



Treatment of Attention Deficit/ Hyperactivity Disorder and comorbid Bipolar Disorder: a brief review and preliminary clinical data

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Treatment of Attention Deficit/Hyperactivity Disorder (ADHD) and Bipolar Disorder (BD) are closely related, and adults with ADHD are four times more likely to have any mood disorder ¹. Rates of ADHD comorbidity in bipolar disorder are between 9.5% and 21.2%, and rates of comorbid bipolar disorder in ADHD at 5.1% and 47.1% in some studies ². Several studies suggest that adults with ADHD and BD may have worse outcomes and more severe clinical presentations compared to subjects without this comorbidity. In particular they usually display earlier age of onset of bipolar disorder ³, more frequent affective episodes ^{4,5}, more severe affective symptoms, shorter duration of wellness, lower educational achievement, more suicide attempts and more legal problems ⁶⁻⁸. Due to a substantial overlap between mood and ADHD symptoms, it could be difficult to differentiate between the two conditions and some authors speculate that this large comorbidity is artifactual ⁹. However ADHD symptoms generally do not respond to mood-stabilizers, persist after mood episodes have resolved, and improve with the administration of ADHD treatments ⁹⁻¹³. Moreover neurobiologic studies suggest that BD + ADHD and MDD + ADHD are subtypes of BD and MDD that are heritable, have overlapping pathophysiologies, and are distinguishable from BD and MDD on a number of neurobiologic features ⁹.

Even if data on literature and some expert opinion seems to clarify that the use of certain antidepressant and antipsychotic drugs used to control BD symptoms may worsen ADHD ¹⁴, it has pointed out that specific treatments for ADHD symptoms (stimulants and atomoxetine) may be destabilizing for BD due to induction of psychotic and manic-like symptoms or Hypo/manic switches ¹⁵. In a randomized, double-blind, crossover study Dorrego et al. ¹⁶, compared lithium and MPH in the treatment of ADHD core symptoms. The results suggest that lithium is less effective than MPH.

At the best of our knowledge, only a few studies have been conducted in order to test the efficacy and/or safety of ADHD medications in adult populations with comorbid BD. Some evidences can be taken from studies on pediatric populations or on prescription of stimulants in patients with affective disorder without ADHD. More conclusions came from case report and case series.

McIntyre et al. ¹⁷, conducted an open-label study of adjunctive flexible dose of LDX in the treatment of adults with stable bipolar I/II disorder and comorbid ADHD. 40 subjects received adjunctive LDX (mean dose = 60 ± 10 mg/day) to conventional pharmacotherapy and psychosocial interventions for BD. After 4 weeks, there was a significant reduction from baseline in the *ADHD Self-Report Scale* and in the *Montgomery-Åsberg Depression Rating Scale* total scores as well as the Clinical Global Impression Severity and Improvement score.

Two controlled studies were performed in pediatric populations with ADHD and BD. In the first, 40 subjects (6-17 years) with bipolar I disorder or bipolar II disorder (*Young Mania Rating Scale* score ≥ 14) were treated with divalproex sodium. 32 subjects achieved ≥ 50% reduction in YMRS baseline scores,

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no significant improvement in ADHD symptoms was observed. In placebo-controlled crossover phase, Mixed amphetamine salts was significantly more effective than placebo for ADHD symptoms. No significant side effects or worsening of manic symptoms was observed¹⁰. In the second, 16 patients (5-17 years) with ADHD and comorbid BD currently euthymic and treated with at least a mood stabilizer were randomized to receive placebo or MPH. At the endpoint, patient on MPH showed an improvement in ADHD symptomatology. Authors concluded that the addition of MPH did not cause a destabilization of mood symptoms¹¹.

Recently Viktorin et al.¹⁸, identified 2,307 adults with bipolar disorder who initiated therapy with methylphenidate and compare the rate of mania between subjects with and without concomitant mood-stabilizing treatment. Patients on methylphenidate without a concomitant mood-stabilizer showed an increased rate of manic episodes both within 3 months of medication initiation and between 3 and 6 months. Conversely, patients taking mood stabilizers had a significantly lower risk of mania after starting methylphenidate.

In 2000 another open label study try to demonstrate the efficacy and safety of methylphenidate in adult BD patients, type I and II, with a moderate depressive episode and without ADHD. 14 patients received MPH added to mood stabilizers and/or antipsychotics. At week 1 no proper (Hypo)manic switches were reported and half of the patients showed a decrease of severity of depressive symptoms¹⁹.

Few other naturalistic studies provide more evidence supporting a safe use of stimulants in adult BD patients without comorbid ADHD. Lydon and EL-Mallakh²⁰ found that MPH was well tolerated and efficacious for the treatment of depressive symptoms in 16 BD subjects observed after a long-term period (14 months). Similar results were reported by Carlson based on 8 charts of BD patients²¹. In a naturalistic trial 27 bipolar patients with treatment resistant depression were treated with stimulants. 5 experienced transient mood elevation and one reported a manic episode²².

