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ORIGINAL RESEARCH ARTICLE

Treatment Patterns During Major Depressive Episodes Among Patients with Major Depressive Disorder: A Retrospective Database Analysis

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Abstract

Background Major depressive disorder, a highly prevalent mental health condition, can be challenging to treat.

Objective We aimed to characterize treatment patterns within and across multiple major depressive episodes in patients receiving treatment for major depressive disorder.

Methods Adults with newly diagnosed major depressive disorder and one or more major depressive episodes were identified using the IBM® MarketScan® Commercial database. Eligible patients had 12 months of continuous enrollment before and after diagnosis. Lines of therapy were periods of continuous treatment with one or more antidepressant claims. Antidepressant, atypical antipsychotic, or mood stabilizer regimens as monotherapy or adjunctive therapy were characterized by lines of therapy and major depressive episodes. Descriptive analyses were performed.

Results A total of 455,082 patients were included in the analysis. The majority of treatment regimens were monotherapy, which decreased with subsequent lines of therapy, while adjunctive treatments increased with subsequent lines of therapy. There were 1860 unique adjunctive regimens identified. Of the 40,315 patients (9%) who received adjunctive therapy, 8024 (20%; 2% of all patients) received atypical antipsychotic-adjunctive regimens. Only 19% of patients treated with atypical antipsychotic-adjunctive therapy discontinued treatment versus 42% of monotherapy-treated patients. On average, patients who received an adjunctive atypical antipsychotic received it as their third line of therapy and approximately 400 days after the initial antidepressant treatment.

Conclusions In this study, many patients continued monotherapy major depressive disorder regimens and experienced multiple treatment changes. Few patients were treated with adjunctive therapy. These results suggest underutilization of potentially effective treatments, which represents an opportunity to optimize the treatment of patients with major depressive disorder.

Key Points

The majority of patients with major depressive disorder received monotherapy antidepressant regimens and only 9% received adjunctive regimens.

Nearly 2000 unique adjunctive regimens were identified, highlighting a lack of a standardized treatment strategy.

On average, patients received an adjunctive atypical antipsychotic as their third line of therapy and over a year after their initial antidepressant treatment.

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1 Introduction

Major depressive disorder (MDD) is a debilitating mental health condition with a lifetime prevalence of 20.6% in the USA [1]. There is urgency to provide adequate and timely treatment to patients with MDD, as it is the leading cause of disability globally [2] and a major cause of lost productivity and absenteeism in the workplace [3]. Additionally, MDD is associated with a substantial annual economic burden, estimated to be approximately $326 billion in the USA [3]. Common MDD symptoms, which occur with varying degrees of severity, include depressed mood, markedly diminished interest or pleasure in all or almost all activities, considerable weight loss or gain, insomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, and recurrent thoughts of death [4]. Major depressive disorder is a highly heterogenous disorder, as patients with depression can exhibit a wide variety of symptom profiles. For example, over a thousand different symptom profiles were identified in a study of 3700 patients with MDD [5], indicating that very few patients exhibit the same symptom patterns. Given this heterogeneity, determining the optimal treatment regimen for a patient with MDD can be challenging.

First-line pharmacologic treatment options for MDD are selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, mirtazapine, and bupropion [6]. Approved antidepressants generally require several weeks of continued treatment before a clinical response is achieved. Further, there is evidence of poor efficacy with monotherapy antidepressant options [7], with a large proportion of patients not responding to first-line treatment [8, 9]. In a large retrospective study that analyzed treatment patterns within the first major depressive episode (MDE), less than 5% of patients persisted on their initial antidepressant regimen and nearly one-half did not have adequate treatment duration (i.e., 4–8 weeks) to assess a proper response; in addition, most patients either discontinued treatment or cycled through multiple antidepressants [10].

If initial treatment response is inadequate, current practice guidelines recommend initiating second-line treatment with adjunctive medications (inclusion of one or more additional antidepressants or drugs from another pharmacological class, such as atypical antipsychotics, lithium, thyroid hormone, anticonvulsants, or psychostimulants) or switching to another non-monoamine oxidase inhibitor antidepressant [6, 11]. Current MDD treatment guidelines [6] do not offer specific recommendations regarding the number of unresponsive monotherapy regimens attempted prior to initiating adjunctive treatment, and patients may cycle through several antidepressants with similar efficacy profiles (e.g., another first-line treatment) without receiving adequate therapeutic benefit. Antidepressant combinations aim to combine multiple mechanisms of action to enhance efficacy; however, there are no clear prescribing guidelines for antidepressant combinations as the evidence base is limited [12, 13], and there are no guideline recommendations regarding the number of unresponsive antidepressant combination regimens that should be attempted before adding an agent from a different pharmacological class [6]. The addition of some atypical antipsychotics to ongoing antidepressant therapy has demonstrated robust efficacy in MDD, especially in patients with specific treatment-resistant symptoms [14, 15]; however, long-term effectiveness has not yet been established [16, 17] and the risk for adverse effects associated with atypical antipsychotics (e.g., weight gain, extrapyrimidal symptoms) should be considered [18]. Many patients with MDD do not achieve full remission and have residual symptoms even with treatment; these patients with residual symptoms are at a heightened risk of relapse [19]. As such, prevention of recurrent MDE represents a critical unmet need.

Current literature has generally focused on the initial treatment of a single MDE without further investigation into additional MDEs or treatment regimens, and longitudinal treatment over multiple MDEs has not been extensively explored. The objective of this retrospective claims study was to characterize treatment patterns and changes within and across multiple MDEs and to investigate these patterns in patients receiving treatment for MDD.

