Use of Augmentation Agents for Treating Depression: Analysis of a Psychiatric Electronic Medical Record Data Set

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Objective: **This study evaluated the relationship between patient characteristics and augmentation strategies for the treatment of major depressive disorder.** ***Methods:*** **This retrospective, cross-sectional study used data from a psychiatric electronic medical record database for patients with depression without psychosis or psychotic features who initiated augmentation therapy between January 2001 and June 2011. Medical records were evaluated to identify factors predicting use of specific augmentation agents, and a multivariate logistic regression model was used to assess clinical and demographic predictors of augmentation strategy.** ***Results:*** **Of 3,209 patients initiating augmentation therapy for depression, 75% received augmentation with an antidepressant combination and 11% received augmentation with second-generation antipsychotics. Baseline clinical severity (Clinical Global Impressions–Severity score) most strongly and consistently predicted augmentation with second-generation antipsychotics.** ***Conclusions:*** **Treatment of patients in specialty settings with depression was often augmented with an antidepressant combination, whereas those with severe depression had an increased likelihood of augmentation with second-generation antipsychotics. (*Psychiatric Services* 65:1062–1065, 2014; doi: 10.1176/appi.ps.201300288)**

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Major depressive disorder is a common, burdensome, and recurrent illness affecting more than 340 million people worldwide (1). Depressive symptoms are often associated with impaired psychosocial functioning and reduced quality of life (2). Approximately 60% of these patients do not achieve an adequate response or undergo remission after initial antidepressant therapy of standard dosage and duration (3). Response may be delayed for weeks or months, and residual symptoms may cause significant morbidity (4).

Current treatment guidelines for major depressive disorder from the American Psychiatric Association (APA) recommend consideration of augmentation after four to eight weeks of inadequate response to initial therapy (5). Such augmentation involves the addition of another first-line antidepressant or an agent that is not conventionally used as first-line monotherapy. One APA recommendation with considerable supporting evidence, which is the only option approved by the U.S. Food and Drug Administration (FDA) for patients with major depressive disorder who have had a prior inadequate treatment response, is augmentation with second-generation antipsychotics (6–9).

Although APA guidelines and data from clinical trials support the use of augmentation strategies for patients with major depressive disorder, there are limited data on the utilization of these strategies in real-world practice. The only study that has examined this issue was conducted with administrative claims data from 2002 in a U.S. Department of Veterans Affairs (VA) setting (10). The retrospective, cross-sectional analysis reported here examined current patterns of real-world utilization of treatment augmentation for major depressive disorder by specialty psychiatry providers and assessed demographic and clinical characteristics of patients receiving these agents.

Methods

In this retrospective, cross-sectional study, patients at least 18 years old with major depressive disorder without psychosis or psychotic features who initiated augmentation therapy between January 2001 and June 2011 were identified in MindLinc, a psychiatric electronic medical record (EMR) database representing an anonymous subset of clinical data generated from use at multiple sites. Institutional review board approval was not required because MindLinc data are anonymized and thus exempt from HIPAA requirements. The data set included diagnoses, clinical measure (Clinical Global Impressions–Severity [CGI-S] score), medications prescribed, and other medical conditions and services rendered.

The earliest date of augmentation was flagged as the index date. Augmentation was defined as prescription of a combination of antidepressants or an antidepressant and an agent not conventionally used as first-line monotherapy (second-generation antipsychotics, mood stabilizers or anticonvulsants, or stimulants). Medical records from a one-year preindex period were evaluated to identify patient demographic and clinical profiles, comorbid psychiatric and medical conditions, psychiatric drug utilization patterns, and site characteristics. Clinical severity of patients at the time of augmentation was classified as mild, CGI-S score of 2 or 3; moderate, 4; or severe, 5–7.

Descriptive statistics and frequency distributions were used to describe the sample and the type of augmentation strategy. Clinical and demographic differences between patients who received different augmentation strategies were examined by bivariate chi square analysis. Clinical and demographic predictors of the type of augmentation agent in a multivariate framework were assessed with logistic regression models. Variables that showed bivariate associations with the type of augmentation strategy at $p \leq .10$ were used in the multivariate model. Augmentation with a second-generation antipsychotic was used as the reference category because it constitutes the only FDA-approved augmentation option. [Additional information about the study methods is available in an online data supplement to this report.]

Results

A total of 3,209 patients initiated augmentation therapy for depression. Most patients had a diagnosis of recurrent major depressive disorder (58%), and many had moderately severe depressive symptoms (48%). A comorbid anxiety disorder diagnosis was documented for 48% of the patients. Antidepressant combination therapy was the most commonly used augmentation strategy (75%, N=2,420), followed by second-generation antipsychotics (11%, N=356), mood stabilizers or anticonvulsants (8%, N=266), and stimulants (5%, N=167).

