Appendix

Data source

The data for the study were obtained from MindLinc, a psychiatric electronic medical record (EMR) database representing an anonymous subset of clinical data generated from the use of EMR at multiple sites. The repository is made up of medical records from a national sample of academic centers, behavioral health departments, community mental health centers, and regional hospitals. MindLinc was initially deployed in 2000 and used since then by the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center, functioning as a full patient EMR for all psychiatric services across all treatment settings (inpatient, outpatient, and emergency room). The system was designed and developed by practicing psychiatrists and requires clinicians to collect a certain subset of data called a ”qualified clinical visit.” This data set includes a diagnosis, a clinical measure (Clinical Global Impressions – Severity [CGI-S]), medications prescribed, other medical conditions, and services rendered.

Inclusion/exclusion criteria

Patients 18 years of age or older who have a diagnosis of depression on the index date (including major depression single episode, major depression recurrent, depression not otherwise specified [NOS] or dysthymia) and who were initiating augmented therapy for treatment of depression were included in the study.

Patients with other conditions that may warrant the use of augmentation strategies, such as schizophrenia, schizoaffective disorder, bipolar disorder, and epilepsy, were excluded from the analysis. Also excluded were patients with a CGI-S score of 1 or missing on the index date, patients using any of the augmentation agents or combination therapy in the pre-index period, patients having an index visit in an inpatient setting, and patients with psychotic depression. In addition, patients with no antidepressant use (monotherapy) in the 12-month pre-index period or with no visits within the MindLinc system during the 12-month pre-index period were excluded.

Patient demographics and clinical characteristics

Baseline demographics and clinical characteristics of the overall cohort by augmentation agent are summarized in Appendix Table 2. A total of 3,209 patients initiated augmentation therapy for depression, with most receiving treatment in an academic center (54%; n=1,736) or community mental health center (33%; n=1,049). Patients were predominantly white (71%; n=2,269), female (70%; n=2,240) and over 31 years of age (77%; n=2,481). Clinical characteristics are summarized in Appendix Table 3.

Treatment patterns

Treatment patterns are summarized in Appendix Figure 1. Within combination antidepressants, patients most commonly received a combination of selective serotonin reuptake inhibitors (SSRIs) and bupropion (23%; n=558), followed by a SSRI + serotonin modulator or norepinephrine–serotonin modulator (16%; n=385). Quetiapine (40%; n=141) and aripiprazole (31%; n=111) were the most common atypical antipsychotics used for augmentation. The most commonly used mood stabilizer for augmentation was gabapentin (40%; n=104), followed by lamotrigine (21%; n=57); while methamphetamine (56%; n=93) and dextroamphetamine (35%; n=59) were the most commonly used stimulants.

The utilization of augmentation agents showed a time trend, with the utilization of atypical antipsychotics increasing slightly after their approval (2008 and beyond) for the treatment of depression (13%) compared with the pre-approval period (9%). In contrast, there was a slight decrease in the use of antidepressant combinations in 2008 and beyond (73%) compared with previous years (79%). The use of mood stabilizers and stimulants remained relatively consistent throughout the period analyzed (January 2001 to June 2011).

A significantly lower proportion of patients augmented with stimulants had metabolic comorbidities, such as diabetes, hypertension, and hyperlipidemia, compared with patients augmented with other strategies. There was no difference in the proportion of patients with anxiety disorder between the different augmentation strategies. No significant differences in mean baseline CGI-S scores were observed within the atypical antipsychotic group (aripiprazole = 4.2 ± 0.8; quetiapine = 4.3 ± 0.8; risperidone = 4.3 ± 0.9; olanzapine = 4.5 ± 1.0 [p=.636]).

Appendix Table 1 Medications for treatment of depression			
Major class	Subclass	Medication	
Antidepressant	SSRI	Citalopram	Sertraline
		Escitalopram	Paroxetine
		Fluoxetine	Fluvoxamine
	SNRI	Desvenlafaxine	
		Duloxetine	
		Venlafaxine	
	TCA	Amitriptyline	Amoxapine
		Clomipramine	Desipramine
		Doxepin	Imipramine
		Nortriptyline	Protriptyline
		Trimipramine	Maprotiline
	MAO-I	Isocarboxazid	
		Phenelzine	
		Tranylcypromine	
	Bupropion	Bupropion SR	
		Bupropion XL	
		Bupropion	
	Serotonin or norepinephrine–serotonin modulator	Nefazodone	Mirtazapine
		Trazodone	Vilazodone
Antipsychotic	Atypical antipsychotics	Aripiprazole	Quetiapine
		Clozapine	Risperidone
		Olanzapine	Ziprasidone
		Paliperidone	
Mood stabilizer	–	Lithium	
	Anticonvulsant	Carbamazepine	Oxcarbazepine
		Valproate	Pregabalin
		Gabapentin	Tiagabine
		Lamotrigine	Topiramate

