropics, adjunctive modafinil ($n=24$) for 626.9 ± 863.9 (286) days versus pramipexole ($n=39$) for 473.7 ± 613.4 (214; $p=0.51$) days yielded a 26.0% lower somatic/psychiatric intolerability discontinuation rate (12.5% vs. 38.5%; $p<0.05$), with most of the difference accounted for by more pramipexole somatic intolerability discontinuations, due to nausea and sedation, after the first 12 weeks of treatment.
Limitations: No placebo comparison group. Small sample of predominantly female Caucasian insured outpatients, taking complex concurrent medication regimens.
Conclusions: Further studies are warranted to assess our preliminary observation that modafinil, compared to pramipexole, may be better tolerated for longer-term BD treatment.

1. Introduction

Bipolar disorder is a common and recurring mood disorder (Merikangas et al., 2007), associated with some of the highest levels of disability, comorbidity and suicidality among psychiatric disorders (Judd et al., 2008). While long-term approved treatments including mood stabilizing compounds and second-generation antipsychotics, alone and in two-drug combinations, may be effective for some patients, individuals with more challenging illness commonly require complex combination therapy (involving 4 or more medications) interventions, which may entail unapproved (for mood disorders), adjunctive treatments to achieve response and overcome residual symptoms (Goldberg et al., 2009). Depressive symptoms are commonly resistant to treatment, with only some patients benefitting from antidepressants, and the overall effectiveness of these agents being highly controversial, due to concerns regarding the risks of inefficacy/suicidality, switching to mood elevation, and cycle acceleration (Ghaemi et al., 2003; Grunze, 2008; Yatham et al., 2009; Grunze et al., 2010).

Among novel adjunctive treatments, compounds that enhance dopaminergic neurotransmission have shown promise in the treatment of bipolar depression. Such compounds may be broadly dichotomized as: stimulant/stimulant-like agents (e.g., methylphenidate and modafinil) and dopamine agonists (e.g., pramipexole and ropinirole). To date, modafinil/armodafinil (Frye et al., 2007; Calabrese et al., 2010) and pramipexole (Goldberg et al., 2004; Zarate et al., 2004) are the only such dopaminergic agents

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assessed with randomized controlled trials (RCTs) in the treatment of bipolar depression.

Modafinil (2-(benzhydrylsulfinyl) acetamide) is a stimulant-like agent, previously thought to primarily enhance dopaminergic and noradrenergic neurotransmission, secondarily enhance serotonergic, glutamatergic and histaminergic neurotransmission, and influence orexinergic neurotransmission (Minzenberg and Carter, 2008). Modafinil's current putative chief mechanism is low-affinity dopamine transporter inhibition (Zolkowska et al., 2009; Schmitt and Reith, 2011). Modafinil's low affinity at the dopamine transporter compared to other agents could contribute to its lower abuse liability Vosburg et al. (2010). Modafinil is currently approved by the United States Food and Drug Administration (US–FDA) for improving wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea and shift-work sleep disorder, whereas the European Medicines Agency (EMEA) has limited its approved use to narcolepsy.

Pramipexole is a non-ergot, aminobenzothiazole dopamine D2/D3 receptor agonist (Mierau et al., 1995; Piercey et al., 1996; Bennett and Piercey, 1999; Antonini and Calandrella, 2011). Such receptors are densely distributed in the mesolimbic system (Lévesque et al., 1992; Gurevich and Joyce, 1999; Gerlach et al., 2003), where they implicated in the pathogenesis of motoric and anhedonic symptoms (Willner et al., 1994; Aiken, 2007). Pramipexole is currently approved by the US–FDA and the EMEA for the treatment of Parkinson's disease and restless legs syndrome.

Though neither specifically developed nor approved for the treatment of major depressive disorder and bipolar depression, both modafinil and pramipexole have been widely used off-label for such problems, mostly as adjunctive agents in patients with treatment resistance. Currently available evidence for the use of adjunctive modafinil in the treatment of bipolar depression consists of 5 reports, including one RCT (for review see Dell'Osso and Ketter, 2012a,b), whereas that of adjunctive pramipexole is based on 10 reports, including 2 RCTs (for review see Aiken, 2007 and Dell'Osso and Ketter, 2012a,b, submitted).

