

Impact of Formulary-Related Rejections of Initial Auvelity® (Dextromethorphan-Bupropion [45 mg/105 mg]) Claims on Healthcare Resource Utilization and Costs Among Patients With Major Depressive Disorder

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Key Objective

To evaluate the impact of formulary-related rejections of initial dextromethorphan-bupropion claims on subsequent healthcare resource utilization and costs among patients with major depressive disorder

Introduction

- Major depressive disorder (MDD) is a leading cause of disability in the US and is associated with substantial healthcare resource utilization (HCRU) and a high economic burden^{1,2}
- Dextromethorphan-bupropion (45 mg/105 mg; Auvelity®) is a first-in-class oral therapy approved in the US since 2022 for the treatment of MDD in adults³
- Previous studies indicate that initiation of dextromethorphan-bupropion may lead to reductions in HCRU and healthcare costs when initiated early, as well as relative to the use of other branded treatments for MDD^{4,5}
- Formulary restrictions of pharmacotherapies are intended to ensure appropriate treatment use and minimize pharmacy costs, without impacting the quality of care a patient receives;⁶ however, such restrictions may also delay or prevent access to more recently approved therapies, with potential downstream clinical and economic consequences⁷⁻⁹
- This study sought to examine how formulary-related rejections of initial dextromethorphan-bupropion prescriptions affect health economic outcomes

Methods

Study Design

- Data source and study population:** Methods adapted from similar previous study of formulary restrictions in MDD.⁹ Commercially insured adults with MDD (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM]: F32.xx and F33.xx) identified from real-world open claims data in the Symphony Health Integrated Dataverse (IDV) database from March 1, 2024 to October 31, 2025, stratified based on initial dextromethorphan-bupropion prescription claim (index date = date of first prescription claim between September 1, 2024 and September 30, 2025) and with ≥ 6 months continuous clinical activity pre-index and claim for a subsequent MDD-related treatment post-index
 - Initial claim approved cohort
 - Initial claim rejected cohort: Rejection for a formulary-related reason (noncoverage, prior authorization requirement, or step therapy requirement)

Outcomes

- Baseline characteristics:** Demographics at index and comorbidities, MDD-related medication use, and HCRU over the 6 months pre-index
- HCRU:** All-cause emergency room (ER) visits and inpatient admissions over follow-up
- Excess healthcare costs:** Annualized ER and inpatient costs over follow-up for patients with initial claim rejection
- Treatment patterns:** Dextromethorphan-bupropion treatment use and treatment adherence (medication possession ratio [MPR]) over follow-up and the first MDD-related medication filled after rejection of an initial dextromethorphan-bupropion claim

Statistical Analysis

- Descriptive statistics:** Baseline characteristics summarized as means (standard deviations) for continuous variables and frequencies (%) for categorical variables
- Multivariable regression analyses:** HCRU assessed using negative binomial models adjusted for age, sex, baseline HCRU, and follow-up time (offset) to estimate incidence rate ratios and 95% confidence intervals for the rejected versus approved cohorts; $P < 0.05$ was considered statistically significant
- Cost estimates:** Excess annual healthcare costs associated with initial dextromethorphan-bupropion rejection estimated using adjusted post-index HCRU compared with expected HCRU under initial claim approval. Mean annual unit costs derived from Merative MarketScan Commercial and Medicare databases and adjusted to 2023 US dollars

References

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Disclosures

SC Stoner has served on speaker bureaus for Neurocrine Pharmaceuticals and on advisory boards for Alkermes Pharmaceuticals and Neurocrine Pharmaceuticals.

C Zeni, SP Alter, R DePue, and Y Zhao are employees of Axsome Therapeutics, Inc. J Cong and Y Zhang are employees of KMK Consulting, Inc.

Results

Baseline Patient Characteristics

	Initial claim approved N = 28,329	Initial claim rejected N = 1963
Age, years, mean (SD)	42.7 (13.3)	43.0 (13.3)
Female, n (%)	19,471 (68.7%)	1390 (70.8%)
CCI, mean (SD)	0.2 (0.7)	0.2 (0.8)
Comorbidities, n (%) ^a		
Mental health disorders		
ADHD ^b	11,341 (40.0%)	752 (38.3%)
Anxiety	3702 (13.1%)	215 (11.0%)
Bipolar disorder ^c	9607 (33.9%)	630 (32.1%)
PTSD	1521 (5.4%)	121 (6.2%)
PTSD	1845 (6.5%)	123 (6.3%)
Metabolic disorders		
Diabetes/prediabetes	4738 (16.7%)	326 (16.6%)
Hyperlipidemia	1584 (5.6%)	125 (6.4%)
Obesity	2574 (9.1%)	175 (8.9%)
Obesity	2583 (9.1%)	169 (8.6%)
Cardiovascular disease		
Hypertension	3006 (10.6%)	218 (11.1%)
Hypertension	2699 (9.5%)	201 (10.2%)
Sleep disorders		
Sleep apnea	2974 (10.5%)	177 (9.0%)
Sleep apnea	1785 (6.3%)	107 (5.5%)
Musculoskeletal/pain disorders		
Low back pain	2888 (10.2%)	203 (10.3%)
Low back pain	1773 (6.3%)	126 (6.4%)
Autoimmune disorders		
Rheumatoid arthritis	2289 (8.1%)	151 (7.7%)
Rheumatoid arthritis	1511 (5.3%)	100 (5.1%)
Substance use disorders		
Substance use disorders	1492 (5.3%)	104 (5.3%)

