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Research paper

Predicting persistence to antidepressant treatment in administrative claims data: Considering the influence of refill delays and prior persistence on other medications

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ABSTRACT

Background: Many patients with major depressive disorder (MDD) who begin antidepressant treatment discontinue use before for six months, the recommended minimum treatment length. This study sought to identify predictors of six-month antidepressant persistence including predictors utilizing patients' electronic prescription records.

Methods: Commercially insured children (3–17 years) and adults (18–64 years) with MDD who initiated antidepressant treatment, 1/1/2003–2/28/2010, were assessed for six-month persistence (based on prescriptions' days supply, allowing a 30-day grace period). Antidepressant persistence prediction models were developed separately for children and adults. Two additional measures, days without medication between the first and second antidepressant fill (children and adults) and prior persistence on other medications (adults only), were added to the models, concordance (c) statistics were compared and risk reclassification evaluated.

Results: Among children (n=8837 children) and adults (n=47,495) with MDD, six-month antidepressant persistence was low and varied by age (37%, 18–24 years to 52%, 3–12 and 50–64 years). Independent baseline predictors of persistence were identified, with model c-statistics: children=0.582, adults=0.584. Patients with more days without medication between fills were less likely to be persistent (10–30 vs. 0 days, children: RR=0.72, adults: RR=0.74), as were adults not previously persistent to other medications (RR=0.73).

Limitations: The definition of six-month persistence is dependent on correct days supply values and the grace period utilized; potential predictors were limited to measures available in claims data.

Conclusions: Six-month antidepressant persistence was low and overall prediction of persistence was poor; however, days without medication between fills and prior persistence on other medications marginally improved the ability to predict antidepressant persistence.

1. Introduction

The American Psychiatric Association (APA) recommends that patients with mild to severe major depressive disorder (MDD) treated with antidepressants receive a minimum of 6–12 weeks of treatment to achieve symptom remission followed by 4–9 months of treatment to prevent relapse (American Psychiatric Association, 2010). Organizations outside the United States (US) also recommend that patients with MDD continue antidepressant treatment for ≥6 months following symptom remission (Kennedy et al., 2009; National Collaborating Centre for Mental Health, 2005; National Institute for Health and Care Excellence, 2009; Nutt et al., 2010). Nevertheless, low rates of 6-month antidepressant persistence have been observed in children and adults (Esposito et al., 2009; Fontanella et al., 2011; Hansen et al., 2004; Lu and Roughead, 2012; Mullins et al., 2005; Sawada et al., 2009; Tournier et al., 2009; Wu et al., 2013; Yau et al., 2014).

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Persistence, defined as the length of time between medication initiation and medication discontinuation, is a component of adherence, which is defined as the process by which patients take medication as prescribed (Vrijens et al., 2012). Most previous studies examining factors related to persistence focused on adults. Factors identified in these studies include gender, age, race, education, co-morbidities, concomitant medication use, medication cost, adverse side effects, antidepressant agent, insurance type, follow-up visits, and symptom improvement (Assayag et al., 2013; Bull et al., 2002; Esposito et al., 2009; Hansen et al., 2004; Lu and Roughead, 2012; Mullins et al., 2005; Sawada et al., 2009; Wu et al., 2012, 2013; Yau et al., 2014). Beyond baseline measures, gaps in antidepressant prescription refills based on administrative pharmacy records predicted antidepressant discontinuation in adults. Specifically, a 14-day gap in medication supply during the first 90 days of treatment identified four of every five patients at risk for discontinuing (Hansen et al., 2010). Additionally, in other settings, adherence (measured by the medication possession ratio) to medications taken for unrelated chronic indications improved the prediction of oral bisphosphonate adherence (Curtis et al., 2009). Adherence to antidepressant treatment (90 days of medication supply in first 180 days after initiation) was a marginal predictor of concurrent antihypertensive and lipid-lowering medication adherence (medication possession ratio $\geq$80%) (Simon et al., 2013). It was unknown whether prior persistence on other chronic medications, a measure available prior to antidepressant initiation, and antidepressant refill gaps, a measure available soon after antidepressant initiation, would improve the ability to predict antidepressant persistence. As these measures could be made readily available to clinicians through prescription refill records (or by patient self-report), estimating whether they offer an advantage over standard predictors could potentially prove useful.