A larger proportion of patients who were prescribed second-generation antipsychotics had recurrent major depressive disorder, compared with those who were prescribed an antidepressant combination, mood stabilizers, or stimulants ($p=.034$), and a larger proportion who were prescribed mood stabilizers had a diagnosis of major depressive disorder not otherwise specified ($p=.039$). Use of second-generation antipsychotics was associated with having a comorbid adjustment disorder ($p=.016$) and with having a personality disorder ($p<.001$), whereas augmentation with mood stabilizers was associated with having a comorbid somatic disorder ($p<.001$).

Among patients who were prescribed second-generation antipsychotics, a significantly larger proportion were classified as having severe symptoms at baseline (41%), compared with those who were prescribed a combination of antidepressant therapies (25%), mood stabilizers (27%), or stimulants (22%) ($p<.001$). Although patients who were prescribed second-generation antipsychotics had severe clinical symptoms (CGI-S scores=5–7), no significant differences in mean baseline CGI-S scores were observed by the specific agent prescribed.

A summary of predictors of augmentation with second-generation antipsychotics compared with other agents in a multivariate framework is presented in Table 1. Patients with adjustment disorder, personality disorders, somatic disorders, and prior use of benzodiazepines were more likely to receive augmentation with second-generation antipsychotics than with an antidepressant combination. Race and gender were strong predictors of augmentation with second-generation antipsychotics compared with mood stabilizers. Patients with substance use disorders and nonwhite patients were more likely to receive second-generation antipsychotics than stimulants. Disorders of infancy and childhood and adolescence were also strong predictors of stimulant use rather than use of second-generation antipsychotics.

Logistic regression analysis indicated that the baseline clinical severity of patients was the strongest and most consistent predictor of augmentation strategy. Patients with moderate clinical symptoms were 2.8 times more likely to receive a second-generation antipsychotic than combination antidepressant therapy compared with patients with mild depression (95% confidence interval [CI]=1.9–4.0). Similarly, moderate severity was associated with the selection of second-generation antipsychotics rather than mood stabilizers (odds ratio [OR]=3.4, CI=1.9–5.9) or stimulants (OR=4.1, CI=1.8–9.2). [Details of the results of all analyses are presented in the online supplement.]

Discussion

This study provides real-world evidence of the treatments that specialty psychiatric providers use when managing patients with depression who do not adequately respond to initial antidepressant therapies. When a change in the treatment plan is necessary, current APA practice guidelines recommend that additional options include augmentation with either another antidepressant or with a nonantidepressant medication, such as lithium, thyroid hormone, or a second-generation antipsychotic (5). The augmentation patterns in this study are consistent with these recommendations: 75% of patients received an antidepressant combination, 11% were prescribed second-generation antipsychotics, 8% received mood stabilizers, and 5% received augmentation with stimulants.

The utilization rates of augmentation agents found in this study differ from those in the only previously published study on this topic (10), which found that among patients with major depressive disorder receiving antidepressant therapy augmentation, approximately half received a combination of antidepressants, one-third received second-generation

Table 1

Analysis of predictors of augmentation with second-generation antipsychotics compared with other types of augmentation agents

Variable	Second-generation antipsychotic vs. combination of antidepressants		Second-generation antipsychotic vs. mood stabilizer		Second-generation antipsychotic vs. stimulants	
	OR	95% CI	OR	95% CI	OR	95% CI
Males	1.22	.91–1.65	1.83	1.14–2.95	.84	.44–1.59
White	.85	.63–1.15	.55	.34–.87	.17	.07–.40
Index year	1.04	.98–1.11	1.09	.99–1.19	1.03	.92–1.16
Baseline CGI-S score (reference: mild [score of 2 or 3])[a]						
Moderate (score of 4)	2.75	1.87–4.04	3.35	1.90–5.91	4.05	1.78–9.21
Severe (score of 5–7)	1.73	1.19–2.52	1.60	.95–2.70	1.90	.91–3.96
Age (reference: ≥65)						
18–30	1.20	.70–2.06	1.32	.55–3.15	.31	.07–1.30
31–45	.83	.50–1.38	.52	.24–1.12	.42	.11–1.63
46–64	.95	.59–1.54	.68	.32–1.44	.45	.12–1.68
Site type (reference: academic center)						
Community mental health care center	1.45	1.00–2.10	.81	.45–1.47	1.64	.74–3.67
Regional hospital	1.18	.77–1.80	.97	.48–1.93	6.99	1.72–28.43
Depression diagnosis (reference: major depressive disorder [MDD])						
Recurrent MDD	1.34	.91–1.97	1.37	.76–2.47	.56	.21–1.51
MDD not otherwise specified	.94	.57–1.55	.64	.31–1.31	.76	.24–2.47
Dysthymia	.76	.42–1.37	.55	.24–1.28	.33	.09–1.22
Other *DSM-IV* diagnosis						
Adjustment disorder	1.79	1.14–2.81	1.51	.72–3.16	1.19	.42–3.42
Disorder of infancy and childhood and adolescence	1.20	.69–2.09	2.04	.78–5.29	.08	.04–.16
Eating disorder	.20	.03–1.46	.07	.01–.68	.50	.03–7.91
Personality disorder	1.81	1.22–2.70	.92	.51–1.63	1.39	.53–3.64
Somatic disorder	2.55	1.67–5.59	.75	.27–2.12	3.23	.50–20.65
Substance use disorder	1.13	.80–1.61	1.15	.68–1.95	2.90	1.21–6.93
Use of benzodiazepines before index date	1.39	1.05–1.84	1.08	.71–1.65	1.65	.89–3.05
Medical comorbidity						
Diabetes	.81	.48–1.37	.66	.31–1.43	.95	.25–3.57
Hypertension	1.17	.81–1.69	1.46	.83–2.56	1.33	.48–3.64
Lipid disorder	.75	.45–1.23	.76	.36–1.57	1.21	.29–5.13

