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Research paper

Major depressive disorder with subthreshold hypomanic (mixed) features: A real-world assessment of treatment patterns and economic burden

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ABSTRACT

Background: To compare outcomes for individuals with major depressive disorder (MDD) with or without subthreshold hypomania (mixed features) in naturalistic settings.

Methods: Using the Optum Research Database (1/1/2009—10/31/2014), a retrospective analysis of individuals newly diagnosed with MDD was conducted. Continuous enrollment for 12-months before and after the initial MDD diagnosis was required. MDD with subthreshold hypomania (mixed features) (MDD-MF) was defined based on ≥1 hypomania diagnosis within 30 days after an MDD diagnosis during the one-year follow-up period, in the absence of bipolar I diagnoses. Psychiatric medication use, healthcare utilization, and costs during the one-year follow-up period were compared using multivariate logistic and gamma regressions, controlling for baseline differences.

Results: Of 130,626 MDD individuals, 652 (0.5%) met the operational definition of MDD-MF. Compared to the MDD-only group, the MDD-MF group had more suicidality (2.0% vs. 0.5%), anxiety disorders (46.8% vs. 34.0%), and substance use disorders (15.5% vs. 6.1%, all $P < 0.001$). More individuals with MDD-MF were treated with antidepressants (83.6% vs. 71.6%), mood stabilizers (50.5% vs. 2.7%), atypical antipsychotics (39.0% vs. 5.5%), and polypharmacy with multiple drug classes (72.1% vs. 22.7%, all $P < 0.001$). Individuals with MDD-MF had higher hospitalizations rates (24.2% vs. 10.5%) and total healthcare costs (mean: $15,660 vs. $10,744, all $P < 0.001$).

Limitations: The commercial claims data used were not collected for research purposes and may over- or under-represent certain populations. No specific claims-based diagnostic code for MDD with mixed features exists.

Conclusions: Greater use of mood stabilizers, atypical antipsychotics, polypharmacy, and healthcare resources provides evidence of the complexity and severity of MDD-MF. Identifying optimal treatment regimens for this population represents a major unmet medical need.

1. Introduction

For over a century, psychiatry has recognized the existence of mood states that include the co-occurrence of both manic and depressive symptoms (Faedda et al., 2015; Verdolini et al., 2015). In 1980, the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III) (American Psychiatric Association, 1980) subcategorized manic-depression into unipolar and bipolar disorder with the tacit implication that subsyndromal hypomanic (mixed) symptoms were a variant of bipolar disorder (Faedda et al., 2015). Subsequently, the DSM-IV (American Psychiatric Association, 1994) and DSM-IV-TR (American Psychiatric Association, 2000), defined and operationalized

Abbreviations: MDE, major depressive episodes; MDD, major depressive disorder; MDD-MF, major depressive disorder with mixed features; ICD-9-CM, International and Statistical Classification of Diseases, Ninth Revision, Clinical Modification; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System

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mixed episodes that required the co-occurrence of syndromal manic and major depressive episodes (American Psychiatric Association, 2000; Vieta and Valentí, 2013). The DSM-IV-TR-defined mixed episodes were limited by insufficient ecological validity, i.e. – the most common clinical presentation of mixed states was syndromal depression or mania with "opposite polarity" subsyndromal symptoms. Consequently, the DSM-5 (American Psychiatric Association, 2013) eliminated the diagnosis of mixed episodes as part of bipolar disorder and supplanted it with the mixed features specifier that can be applied not only to bipolar disorder (manic, hypomanic, or MDE), but also to MDEs that occur in the context of MDD (American Psychiatric Association, 2013; Hu et al., 2014; Vieta and Valentí, 2013).

MDD-MF is defined by DSM-5 as meeting the criteria for MDD while simultaneously experiencing ≥3 manic symptoms during the majority of days of the index MDE (American Psychiatric Association, 2013; Hu et al., 2014). The conceptual framework of the mixed features specifier was dimensional, rather than categorical with a continuum of opposite polarity symptoms during a manic or a major depressive episode. MDD-MF appears to be a stable phenotype insofar as the majority of affected individuals do not later present with a pure hypomanic or manic episode (Fiedorowicz et al., 2011).

Extant studies have examined individuals with an MDE associated with mixed features in the context of MDD or bipolar disorder. Several clinical studies have contrasted individuals with an MDE with or without mixed features (Azorin et al., 2012; McIntyre et al., 2015; Pacchiarotti et al., 2011; Perugi et al., 2015). These studies indicate that individuals with MDD-MF have higher rates of substance use and suicide attempts (Azorin et al., 2012; McIntyre et al., 2015; Perugi et al., 2015). When compared to MDD without mixed features (Azorin et al., 2012), individuals with MDD-MF were more likely to be receiving prescriptions for mood stabilizers (Azorin et al., 2012; Perugi et al., 2015), antipsychotics (Perugi et al., 2015), and polypharmacy (Perugi et al., 2015). Antidepressants are commonly used to treat individuals with MDD-MF, but their efficacy, safety, and tolerability have not been sufficiently addressed in controlled trials. The recently published 2015 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults reported minimal evidence for treating MDD-MF, and recommended providers consider monotherapy with a second generation antipsychotic, mood stabilizer, or antidepressant as the initial treatment option (The University of South Florida, 2015). Only two randomized, placebo-controlled, clinical trials have identified effective treatments for mixed features. One trial provided preliminary support for treating mixed features in MDD or bipolar II disorder with the atypical antipsychotic, ziprasidone (Patkar et al., 2012), and another trial provided support specifically for treating MDD-MF with the atypical antipsychotic, lurasidone (Suppes et al., 2015).