		Levetiracetam	
Stimulant		Amphetamine	Methylphenidate
		Dextroamphetamine	Modafinil
		Methamphetamine	Mazindol

MAO-I, monoamine oxidase inhibitor; SNRI, selective norepinephrine reuptake inhibitor; SR, sustained-release; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; XL, extended-release.

Appendix Table 2

Baseline demographic characteristics

	Total (N=3,209)	Atypical antipsychotics (n=356)	Combination of antidepressants (n=2,420)	Mood stabilizers (n=266)	Stimulants (n=167)	p Value[a]
Males, %	30.2	32.3	29.9	23.3	40.7	.001
White, %	70.7	65.8	69.8	74.8	89.6	<.001
Age categories, %						<.001
18–30 y	22.7	24.2	22.3	15.4	37.1	
31–45 y	32.8	31.2	32.4	38.7	32.9	
46–64 y	34.5	34.0	34.9	38.0	25.1	
65+ y	9.9	10.7	10.4	7.9	4.8	
Site type, %						<.001
Academic center	54.1	40.2	56.1	47.0	65.9	
CMHC	32.7	43.3	30.3	40.6	31.7	
Regional hospital	13.2	16.6	13.6	12.4	2.4	

Index year, %						.051
2001	4.1	1.4	4.5	4.1	4.2	
2002	5.8	4.5	6.0	6.4	3.6	
2003	6.0	3.9	6.6	5.3	4.2	
2004	4.9	2.5	5.2	6.0	3.0	
2005	3.6	3.4	3.7	4.5	1.8	
2006	6.5	6.7	6.7	3.0	7.8	
2007	8.8	8.1	8.8	10.2	9.0	
2008	11.3	10.7	11.2	12.0	13.2	
2009	16.3	18.0	16.2	14.7	16.8	
2010	20.4	26.7	19.5	19.9	21.6	
2011	12.2	14.0	11.6	13.9	15.0	

[a] Chi-squared bivariate analysis and analysis of variance. CMHC, community mental health care center.

Appendix Table 3

Baseline clinical characteristics

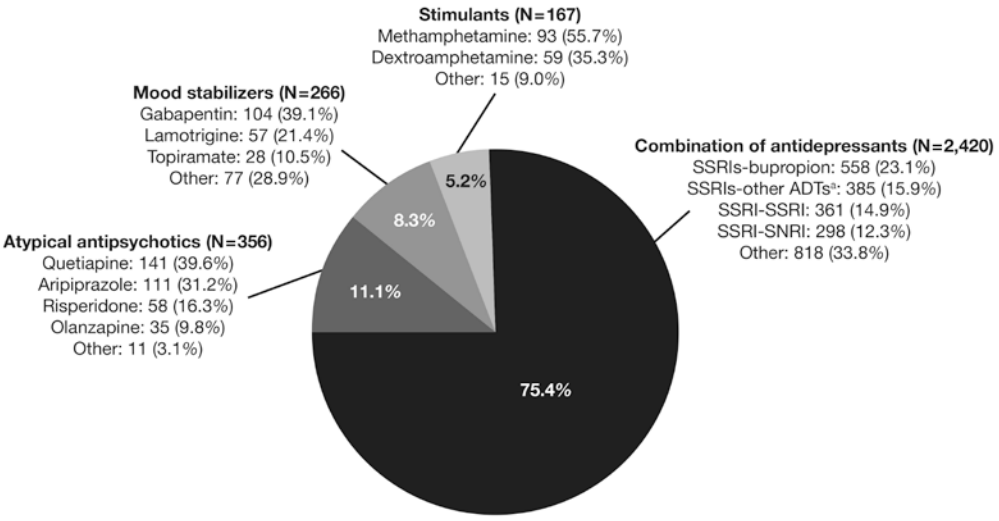
	Total (N=3,209)	Atypical antipsychotics (n=356)	Combination of antidepressants (n=2,420)	Mood stabilizers (n=266)	Stimulants (n=167)	p Value[a]
Type of depression diagnosis, %						
MDD-naive	15.9	14.0	16.6	13.9	12.6	.261
MDD-recurrent	58.5	64.9	58.0	53.8	58.7	.034
MDD-NOS	15.1	14.0	14.5	21.1	15.6	.039
Dysthymia	10.6	7.0	10.9	11.3	13.2	.098
CGI-S, %						<.001
Mild/moderate (2–3)	25.0	13.0	26.5	22.8	33.6	
Moderate (4)	47.9	46.2	48.2	50.2	44.3	
Severe (5–7)	27.0	40.8	25.3	27.0	22.1	
Other DSM diagnosis, %						
Adjustment disorder	6.3	10.1	5.8	6.8	4.8	.016