[a] CGI-S, Clinical Global Impressions–Severity

antipsychotic augmentation, and the rest received anticonvulsants. Differences between our findings and the previously published evidence may be attributed to differences in setting, time frame, and data source. Our study used EMRs with a *DSM-IV* diagnosis, whereas the previous study identified VA patients by codes in administrative claims data, which are prone to missing and inaccurate diagnoses (11). It is also possible that the VA study included a disproportionately high number of patients with undocumented psychosis and other conditions who should have been excluded. Also, the previous study defined augmentation on the basis of a conservative estimate of a 60-day overlapping supply by using pharmacy claims (10), whereas our analysis assessed data on medication use with prescription records from providers. Use of a more stringent criterion through a different data set on medication use could have identified a lower proportion of patients treated with combination antidepressants compared with our estimates (10).

Our analysis showed that clinicians mainly prescribed a combination of antidepressants and used second-generation antipsychotics primarily for patients with severe depression; concomitant psychiatric conditions, such as adjustment disorder and personality disorders; and prior use of benzodiazepines. This finding is consistent with prior evidence showing that patients were more likely to receive augmentation with an antipsychotic agent if they had previous hospitalizations or comorbid posttraumatic stress disorder or were nonwhite (10).

Consistent with previous evidence, race and gender were strong predictors of augmentation with second-generation antipsychotics compared with mood stabilizers; second-generation antipsychotics were prescribed mainly to nonwhite males. Although African Americans and Hispanics were more likely to receive augmentation with second-generation antipsychotics, the overall rate of augmentation was lower for this population than for white patients (10). It is possible that these racial differences are driven by insurance status or treatment settings. In addition, the different rates of augmentation may result from differences in provider-patient communication or patient treatment preferences (10). In the current analysis, consistent with previous findings, patients with substance use disorders were more likely to receive augmentation with second-generation antipsychotics than with stimulants, possibly because these antipsychotic agents have been used off-label in the management of substance use disorders (12).

Although this study provides information on the type of augmentation agents used in clinical practice for major depressive disorder, it does not provide insight into the overall rate of use of augmentation therapy. Prior evidence has shown that only 4.2% of patients receive augmentation with an antipsychotic, anticonvulsant, or lithium, despite evidence showing significantly longer overall treatment duration compared with patients who continued on their initial antidepressant monotherapy or were switched to another antidepressant (13). In primary care settings alone, augmentation use was found to be only about 2% over a six-month

follow-up period from the start of antidepressant monotherapy (14).

The main limitation of this study was the possible lack of comprehensive health care information in an EMR data set. Although medical records should have a detailed medical history, the data set is not based on a closed system and may lead to underestimation of medical conditions or prescription use. Therefore, it is possible that augmentation therapies were recorded at a date later than their initiation. However, exclusion criteria were established to ensure that the initiation of augmentation therapy was captured as accurately as possible. In addition, these results may underestimate comorbidities because some patients might not have been systematically evaluated for all psychiatric diagnoses, and diagnostic patterns are affected by variations in clinical detection over time. Insurance status was not available and can be an important factor affecting choice of treatment in real-world settings. Also, the longitudinal data repository is built through the use of EMRs, and not all data fields are mandatory or completed in full by physicians. Finally, the database is specific to specialty psychiatric providers, and the results may not be generalizable to the primary care setting.

Nonetheless, this study has unique strengths not available from claims data sets or survey research. MindLinc serves large, diverse populations, care settings, and a variety of treatment centers. This diversity and inclusion of all available psychiatric diagnoses provides an opportunity to examine more wide-ranging patterns of comorbid diagnoses in real-world settings and to document clinically important diagnoses omitted or overlooked in major surveys or administrative claims data. Another strength was the assessment of utilization patterns in relation to clinical severity, a data point generally not available in traditional sources of treatment pattern data, such as insurance claims.

Conclusions

In specialty settings, patients with major depressive disorder were often treated with a combination of antidepressants, whereas second-generation antipsychotics were more often used for patients with severe depression than for those with mild symptoms.

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