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Adjunctive antidepressants in bipolar depression: A cohort study of six- and twelve-months rehospitalization rates

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Abstract
Although antidepressants (ADs) are widely used in bipolar depression, there is weak evidence for their effectiveness and safety in this condition. Furthermore, there is a paucity of studies on the risk-benefit ratio of AD maintenance treatment in bipolar disorder (BD). We compared rehospitalization rates of patients with BD-I depressive episode who were discharged with mood stabilizers (MSs) and/or atypical antipsychotics (AAPs) with or without adjunctive AD. Ninety-eight patients with BD-I who were hospitalized with a depressive episode between 2005 and 2013 were retrospectively followed for 6-months and 1-year rehospitalization rates, as well as time to rehospitalization, according to treatment at discharge: MSs and/or AAPs with or without AD. Multivariable survival models adjusted for covariates known to influence rehospitalization were conducted. Six-months and 1-year rehospitalization rates were significantly lower in the adjunctive-AD treatment group compared to the no-AD group (9.2% vs. 36.4%, $P = .001$, power = 0.87 and 12.3% vs. 42.4%, $P = .001$, power = 0.89, respectively). Time to rehospitalization within 6-months and 1-year was significantly longer in the adjunctive-AD treatment group (169.9 vs 141 days, $P = .001$ and 335.6 vs 252.3 days, $P = .001$, respectively). Adjunctive-AD treatment at discharge reduced significantly the adjusted risk of rehospitalization within 6-months (HR = 0.081, 95% CI: 0.016-0.412, $P = 0.002$) and 1-year (HR = 0.149, 95% CI: 0.041-0.536, $P = 0.004$). Moreover, adjunctive-AD treatment did not increase rehospitalization rates of manic episode. In conclusion, adjunctive-AD therapy to MS/AAP at discharge from BD-I depressive episode hospitalization is associated with a lower rate of and a longer time to rehospitalization during a 1-year follow up period.

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1. Introduction

Bipolar disorder (BD), ranked as the sixth-leading cause of disability worldwide (Merikangas et al., 2007), is a chronic mental illness characterized by recurrent manic and depressive episodes that usually begin in early adulthood and affects 1% to 4% of the general population (Henry et al., 2013). Although the occurrence of mania or hypomania distinguishes between BD and recurrent major depressive disorder, it is depression that dominates the course of bipolar disorder (Judd et al., 2002, 2003; Kupka et al., 2007; Thase, 2006), leading to poor quality of life, functional impairment and increased suicide risk (Judd et al., 2005; López et al., 2001). Quetiapine, olanzapine-fluoxetine treatment combination, lamotrigine and lurasidone, alone or in conjunction with lithium or valproate, are among the few evidence- based treatments for BD depression (Grunze et al., 2010; Loebel et al., 2014). However, numerous patients are refractory to these medications or do not tolerate their side effects. Thus, there is an unmet need for an effective and safe antidepressant treatment for BD depression.

Although the effectiveness of antidepressants (ADs) is well established in unipolar depression, an incongruity exists between the wide use and the weak evidence for the effectiveness and safety of ADs in bipolar depression (Pacchiarotti et al., 2013). While findings from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study suggest adjunctive AD to mood stabilizers (MSs) to be inefficacious but safe with regard to treatment emergent affective switch (TEAS) risk (Sachs et al., 2007), a recent meta-analysis (McGirr et al., 2016) supports the effectiveness and safety of adjunctive modern ADs to MS or atypical antipsychotics (AAP) in the acute treatment of bipolar depression.