While evidence supporting the diagnosis of MDD-MF has been developed using clinical interviews and randomized trials, real-world outcomes associated with MDD-MF at the population level are lacking. Herein, we report the results of a real-world assessment of suicidality, comorbidities, medication prescription patterns, healthcare resource use, and healthcare cost for individuals with MDD with subthreshold hypomania (mixed features) compared to those with MDD only.

2. Methods

2.1. Study design and database

This retrospective cohort study used commercial claims data from the Optum Research Database (Optum, Eden Prairie, MN). The Optum Research Database contained claims on more than 150 million unique individuals since 1993. The medical and pharmacy claims data were linked to enrollment information. The Optum Research Database did not include any identifiable protected health information and, pursuant to the Health Insurance Portability and Accountability Act of 1996 (United States Congress, 1996), the study did not require institutional review board waiver or approval.

2.2. Inclusion/exclusion criteria

The study period of this analysis spanned from January 1, 2009 to October 31, 2014. Individuals with a non-remission diagnosis of MDD were identified (based on the ICD-9-CM codes 296.20–296.24, 296.30–296.34, 296.82, 300.4 and 311; eAppendix 1) between January 1, 2010 and October 31, 2013. The index date was defined as the date of the individual's first primary MDD diagnosis. Each individual with MDD was required to have 12 months of continuous enrollment prior to the index date (baseline period) and 12 months following the index date (follow-up period). All individuals were required to be at least 18 years of age and to have a second MDD diagnosis (as defined above) at least 14 days after the index date.

Individuals were excluded from the study if they had a MDD diagnosis prior to the index date. Individuals were also excluded from the study if they had a diagnosis of bipolar I disorder (based on ICD-9-CM codes 296.0x, 296.1x, 296.4x-296.81; eAppendix 1) at any time during the entire study period. However, all individuals with a concurrent claim for ICD-9-CM 296.89 (i.e., other bipolar disorders; eAppendix 1) during the follow-up study period were included for consideration for MDD with subthreshold hypomania or mixed features. In the field of psychiatry mental disorders are defined based on the DSM coding, while US insurance coding is based on the ICD-9-CM coding, which include both mental and physical conditions. ICD-9-CM codes are the US health care systems adaptation of the World Health Organizations ICD-9 codes. The DSM and ICD-9-CM codes for mental disorders are not always comparable and ICD-9-CM does not include any codes for DSM-IV's bipolar II disorder. The ICD-9-CM code 296.89 corresponds to the broad category of "other bipolar disorders." A detailed list of all ICD-9-CM codes for affective disorders goes beyond the scope of this paper.

MDD-MF cohort: Due to the absence of a specific mixed features diagnostic code, it was assumed that a concurrent claim with an ICD-9-CM code 296.89 (i.e., other bipolar disorders; eAppendix 1) could serve as a reasonable proxy definition for identifying MDD patients with potential subthreshold hypomania or mixed features. In order to ensure a conservative, yet pragmatic definition that would identify a cohort of MDD individuals with mixed features, only individuals with at least one claim for ICD-9-CM code 296.89 within 30 days after the initial MDD diagnosis were defined as MDD-MF. All individuals who had a non-concurrent diagnostic claim for ICD-9-CM 296.89, one that was at least 30 days after the initial MDD diagnosis were not considered to have MDD-MF and were excluded from the final analysis.

MDD-only cohort: The MDD-only comparison cohort was made up of individuals with MDD who did not have any diagnostic claim for ICD-9-CM 296.89 during the follow-up period.

2.3. Suicidality and comorbidities

Incidence of suicidality and clinically relevant comorbidities (i.e., anxiety disorder and substance use disorder) were defined using ICD-9-CM diagnosis codes (eAppendix 1). Suicidal ideation was defined based on a single code, while suicidality included codes for suicide, suicide attempt, and self-inflicted poisoning or injury.

2.4. Medication prescription patterns

Medication use was examined in terms of classes of medications: SSRI, SNRI, mood stabilizers, and atypical antipsychotics. See eAppendix 1 for a list of medications included in each class. Polypharmacy was defined as the use of multiple classes of psychiatric medication within 45 days of each other during the follow-up period.

Psychotherapy was defined using CPT codes, HCPCS codes, and