2 Methods

2.1 Study Design and Patient Selection

This retrospective analysis used de-identified health insurance claims from the IBM® MarketScan® Commercial Claims and Encounters Database, which contains medical and prescription drug data from employers and health plans; this includes employees, their spouses, and their dependents who are covered by employer-sponsored commercial health insurance in the USA. Patients at least 18 years of age with an MDD diagnosis between 1 January, 2009 and 31 December, 2017 were included in the analysis (Fig. 1). An MDE was defined as the time period over which symptoms of MDD were assumed to be present (based on healthcare utilization); this was identified in patients who had one or more medical claims with a diagnosis of MDD (ICD-9 296.20–296.24, 296.30–296.34, 300.4, 311 or ICD-10 F32.*, F33.*, F34.1; any position for outpatient and primary position for inpatient) and one or more antidepressant pharmacy claims within 60 days of the medical claim. There was a 'washout period' prior to the first and subsequent

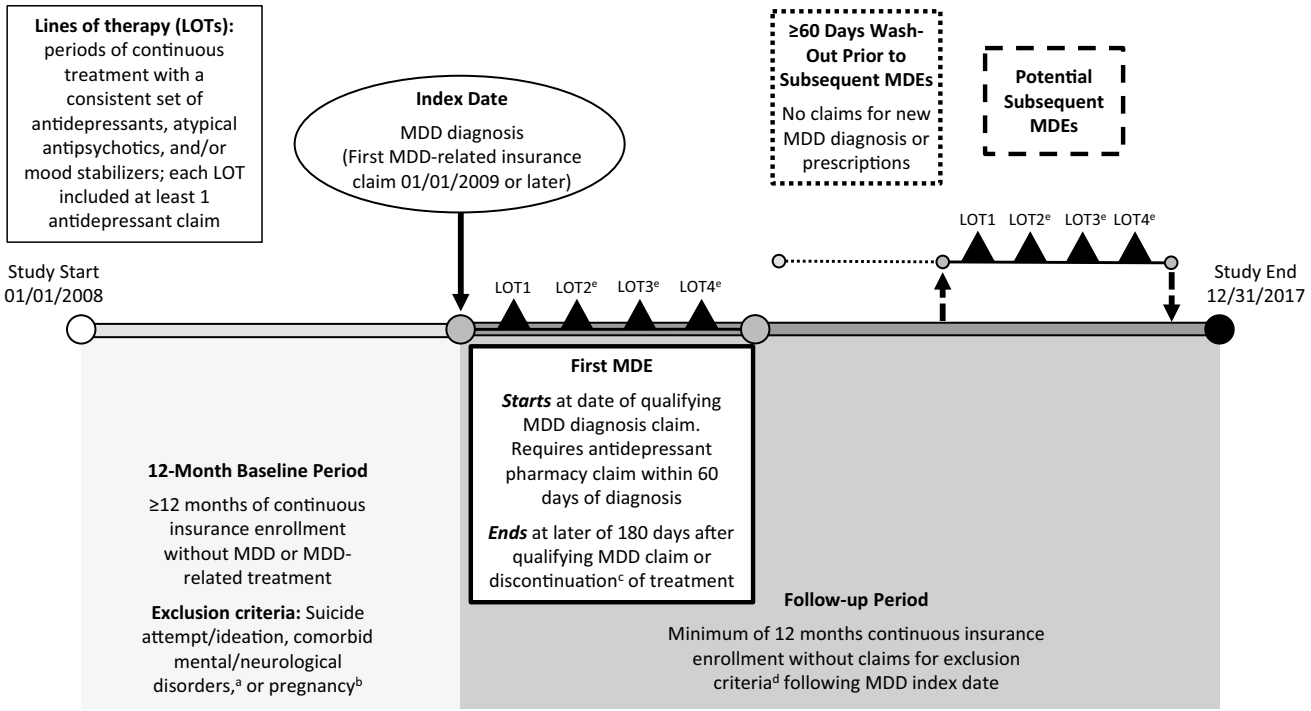


Fig. 1 Study design. [a]Schizophrenic disorder, psychosis-related disorders or paranoid states, drug-induced depression, depressive-type psychosis, bipolar or other mood disorder, Alzheimer's disease, Parkinson's disease, or dementia. Applied throughout the entire study period. [b]Pregnancy, childbirth, or breastfeeding. Applied throughout the entire study period. [c]Discontinuation was defined as a gap in days of supply of the current medication of greater than 30 days. [d]Severe mental health comorbidities excluded for baseline period only. [e]Not all patients received more than one line of therapy (LOT) within one major depressive episode (MDE) and not all patients experienced more than one MDE. *MDD* major depressive disorder

MDEs, where no claims of MDD diagnosis, subthreshold depression diagnosis (ICD-9 309.0, 309.01, 309.28; ICD-10 F43.21, F43.23) [20], or antidepressant/any adjunctive agent prescriptions during the minimum of 60 days before the start date of each MDE could occur.

Patients with medical claims for bipolar or other mood disorders (schizophrenic disorder, psychosis-related disorders or paranoid states, drug-induced depression, depressive-type psychosis, bipolar or other mood disorder), pregnancy/childbirth/breastfeeding, or neurocognitive/developmental disorders (Alzheimer's disease, Parkinson's disease, or dementia) at any point during the entire study period were excluded. Severe mental health comorbidities were excluded during the baseline period only. Further, included patients had no evidence of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or pharmacy claims for ketamine use during the baseline period (12 months prior to the start of the first MDE).