- Baseline demographics and comorbidity profiles were comparable between the approved and rejected cohorts

Patient characteristics measured during the 6-month pre-index period or at index.
^aEvaluated medical conditions occurring in ≥ 5% of either cohort based on diagnosis codes in claims. ^bIncludes ADHD, conduct disorders, hyperkinetic syndrome. ^cBipolar disorder reflects historical or concurrent diagnostic codes and may represent diagnostic reclassification or variation in coding rather than true comorbidity.
ADHD, attention deficit/hyperactivity disorder; CCI, Charlson Comorbidity Index; PTSD, post-traumatic stress disorder.

Medication Use and HCRU Over 6 Months Pre-Index

	Initial claim approved N = 28,329	Initial claim rejected N = 1963
MDD-related medication use, n (%)^a		
Any MDD-related treatment	23,592 (83.3%)	1688 (86.0%)
SSRIs	12,647 (44.6%)	845 (43.0%)
Atypical antipsychotics	9625 (34.0%)	671 (34.2%)
NDRI ^b	9758 (34.4%)	610 (31.1%)
SNRIs	7303 (25.8%)	469 (23.9%)
SARIs	4929 (17.4%)	339 (17.3%)
TCAs	1627 (5.7%)	130 (6.6%)
TeCAs	1442 (5.1%)	84 (4.3%)
Esketamine/ketamine	1124 (4.0%)	67 (3.4%)
Typical antipsychotics	125 (0.4%)	14 (0.7%)
MAOIs	49 (0.2%)	3 (0.2%)
All-cause HCRU, n (%)		
ER visits	2071 (7.3%)	145 (7.4%)
Inpatient admissions	983 (3.5%)	80 (4.1%)

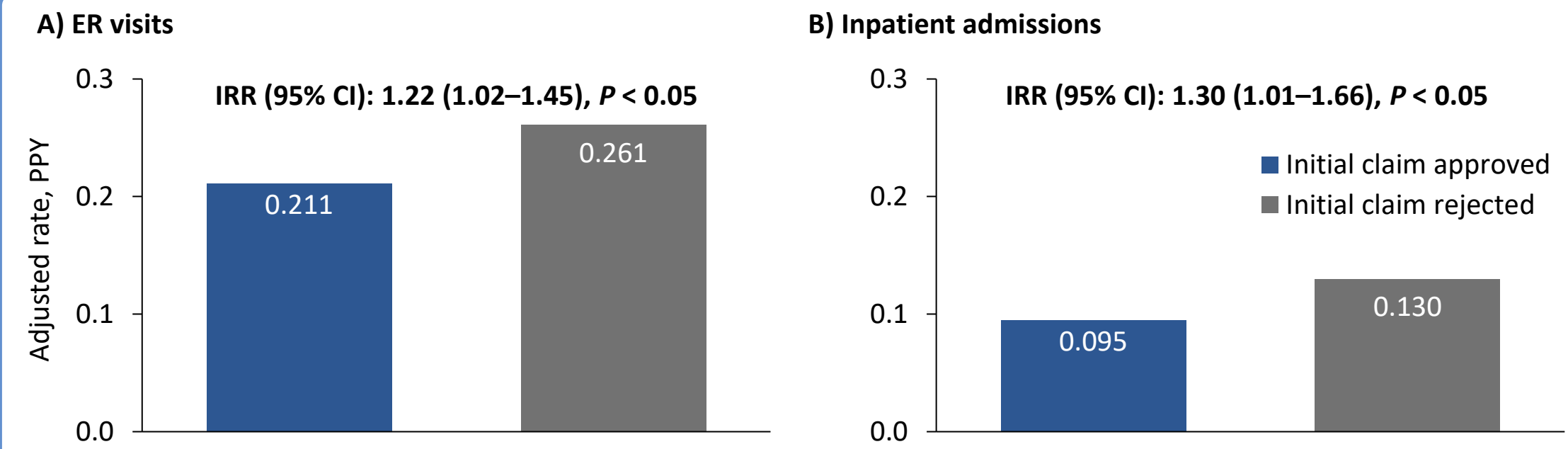
- Pre-index MDD-related medication use and HCRU were comparable between cohorts

^aMDD-related medication use over 6 months pre-index with treatments other than the index treatment.