Even more controversial, is the use of adjunctive AD in the maintenance treatment of BD. Long-term trials involving addition of AD to ongoing MS treatments are scant and have yielded inconclusive findings (Pacchiarotti et al., 2013). Despite evidence from two large open studies that indicate that continuation of adjunctive AD may be beneficial in non-rapid cycling BD patients (Altshuler et al., 2003; Ghaemi et al., 2010),two meta-analyses of randomized controlled trails (Ghaemi et al., 2008; McGirr et al., 2016) found that compared with MS monotherapy, long-term adjunctive AD provided little protection from relapse of depression and tended to increased TEAS rates, resulting in an unfavorable risk-benefit ratio for long-term AD use in BD. Consequently, most guidelines recommend the use of AD only in combination with an antimanic agent and to consider discontinuation at twelve weeks in remission, in order to avoid TEAS (Goodwin et al., 2016).

Thus, further studies, reflecting more generalizable BD samples, are needed to evaluate the effectiveness and safety of adjunctive AD therapy in both acute and maintenance treatments of BD patients. In the current study, we used a naturalistic design of retrospective chart review to compare six-months and 1-year rehospitalization rates of BD-I patients hospitalized with depressive episode and treated at discharge with MS and/or AAP with or without ADs.

2. Experimental procedures

2.1. Population

We conducted a retrospective cohort study, using electronic medical record (EMR) review of all consecutive admissions to Geha Mental Health Center ([GMHC], Petach Tikva, Israel) between 1 January 2005 and 31 July 2013. GMHC is a large, tertiary referral mental health center covering catchment area of about 800,000 inhabitants with mixed ethnicity. We included patients in the study who met DSM-IV-TR criteria for bipolar I disorder (BD-I) and were admitted to GMHC during the study period due to an acute depressive episode. All patients were at least 18 years of age at the index hospitalization. The type of psychiatric diagnosis and exacerbation leading to each hospitalization (index hospitalization and rehospitalization) was classified as DSM-IV-TR BD-I manic, major depressive or mixed episode as established by consensus of two senior psychiatrists during each hospitalization and validated retrospectively by the study team according to the medical records. In order to increase the diagnostic clarity of the sample, we excluded from the study patients who met DSM-IV-TR criteria for BD-II, schizoaffective disorder, mood exacerbations related to substance use or to a general medical condition and hospitalizations not related to a primary major mood episode. We further excluded BD-I patients with rapid cycling pattern, as current data suggest negative risk-benefit ratio for AD use in this sub-population (Yatham et al., 2013). In a patient with multiple hospitalizations, we included in the study the first hospitalization as the index hospitalization. To ascertain a clear distinction between separate hospitalizations, a rehospitalization within a 1-week period following discharge from the index hospitalization (since 2005) was not considered as a new hospitalization unless the polarity was reversed in the second hospitalization. In the case of rehospitalization within 1 week following discharge, patients were followed for 1 year from their discharge from the second hospitalization.

To examine the effects of specific medication regimens on rehospitalization rates, we included in the study all the patients who were treated at discharge with MS (lithium, valproate, carbamazepine or lamotrigine) and/or AAP (risperidone [including Risperdal Consta], olanzapine, quetiapine and ziprasidone) with or without an adjunctive AD (selective serotonin reuptake inhibitors [SSRI, including citalopram, escitalopram, sertraline, paroxetine, fluoxetine, fluvoxamine], norepinephrine dopamine reuptake inhibitors [NDRI, including bupropion], serotonin norepinephrine reuptake inhibitors [SNRI, including venlafaxine, duloxetine], tricyclic antidepressants [TCAs, including nortriptyline, imipramine, doxepine, clomipramine] and atypical antidepressants [including mirtazapine]). Three patients were treated with the combination of SSRI and SNRI or atypical AD. The classification of the type of AD treatment for these patients was determined by the second AD agent (SNRI/atypical). Concomitant typical antipsychotics (TAP) or anxiolytic medications at discharge from index hospitalization were noted and were considered as covariates in the analysis. Patients who were discharged from the index hospitalization without any antimanic agent or only with TAP were excluded from the study. Patients were divided into two groups according to the type of treatment at discharge: (i) MS and/or AAP with AD; (ii) MS and/or AAP without AD. The study was approved by the GMHC review board.

2.2. Measures

The primary outcome measures of this study were six-months and 1-year rehospitalization rates due to major mood episode. The

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