2.2 Outcomes and Data Analysis

Lines of therapy (LOTs) were defined as periods of continuous treatment with a consistent set of antidepressants, atypical antipsychotics, and/or mood stabilizers; each LOT included at least one antidepressant claim. For study inclusion, LOT1 of the first MDE (i.e., initial treatment) was required to be a monotherapy antidepressant regimen. During the study, a monotherapy LOT was defined as only one antidepressant, with no other antidepressant or adjunctive therapies used within 60 days after the first pharmacy claim. An adjunctive LOT was defined as at least one other antidepressant (antidepressant combination), mood stabilizer (mood stabilizer-adjunctive), or atypical antipsychotic (atypical antipsychotic-adjunctive) used in addition to one antidepressant. Lines of therapy were evaluated during each MDE. The first medical or pharmacy claim defined the start of a LOT, and a change in treatment was defined as the end of a LOT and included discontinuation (gap in days of supply of >30 days); switching medications; adding or changing adjunctive therapy; or adding, changing, or de-escalating adjunctive therapy (discontinuation of an adjunctive therapy while continuing at least one antidepressant therapy). Re-initiation was defined as resumption of a LOT starting more than 30 days after discontinuation of the original LOT.

The proportion of patients who received antidepressant monotherapy or adjunctive therapy and atypical antipsychotic or mood stabilizer adjunctive therapy regimens was analyzed for up to 4 LOTs within an MDE and across

multiple MDEs. The proportion of patients who experienced changes in treatment during these LOTs was also analyzed.

2.3 Statistics

Data for all regimens, as well as the top 30 regimens, were analyzed using descriptive statistics. World Programming System software was used to analyze data.

3 Results

3.1 Demographic and Clinical Characteristics

De-identified health insurance claims from a total of 455,082 patients with MDD were included in the analysis. Overall, the majority of patients were female (63.9%) with an average age of approximately 40 years. Over 80% of patients had only one MDE throughout the follow-up; the number of patients with two or more MDEs was 52,539 (11.5%).

3.1.1 Provider Types Across MDEs

More patients saw primary care physicians versus psychiatrists or other provider types. Based on the proportion of patients who saw each provider type, primary care physicians were approximately 1.5 to two times less likely to prescribe adjunctive therapy and two to three times less likely to prescribe atypical antipsychotic-adjunctive therapy (Table 1 of the Electronic Supplementary Material [ESM]).

3.2 Treatment Patterns Across MDEs and LOTs

Out of the 455,082 patients with MDD included in the analysis, 91.1% received only monotherapy regimens, while 8.9% of patients received adjunctive therapy and 1.8% received atypical antipsychotic-adjunctive therapy. By design, all patients were on monotherapy regimens for LOT1, and 26.4% of patients had a second LOT in their first MDE. Monotherapy regimens decreased slightly with each successive LOT in MDE 1 (proportion within each LOT: LOT2, 79%; LOT3, 71%; LOT4, 58%); this trend was similar for subsequent MDEs (LOT2, 82–84%; LOT3, 70–75%; LOT4, 48–58%; Fig. 2). The number of patients in subsequent LOTs was approximately 21–36% of the previous LOT. By