^bNDRI^s comprise bupropion.

ER, emergency room; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NDRI, norepinephrine-dopamine reuptake inhibitor; SARI, serotonin antagonist reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant.

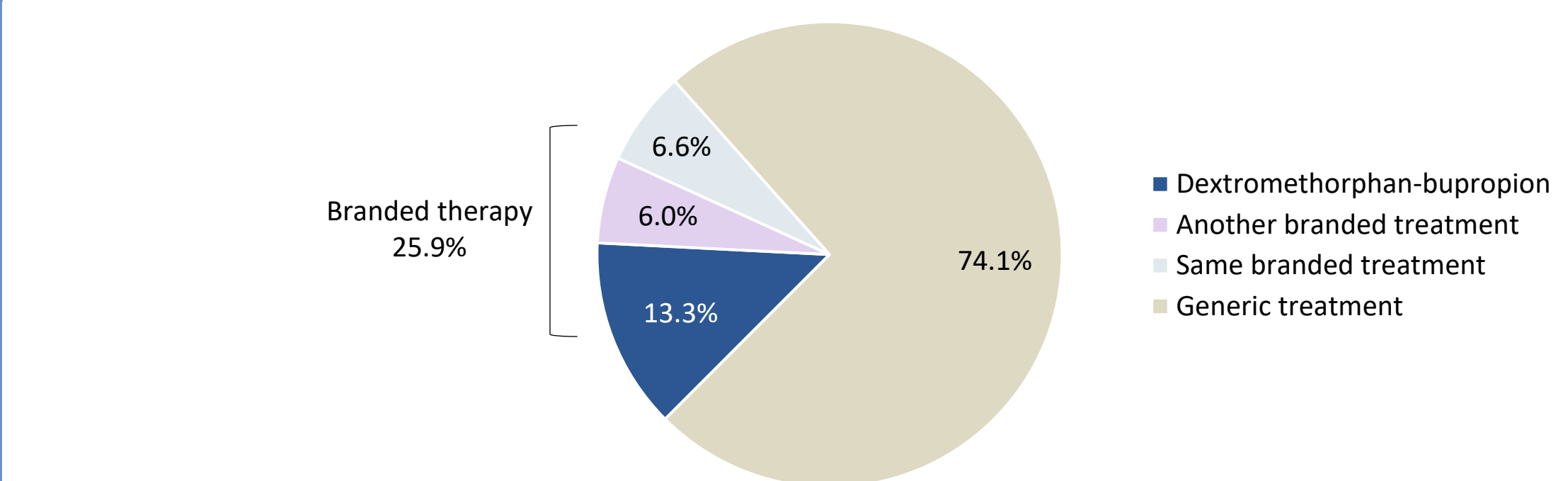
Adjusted All-Cause HCRU Per Patient-Year Post-Index



- Rejection of the initial dextromethorphan-bupropion claim was associated with significantly higher adjusted post-index HCRU — approximately 22% more ER visits and 30% more inpatient admissions per patient-year

CI, confidence interval; ER, emergency room; IRR, incidence rate ratio; PPY, per patient-year.