While both modafinil and pramipexole have shown some encouraging preliminary results, in terms of efficacy and effectiveness in acute and chronic treatment of bipolar depression, data on tolerability, particularly longer-term versus acute comparative tolerability, are substantially lacking. Assessment of longer-term tolerability of such adjunctive interventions could inform investigators and clinicians regarding the strengths and limitations of these agents, guiding decision-making regarding not only clinical trial design but also clinical management.

In order to provide preliminary data regarding the comparative longer-term versus acute tolerability of these agents, we retrospectively analyzed systematic clinical data in a group of bipolar outpatients, who were naturalistically treated with adjunctive modafinil or pramipexole, comparing with specific discontinuation rates and times to discontinuation across treatment groups in both acute and longer-term time frames.

2. Methods

2.1. Study design

The Stanford Administrative Panel on Human Subjects approved the protocol for the assessment and longitudinal monitoring of naturalistic treatment, and all patients provided verbal and written informed consent prior to participation. At intake, participants were assessed with the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Affective Disorders Evaluation (Sachs et al., 2003) and the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). They were followed longitudinally with the STEP-BD Clinical Monitoring Form (Sachs et al., 2002). Bipolar outpatients, treated most often for depressive symptoms, between January 2002 and June 2012, were evaluated in relation to naturalistic adjunctive therapy with either modafinil or pramipexole.

2.2. Participants

Participants were adults (age ≥ 18 years) with a primary diagnosis of bipolar I disorder (BDI), bipolar II disorder (BDII), or BD not otherwise specified (NOS), who were receiving outpatient treatment at the Stanford University Bipolar Disorder Clinic. Participants' clinical status ranged from euthymia to syndromal depression, as defined in the DSM-IV-TR or STEP-BD (American Psychiatric Association, 2000; Sachs et al., 2002). Subsyndromal symptoms consisted of having >2 pervasive DSM-IV-TR depressive symptoms, though not meeting criteria for a DSM-IV-TR syndromal depressive, hypomanic, manic, or mixed episode. Patients were excluded if they had a primary diagnosis other than BD, lacked post-baseline data, or took modafinil or pramipexole as needed rather than consistently.

Patients who required additional relevant psychotropic medications (antidepressants, mood stabilizers or antipsychotics), during modafinil or pramipexole therapy were included. However, efficacy for such patients was assessed at the time of adding an antidepressant/mood stabilizer/antipsychotic, in order to avoid overestimating efficacy. In contrast, for such patients, safety/tolerability was assessed at the last observed visit taking modafinil/pramipexole, in order to avoid overestimating tolerability.

2.3. Primary and secondary outcomes

The primary outcome measure was the somatic/psychiatric intolerability discontinuation rate. Secondary outcomes included discontinuation rates for somatic intolerability, psychiatric intolerability, inefficacy, other reasons, and any cause, times to such discontinuations, and intolerability discontinuation rate for the first 12 weeks of treatment. Changes in body weight and percentages of patients with at least 7% weight gain or loss, from baseline to the last visit taking modafinil or pramipexole, were also assessed. Changes in Clinical Global Impression scale for BD-Overall Severity of Illness (CGI-BP-OS) (Spearing et al., 1997) and Global Assessment of Functioning (GAF) (Endicott et al., 1976; American Psychiatric Association, 2000), from baseline (immediately prior to adding modafinil or pramipexole) to week 12, and the last visit taking either drug (or time of adding an antidepressant, mood stabilizer, or antipsychotic), were also assessed. Finally, rates of additional psychotropic pharmacotherapy were assessed.

2.4. Statistical analyses

SPSS version 20 was used for statistical analysis. Descriptive statistics were compiled. Chi-square or Fisher exact tests were used for categorical variables and *t*-tests were used for continuous variables. CGI-BP-OS at week 12 was analyzed using both the last observation carried forward (LOCF, with data at 12 weeks imputed from the last post-baseline data, when discontinuation occurred before 12 weeks) and observed cases methods. All analytic statistical tests were 2-tailed, and results were considered significant if p values were <0.05. There was no correction for multiple comparisons.