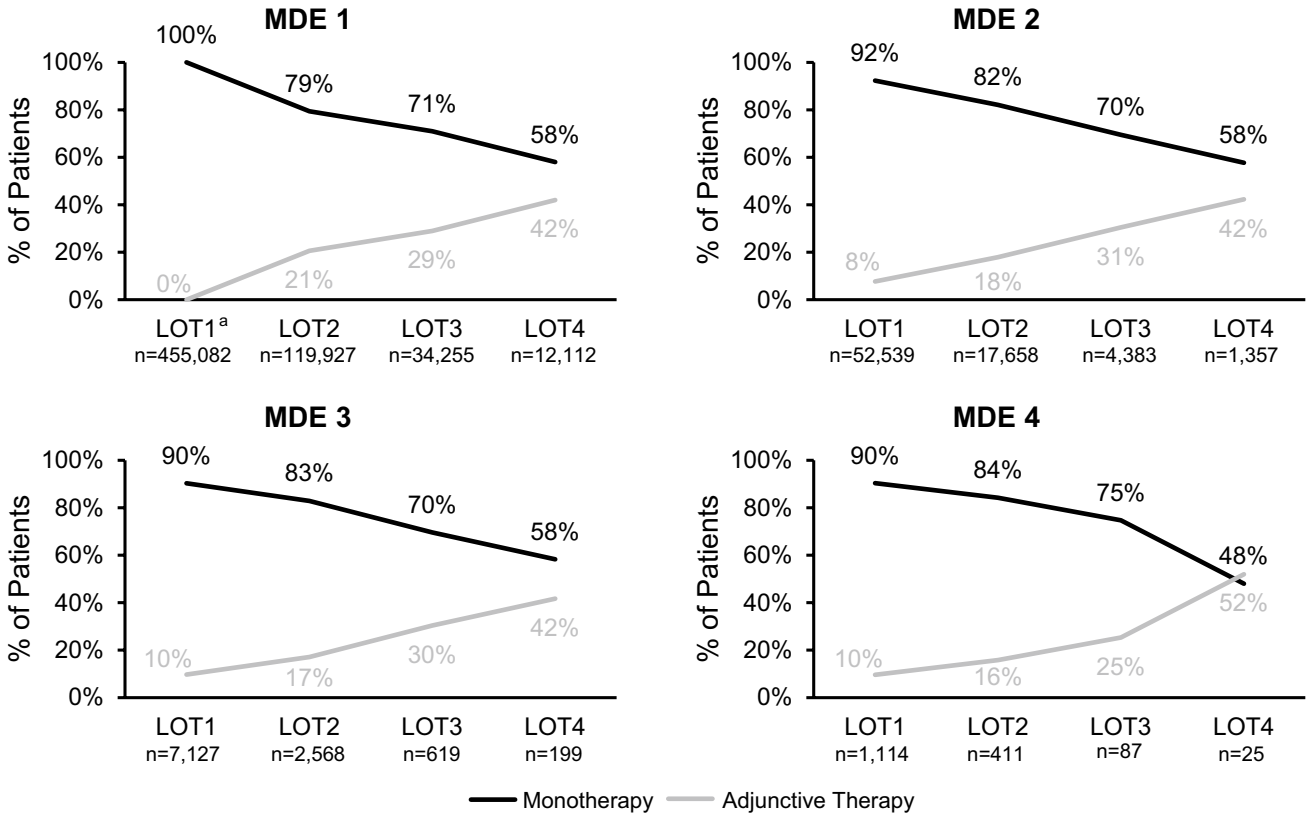


Fig. 2 Proportion of patients utilizing a monotherapy or adjunctive therapy across major depressive episodes (MDEs) and lines of therapy (LOTs). [a]As MDE 1 LOT1 was required to be monotherapy, there were no patients on adjunctive regimens

LOT4, approximately one-half of patients were still taking a monotherapy agent. In contrast, adjunctive regimens were used infrequently in initial LOTs (10% or less) and increased with subsequent LOTs (LOT2, 16–21%; LOT3, 25–31%; LOT4, 42–52%). Overall, there were 1860 unique adjunctive regimens identified.

Both monotherapy (Fig. 1 of the ESM) and adjunctive (Fig. 3a) treatment regimens were relatively consistent across MDEs. Selective serotonin reuptake inhibitors was the most common medication class for monotherapy regimens across all MDEs, although its usage did decrease over LOTs (LOT1, 59–74%; LOT2, 50–54%; LOT3, 36–40%; LOT4, 22–40%), while usage of the other groups (selective norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, bupropion, and other) remained relatively stable (< 20%). With each successive LOT, the proportion of patients on monotherapy regimens decreased but remained above 50% except in LOT4 of MDE 4.

As the initial treatment was required to be monotherapy, there were no adjunctive regimens in LOT1 of the first MDE. However, use of adjunctive treatments generally increased with successive LOTs; the most common adjunctive regimens were antidepressant combinations (> 75%). Mood stabilizers were consistently the least used adjunctive therapy across LOTs and MDEs.

Adjunctive treatment patterns were similar across MDEs and LOTs (Fig. 2 of the ESM). For LOTs except LOTs 3 and 4 in MDE 4, 69–81% of patients were taking an antidepressant combination, 17–25% were taking an atypical antipsychotic-adjunctive, and 2–8% were taking other adjunctive regimens. In general, the proportion of patients on atypical antipsychotic-adjunctive regimens was relatively constant and uncommon (< 5%) for MDEs 1, 2, and 3; however, usage increased with successive LOTs in MDE 4.

Proportions were similar when only the top 30 adjunctive regimens were considered. Among 40,315 patients with any adjunctive LOT during the follow-up, approximately 68% of patients (27,380 patients) had at least one of the top 30 adjunctive regimens (Fig. 3b of the ESM). Antidepressant combinations represented 75% of all adjunctive regimens and approximately 90% of the top 30 adjunctive regimens. Only 20% of all adjunctive regimens and 10% of the top 30 adjunctive regimens involved atypical antipsychotics, and less than 5% of all adjunctive regimens included mood stabilizers (no use among the top 30 adjunctive regimens), indicating that atypical antipsychotic-adjunctive and mood stabilizer-adjunctive therapies were utilized infrequently.

On average, adjunctive regimens were initiated in the third LOT (Table 1). Across all MDEs, the mean (standard deviation) time to receive an adjunctive prescription was 399.6 (431.2) days after the initial treatment; similarly, the mean (standard deviation) time to receive atypical antipsychotic adjunctive therapy after the initial treatment was 393.4 (429.2) days (Table 1). Aripiprazole and quetiapine, which are both approved for adjunctive MDD treatment, accounted for 77% (44% and 33%, respectively) of adjunctive atypical antipsychotic use (Fig. 4 of the ESM).

3.3 Treatment Changes Across MDEs and LOTs

Across all MDEs, more than 50% of patients had treatment changes in each LOT (Fig. 4). Discontinuation rates were highest in the earlier LOTs and, while they gradually declined through subsequent LOTs (LOT1, 75–80%; LOT2, 65–67%; LOT3, 46–51%; LOT4, 24–32%), they remained higher than the other types of treatment changes across all MDEs and all LOTs. All other treatment change types increased with subsequent LOTs, although none greatly exceeded 20%.