Anxiety disorder	47.8	48.3	47.9	48.1	44.9	.891
Eating disorders	2.5	0.8	2.7	2.6	2.4	.207
Personality disorders	11.7	17.1	10.6	16.2	10.2	<.001
Somatic disorders	2.0	3.7	1.4	5.3	1.8	<.001
Substance abuse disorders	17.6	21.1	17.3	17.7	15.0	.270
Benzodiazepines use before the index date, %	35.8	41.6	34.5	43.6	31.1	.001
Medical comorbidities, %						
Diabetes	8.3	7	8.5	11.3	3.6	.031
Hypertension	19.5	22.2	20.1	18.4	7.2	<.001
Lipid disorders	10.0	8.1	10.7	9.8	4.2	.030
Obesity	7.4	7.3	7.4	7.5	7.2	.999

[a] Chi-squared bivariate analysis and analysis of variance. CGI-S, Clinical Global Impressions – Severity; DSM, Diagnostic and Statistical Manual; MDD, major depressive disorder; NOS, not otherwise specified. Only conditions with a prevalence of ≥2% are reported in the table.

Appendix Figure 1

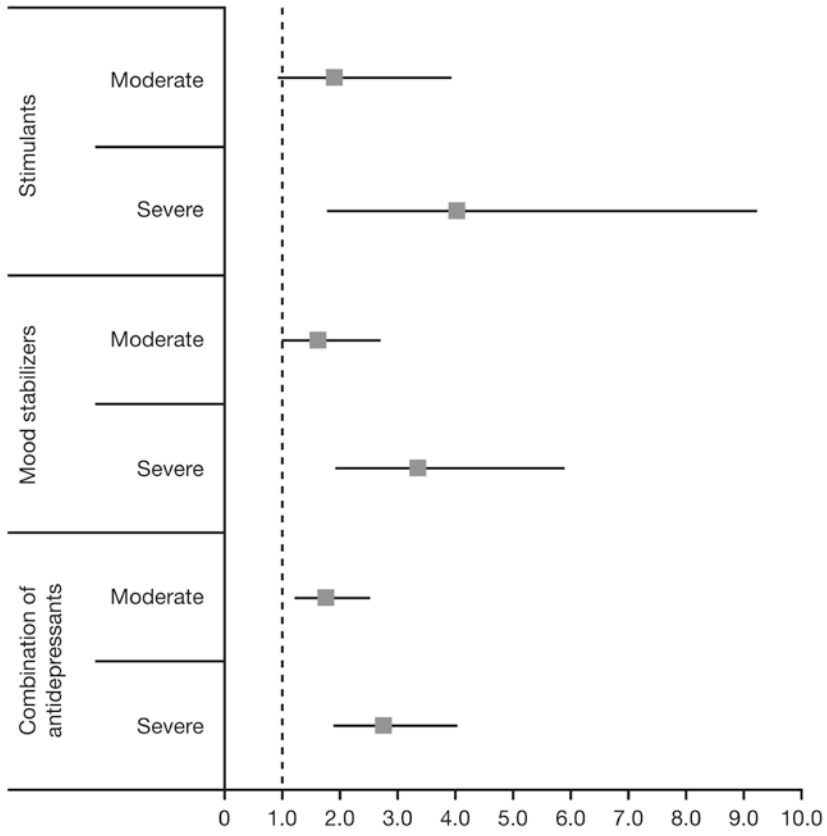
Augmentation agents used for the treatment of major depressive disorder (N=3,209)



ADT, antidepressant treatment (nefazodone, trazodone, mirtazapine, and vilazodone); SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Appendix Figure 2

Logistic regression analysis showing predictors of atypical antipsychotic augmentation treatment compared with other agents based on baseline CGI-S score. A mild CGI-S score was used as reference.



CGI-S, Clinical Global Impressions – Severity.