Many authors point out the risk of stimulant induced psychotic and manic like symptoms. It has been estimated that such reactions are infrequent in children at therapeutic doses and they are dose dependent and of brief duration^{23,24}. However they could not be preventable²⁵, so patient treated with stimulant should be carefully monitored and comorbid conditions, such as BD, should be treated firstly^{2,26}.

At the date no RCT or other clinical studies on Atomoxetine (ATX) treatment in adult with ADHD and BD were published. Only one open label study exists in a pediatric population of 12 ADHD children and adolescents with ADHD and comorbid type I or II BD. ATX was added to mood stabilizer or antipsychotic, 8 subjects showed a good response and no one developed mania or mixed state even if 2 patients discontinued ATX due to worsening of mood symptoms¹³.

There are some reports of ATX-induced mania in pediatric populations²⁷⁻³⁰ and one in adults³¹. In a report of 153 pediatric patients treated with ATX, after a follow up (aver-

age time 6.39 weeks) 33% reported extreme irritability, aggression, mania, or hypomania. The concomitant treatment with mood stabilizers or antipsychotics did not protect or delay the onset of mood symptoms. Interestingly, 80% of patients showing "activation" had a prior personal history for mood symptoms, 61% had a positive family history for mood disorders, and 53% reported both³².

A naturalistic study has been conducted on a cohort of 168 adults diagnosed with ADHD, followed-up on an average of 6 years after first evaluation. 57 (51%) were still on treatment with methylphenidate (MPH) at follow-up. The second most common reason for discontinuation of treatment was the onset of affective symptoms. None of the subjects who had reported elevated mood or hypomania had been diagnosed with a bipolar disorder (BD) at baseline³³.

As regards non-first-line pharmacological treatments for ADHD in adults, Wilens et al. reported efficacy of bupropion on ADHD symptoms in a 6 week open trial on ADHD-BP adults patients without evidence of (hypo)manic switches.

Some authors tried to investigate whether the use of ADHD treatments (methylphenidate and atomoxetine) during childhood influence the risks of developing BD. Wng et al.³⁴, found that, in a cohort of 144,920 patients diagnosed with ADHD, patients with long-term use of methylphenidate were less likely to be diagnosed with BD compared to ADHD patients that had never taken methylphenidate.

Taken together, the results previously exposed seem to support some preliminary conclusions. First, in patients with ADHD and comorbid Bipolar Disorder the treatment of BD alone may result in residual symptoms of ADHD¹⁵. Second, patient should be treated hierarchically: when present, BD should be treated first while ADHD should be treated whenever a sufficient euthymic state is reached^{10,35}, combining ADHD medications and mood stabilizers¹⁵.

As regards our clinical experience, starting in 2015 we assessed 152 subjects at the S. Andrea Hospital's outpatients psychiatric service. The subjects were referred to our service in order to confirm a diagnostic hypothesis of persistent ADHD in adulthood. In a naturalistic setting, we started an observational study on ADHD-BP comorbidity and its treatment (paper in preparation). It was possible to confirm the diagnosis in 130 subjects through DIVA 2.0 clinical semi-structured interview. 90 of these subjects were subsequently treated and followed up at our services according to clinical needs. After achieving adequate mood stabilization, it was possible to treat with atomoxetine or methylphenidate 20 subjects with a diagnosis of bipolar disorder type II and comorbid ADHD. These subjects were matched to 20 subjects with a diagnosis of persistent ADHD and without bipolar comorbidity. Both in ADHD and in BP-II/ADHD subjects the choice between atomoxetine and methylphenidate was based on the efficacy/tolerability profile for each subject, including the presence of previous effective treatments with atomoxetine or methylphenidate in childhood and/or adolescence. The mean dose of atomoxetine was 65 ± 25 mg/day, while the mean dose of methylphenidate was 45 ± 15 mg/day.

As regards ADHD subjects 12 were males and 8 females,

13 were treated with atomoxetine and 7 with methylphenidate. As regards BP-II/ADHD subjects 7 were males and 13 females, 9 were treated with atomoxetine and 11 with methylphenidate. The mean age of the sample was 27.56 years.

After a three-months follow-up no manic, mixed or psychotic symptoms emerged and all the subjects remained clinically stable. Moreover, a one way ANOVA for repeated measures showed a significant decrease in the severity of ADHD symptoms as measured through ASRS in both groups ($F = 11.94$; $p = 0.003$). The BP-II diagnosis did not significantly influence the decrease in ADHD symptom severity at 3 months. This is in line with previous literature results, and supports a response-specificity of ADHD symptom severity and the possibility to effectively treat subjects with a BP-ADHD comorbidity once adequate mood stabilization is achieved.

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