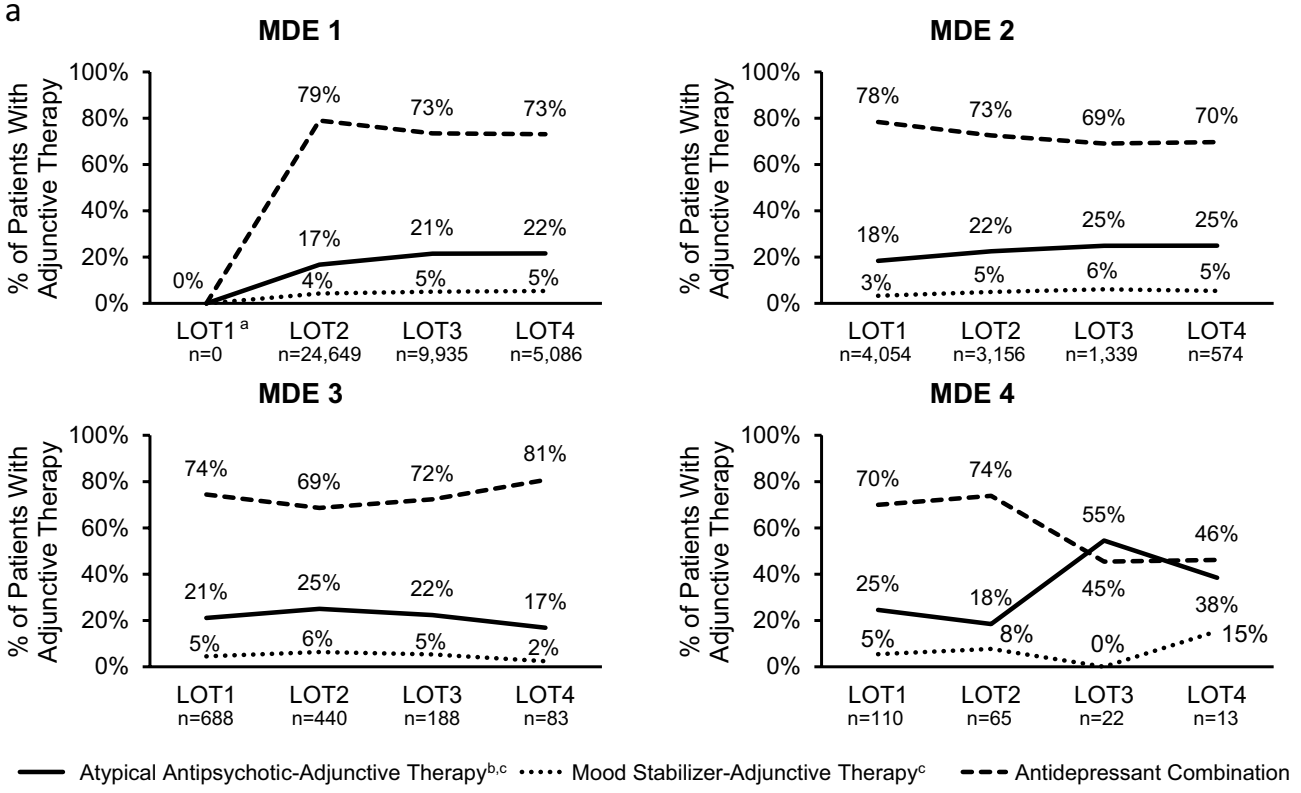
While discontinuation was a common type of treatment change, these rates were numerically lower in patients receiving adjunctive therapy versus monotherapy (Table 2). Of patients who discontinued treatment, less than 50% who were receiving monotherapy, approximately 20% who were receiving adjunctive therapy, and less than 25% who were receiving atypical antipsychotic-adjunctive therapy were re-initiated on a different treatment regimen.

4 Discussion

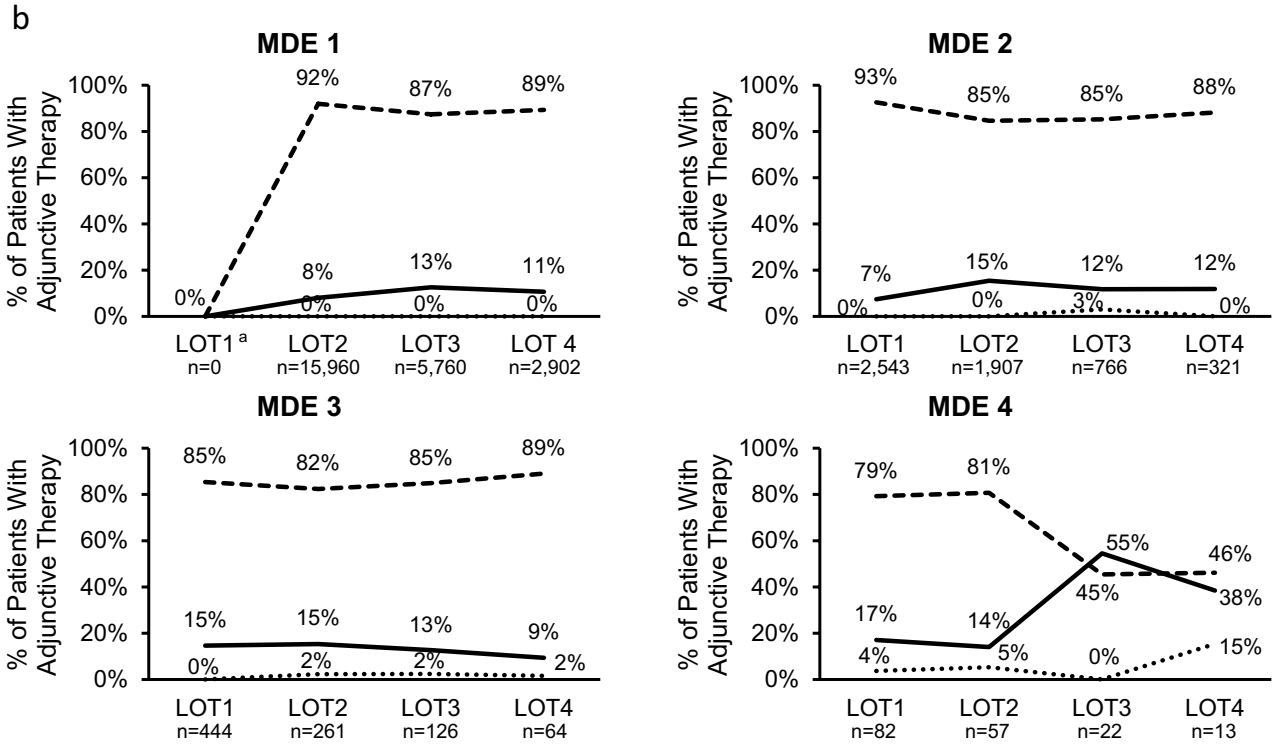
This retrospective study provided an in-depth characterization of MDD treatment patterns identified from a large national claims database in the USA. To our knowledge, this is the first study to follow treatment patterns across multiple LOTs within an MDE and through multiple MDEs. Study results have high internal consistency with existing national comorbidity surveys, epidemiologic research, and claims studies [7, 8, 10]. Initial treatments (LOT1s) for all MDEs were primarily monotherapy regimens, and 91.1% of all patients received only monotherapy regimens. Among all treatment change types, discontinuation was by far the most common. Of those who discontinued, less than one-half re-initiated treatment, suggesting that MDD treatment guidelines may not have been followed. Overall, there were nearly 2000 unique adjunctive regimens prescribed, indicating a lack of a standardized treatment strategy and highlighting the considerable heterogeneity of MDD.