In Medicaid-enrolled children, factors previously identified as associated with higher antidepressant adherence (measured by the proportion of days with medication) during the treatment continuation phase include use of other psychotropic drugs, absence of substance use disorders, and foster-case Medicaid eligibility (Fontanella et al., 2011). By contrast, factors associated with antidepressant persistence in children have not been identified. Whether important variation in predictors of persistence in children and adults differ is unknown. To expand upon the existing literature the current study a) estimates 6-month antidepressant persistence for children and adults with MDD in a large US commercially insured population, b) creates and validates a baseline prediction model for antidepressant persistence separately in children and adults, and c) determines if our baseline prediction model improves when a patient's delay in filling the second antidepressant prescription and a patient's prior persistence on other chronic medications are taken into account.

2. Methods

2.1. Data source and study population

Data for this analysis was drawn from the LifeLink Health Plan Claims Database, purchased from IMS Health (IMS Health Incorporated, 2015). The database covers commercially insured individuals and their dependents across the US, containing medical and pharmaceutical claims for approximately 60 million unique patients from 98+US health plans. The database includes inpatient and outpatient International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes, Current Procedural Terminology, 4th edition, and Healthcare Common Procedure Coding System procedure codes and records for reimbursed, dispensed prescriptions. The database has been used in the past for epidemiologic research involving antidepressants (Miller et al., 2014b; Valuck et al., 2007) including studies describing adults and children initiating antidepressant therapy (Czaja and Valuck, 2012; Milea et al., 2010). The University of North Carolina Institutional Review Board deemed the study exempt from review.

The study cohort includes children (3–17 years) and adults (18–64 years) with a diagnosis of MDD who initiate an SSRI or SNRI between January 2003 and February 2010. MDD was defined as an inpatient or outpatient diagnosis (ICD-9-CM: 296.2x, 296.3x) in the year prior to antidepressant initiation. SSRIs (sertraline, citalopram, escitalopram, fluoxetine, paroxetine) and SNRIs (venlafaxine, duloxetine) included in the study were limited to those FDA approved for depression and those more commonly used. Patients were required to have no record of any antidepressant use in the prior year, to have continuous insurance enrollment in the prior year and in the 6 months following antidepressant initiation, and, to avoid imputation, a days supply value >0 for the index antidepressant prescription and prescriptions in the following 6 months. Patients with a diagnosis of bipolar disorder in the prior year were excluded.

2.2. Antidepressant persistence

To calculate persistence, defined as $\geq$6 months between antidepressant initiation and antidepressant discontinuation, we followed each patient beginning on the index antidepressant's dispensing date. For each prescription dispensing date, the days supply of medication was added to a 30-day grace period, to account for missed doses. If there was no refill by the end of the days supply plus grace period, the patient was considered to have stopped treatment at that point. The patient was categorized as non-persistent if treatment had been stopped before 180 days after the index antidepressant's dispensing date; otherwise the patient was categorized as persistent. A 30-day grace period was selected because the majority (89%) of patients had an initial days supply value for $\leq$30 days (only 5% had an initial days supply for $\geq$90 days). Additionally, a longer grace period would have overestimated 6-month persistence. For a sensitivity analysis we used a more restrictive 15-day grace period. Switching SSRI, SNRI, or between SSRI and SNRI agents was regarded as treatment continuation.

2.3. Potential predictors

Potential predictors of persistence were collected in the year prior to antidepressant initiation and included age, sex, psychiatric and non-psychiatric co-morbidities, healthcare utilization, antidepressant class (SSRI, SNRI), prior suicide attempt (external cause of injury codes: E950.x-E959.x), high and mid-potency prescription opiate usage, recurrent MDD diagnosis (ICD-9-CM: 296.3x), and service provider type for the index antidepressant. Patient copayment for the index antidepressant was calculated by subtracting the amount paid by the insurance plan from the amount the insurance plan allowed per prescription (typically the amount paid plus patient liability). Copayment was categorized as low vs. high based on the copayment value at the 75th percentile for children (low: $<$\$16) and adults (low: $<$\$24). Initial antidepressant dose was categorized into low, non-low, and unknown. Low initial dose was defined per agent based on available guidelines for starting dose (American Psychiatric Association, 2010; British Columbia Ministry of Health, 2013; Geller et al., 2012; National Collaborating Centre for Mental Health, 2005; Nutt et al., 2010). The measures for substance use included patients with a substance use related hospitalization and patients with a substance use disorder diagnosis without a hospitalization. We constructed a hierarchical measure of depression severity with depression-related diagnoses characterized as inpatient vs. outpatient diagnosis and timing of the inpatient diagnosis, i.e. within