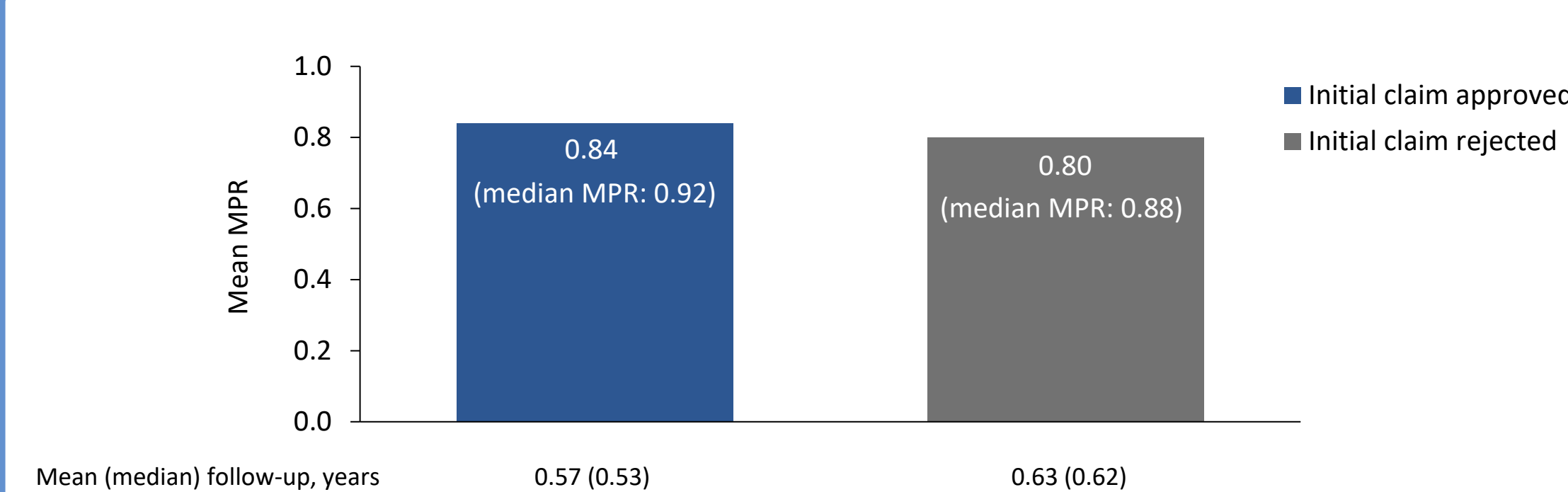
First MDD-Related Medication Dispensed After Rejected Initial Claim



- Over a quarter of patients received a branded therapy after rejection of their initial dextromethorphan-bupropion claim, with half of those patients receiving dextromethorphan-bupropion as the first medication dispensed after initial rejection

Evaluated in the cohort with a rejected initial claim for dextromethorphan-bupropion. 'Another branded treatment' includes both initiation or switching to a branded treatment other than dextromethorphan-bupropion post-index.
MDD, major depressive disorder.

Treatment Use and Adherence with Dextromethorphan-Bupropion



- Among patients with a rejected initial claim, 34.1% eventually received dextromethorphan-bupropion
 - Patients who later received dextromethorphan-bupropion faced a mean delay of 82.6 days (SD 62.4 days) from the initial claim to the first dispensed treatment (data not shown)
- Adherence to dextromethorphan-bupropion remained high once access was obtained, regardless of immediate or delayed initiation (mean MPR 0.84 and 0.80, respectively)

MPR defined as the total days' supply of medication during the refill period divided by the duration of the refill period, where the refill period is the number of days between the first and last prescription dates.
MPR, medication possession ratio.

Excess Annual Healthcare Costs Post-index

Estimated Excess ER Costs	
Excess annual ER visits ^a	92
Mean annual ER costs ^b	\$1655
Excess annual ER costs	\$152,925

Estimated Excess Inpatient Costs	
Excess annual inpatient admissions ^a	58
Mean annual inpatient costs ^b	\$27,400
Excess annual inpatient costs	\$1,596,821

Excess annual costs: **\$1,749,745**

- Rejection of the initial dextromethorphan-bupropion claim was estimated to be associated with \$1.75 million in excess annual healthcare costs in the rejected initial claim cohort

Estimated excess costs associated with rejection of the initial claim for dextromethorphan-bupropion.
^aExcess HCRU defined as the difference between adjusted ER visits and inpatient admissions and the expected rates if all patients with a rejected index claim for dextromethorphan-bupropion had initially received approval for the claim. ^bUnit costs (mean annual costs) for patients with MDD initiating dextromethorphan-bupropion derived from an analysis using Merative MarketScan Commercial and Medicare databases (October 2022 to March 2024), with costs adjusted to 2023 US dollars.
ER, emergency room; MDD, major depressive disorder.

Limitations

- Open claims uniquely capture claim adjudication status but do not allow for the complete capture of each patient's care history
- HCRU analyses adjusted for age, sex, and baseline HCRU; however, residual confounding by factors such as MDD disease severity and duration and benefit plan design could not be excluded
- Cost data were not available in the study dataset, and excess costs were therefore estimated by applying unit costs from an external database over an earlier time period
- Results from this study may not be generalizable to other patient populations

Conclusions

- Among commercially insured adults with MDD, formulary-related rejection versus approval of an initial dextromethorphan-bupropion claim was associated with:
 - 22% more ER visits and 30% more inpatient admissions per patient-year
 - an estimated \$1.75 million in excess annual healthcare costs
- Two-thirds of patients with a rejected initial claim for dextromethorphan-bupropion never received the prescribed treatment over follow-up, while those who eventually received the treatment experienced an average delay of nearly 3 months
- Adherence to dextromethorphan-bupropion treatment was high regardless of the initial claim decision
- These findings suggest that formulary restrictions intended to control pharmacy spending may shift costs to medical services associated with escalated care, including ER visits and inpatient admissions