One of the key goals of acute MDD treatment is complete remission of symptoms [7]. However, only one-third of patients with MDD achieve remission with a first-line monotherapy agent; those with an inadequate response to treatment often require additional treatment steps [7]. The results of this study indicate that patients with MDD may not have been adequately treated and/or followed up appropriately

a


MDE 1
% of Patients With Adjunctive Therapy
100%
80%
60%
40%
20%
0%
79%
73%
73%
17%
21%
22%
0%
4%
5%
5%
LOT1 a
n=0
LOT2
n=24,649
LOT3
n=9,935
LOT4
n=5,086
MDE 2
78%
73%
69%
70%
18%
22%
25%
25%
3%
5%
6%
5%
LOT1
n=4,054
LOT2
n=3,156
LOT3
n=1,339
LOT4
n=574
MDE 3
74%
69%
72%
81%
21%
25%
22%
17%
5%
6%
5%
2%
LOT1
n=688
LOT2
n=440
LOT3
n=188
LOT4
n=83
MDE 4
70%
74%
55%
46%
25%
18%
45%
38%
5%
8%
0%
15%
LOT1
n=110
LOT2
n=65
LOT3
n=22
LOT4
n=13
Atypical Antipsychotic-Adjunctive Therapy b,c
Mood Stabilizer-Adjunctive Therapy c
Antidepressant Combination

b


MDE 1
% of Patients With Adjunctive Therapy
100%
80%
60%
40%
20%
0%
92%
87%
89%
8%
13%
11%
0%
0%
0%
0%
LOT1 a
n=0
LOT2
n=15,960
LOT3
n=5,760
LOT 4
n=2,902
MDE 2
93%
85%
85%
88%
7%
15%
12%
12%
0%
0%
3%
0%
LOT1
n=2,543
LOT2
n=1,907
LOT3
n=766
LOT4
n=321
MDE 3
85%
82%
85%
89%
15%
15%
13%
9%
0%
2%
2%
2%
LOT1
n=444
LOT2
n=261
LOT3
n=126
LOT4
n=64
MDE 4
79%
81%
55%
46%
45%
38%
17%
14%
4%
5%
0%
15%
LOT1
n=82
LOT2
n=57
LOT3
n=22
LOT4
n=13
Atypical Antipsychotic-Adjunctive Therapy b,c
Mood Stabilizer-Adjunctive Therapy c
Antidepressant Combination

◂**Fig. 3** **a** All adjunctive regimens by major depressive episode (MDE) and line of therapy (LOT). **b** Top 30 adjunctive regimens by MDE and LOT. [a]As MDE 1 LOT1 was required to be monotherapy, there are no adjunctive regimens for this cohort. [b]Patients may have had one or more atypical antipsychotics as part of their adjunctive treatment regimen. [c]May include patients with adjunctive therapy receiving antidepressant combination treatment within that LOT

after changes to monotherapy, as evidenced by high discontinuation rates and low rates of treatment switches or adding adjunctive therapy. However, the exact cause of discontinuation cannot be determined by these data, and discontinuation may have reflected recovery, switching because of adverse events, or suboptimal treatment responses. In addition to LOT1 of the first MDE, which was required to be antidepressant monotherapy, most initial treatments (LOT1 of MDEs 2–4) were monotherapy antidepressants (>85%). Monotherapy discontinuation rates were also high across MDEs (~80%), suggesting ineffectiveness of the monotherapy regimens. Despite high discontinuation rates, less than 10% of patients were prescribed adjunctive treatment, even for subsequent LOTs (i.e., LOTs 2–4) across recurring MDEs (i.e., MDEs 2–4). Of the adjunctive treatment regimens, the vast majority were antidepressant combinations, followed by atypical antipsychotic-adjunctive therapy as a distant second; use of adjunctive therapies increased over LOTs across all MDEs for both cohorts. Generally, atypical antipsychotics were used in less than 5% of patients across multiple LOTs within an MDE and across MDEs. Of patients who received adjunctive therapy, approximately 20–25%, which represents about 2–4% of the entire patient population, received an atypical antipsychotic during the follow-up. These results suggest that prescribers may not be accounting for treatment history (e.g., previous discontinuation of monotherapy regimens), which can adversely affect patient outcomes. The high rate of discontinuation in early LOTs underscores the importance of initiating efficacious regimens early in the course of MDD treatment.

There is little evidence to support continuing treatment with the same antidepressant for > 6 weeks with no response or not changing a treatment strategy when a clinical response has not been achieved at 4–8 weeks [6]. Although guidelines recommend initiating adjunctive therapy as early as second line after an adequate trial of a first-line treatment (i.e., 4–8 weeks) [6, 11], the time from the MDE start date to adjunctive therapy initiation in this study was approximately 400 days (or 57 weeks). On average, patients received an atypical antipsychotic as their third line of therapy (LOT3) and after > 1 year of treatment; aripiprazole and quetiapine were most common, representing 77% of atypical antipsychotic-adjunctive treatment. Although the use of adjunctive atypical antipsychotics may be associated with an increased risk of some adverse effects, such as weight gain and extrapyramidal symptoms [18], the consequences of inadequately treated depression must also be considered. For example, as unresolved depression is associated with a higher risk of relapse, a more rapid relapse, a higher suicide risk, and increased healthcare costs [9], adequately treating depressive symptoms to resolution is a clinical imperative. Although the time to receiving any adjunctive and atypical antipsychotic-adjunctive therapy was prolonged, patients receiving adjunctive therapy were less likely to discontinue medication; however, this may also be a consequence of adjunctive therapy being a later-line treatment option and fewer patients receiving later LOTs.

The majority of patients were seen by primary care physicians, who were 1.5 to 2 times less likely to prescribe adjunctive therapy and two to three times less likely to prescribe atypical antipsychotic-adjunctive treatment. Given the high usage of monotherapy antidepressants coupled with the lengthy period of time before a patient received atypical antipsychotic-adjunctive treatment, it appears that although adjunctive therapies can be used as early as second-line treatment, they are typically not utilized early in clinical practice. This may reflect primary care physicians seeing patients with less severe depression, concerns about cost or adverse events, provider comfort level with adjunctive therapy, or a general unawareness of the efficacy data of adjunctive therapy in MDD. As such, education on the use of adjunctive therapy for MDD, especially in patients who have had multiple treatment changes, may be beneficial.

The results of this study should be interpreted within its limitations. This retrospective claims study was limited to data of patients within certain employer health plans. It is possible that treatment patterns obtained for some patients were incomplete, as study inclusion was based on continuous enrollment and not MDD management patterns. Additionally, all data in this analysis were subject to coding limitations and data entry errors. Medication treatment patterns were based on filled prescriptions, and no data were available on whether the medications were actually taken or if they were utilized as prescribed. Because of the nature of filled prescription data, treatment discontinuation could have included patients who had achieved remission. For these reasons, we were unable to assess treatment efficacy using claims data. Additionally, our analysis focused on pharmacotherapy treatment patterns during MDEs; however, nonpharmacologic therapies, which may be used exclusively in some cases, were not captured. For example, mild MDEs may be treated with psychotherapy alone, and in cases of treatment resistance or intolerance to medication side effects, more invasive and costly therapies, such as electroconvulsive therapy, may be used [6]. It is possible that patients who did not re-initiate pharmacologic treatment may have been switched to one of these therapies. Last, the use of descriptive statistics limited the ability to determine causal relationships in the observed treatment pattern data.

Table 1 MDE, LOT, and treatment characteristics

MDE/LOT characteristics, days	All patients (n = 455,082)	
	Mean (SD)	Median (IQR)
Duration of MDEs	388.9 (340.1)	222 (180–466)
Duration between MDEs	428.7 (448.4)	274 (100–600)
Time between LOTs		
MDE 1	30.4 (32.7)	22 (1–47)
MDE 2	36.7 (33.8)	34 (3.5–55)
MDE 3	41.3 (34.5)	38 (8.5–59)
MDE 4	47.4 (35.5)	44 (17–71)
Treatment characteristics, days	Any adjunctive therapy (n = 40,315)	Atypical antipsychotic-adjunctive therapy (n = 8024)
Time from MDE start date to initial treatment start		
Adjunctive therapy		
Mean (SD)	399.6 (431.2)	388.6 (425.4)
Median (IQR)	240 (111–528)	228 (106–510)
Atypical antipsychotic-adjunctive therapy		
Mean (SD)	–	393.4 (429.2)
Median (IQR)	–	235 (108–517)
No. of LOTs preceding treatment start, mean (SD)		
Adjunctive therapy	1.8 (1.3)	1.8 (1.3)
Atypical antipsychotic-adjunctive therapy	–	1.8 (1.3)

IQR interquartile range, *LOT* line of therapy, *MDE* major depressive episode, *SD* standard deviation

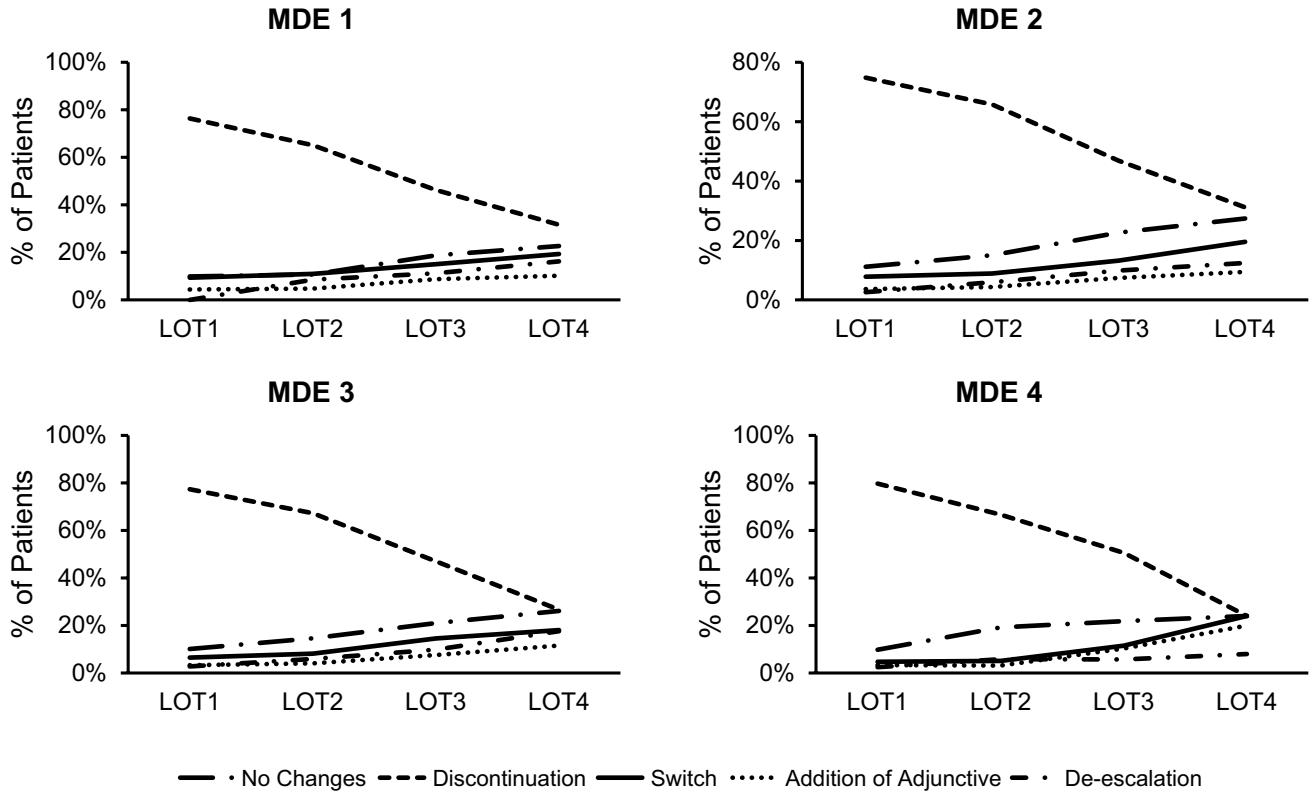


Fig. 4 Types of treatment changes by major depressive episode (MDE) and line of therapy (LOT)

Table 2 Proportions of various types of treatment changes across MDEs and LOTs

Type of treatment changes	*n* (%) among all treatment changes
Monotherapy[a]	*n* = 455,082
Number of treatment changes[b]	508,612
Discontinuation	381,143 (74.9)
Re-initiation	*160,127 (42.0)*[c]
Switch	51,646 (10.2)
Addition of adjunctive therapy	30,900 (6.1)
No treatment changes	44,923 (8.8)
Adjunctive therapy	*n* = 40,315
Number of treatment changes[b]	46,477
Discontinuation	16,852 (36.3)
Re-initiation	*2860 (17.0)*[c]
Switch	5063 (10.9)
De-escalation[d]	18,613 (40.0)
No treatment changes	5949 (12.8)
Atypical antipsychotic-adjunctive therapy	*n* = 8024
Number of treatment changes[b]	9391
Discontinuation	4373 (46.6)
Re-initiation	*811 (18.5)*[c]
Switch	1788 (19.0)
De-escalation[d]	1680 (17.9)
No treatment changes	1550 (16.5)

LOT line of therapy, *MDE* major depressive episode

[a]All patients received at least one monotherapy

[b]Patients may have contributed to more than one treatment change type. If multiple failures of the same type occurred, only the first was counted

[c]All re-initiators must have discontinued treatment prior to the re-initiation; percentage is of discontinuations within the subcategory

[d]De-escalation means: changing back to monotherapy from two therapies (e.g., remove atypical antipsychotics or remove one of the antidepressants if on combination therapy) or, if on three treatments, remove third adjunctive therapy

5 Conclusions

This large retrospective study aimed to characterize MDD treatment patterns over multiple LOTs and across multiple MDEs. Results showed that many patients had several treatment changes but continued on a monotherapy regimen, suggesting a reluctance of providers to prescribe adjunctive therapies that may benefit certain patients. Another reason could be that commonly prescribed monotherapy antidepressants share similar mechanisms of action, highlighting the potential benefit of adding drugs from other medication classes (e.g., atypical antipsychotics, mood stabilizers) earlier in the course of MDD treatment. Longer term studies and linked survey research are needed to understand the reasons behind discontinuation and other treatment changes in MDD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-022-00316-4.

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Declarations

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Ethics Approval This study was exempt from ethics committee approval and institutional review because it is a retrospective analysis that used anonymized and de-identified data certified as fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Allergan (prior to its acquisition by AbbVie) obtained permission to access and use the IBM® MarketScan® data used in the analysis through licensing agreements.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Data that support the findings of this study were used under license from IBM® Watson Health™. Restrictions apply to the availability of these data, which are not publicly available and cannot be shared.

Code Availability Not applicable.

Authors' Contributions AC, RJ, MB, JP, PG, KK, AT, and SH were involved with the study design, analysis, and/or interpretation of the data. MB and JP also performed statistical analyses. All authors contributed to and have approved the final manuscript and are accountable for all aspects of the work, as well as the ability to identify their individual unique contributions and to ensure the integrity of their contributions.

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