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Supplementary Material

Article Title: Direct and Indirect Cost Burden and Change of Employment Status in Treatment-Resistant Depression: A Matched-Cohort Study Using a US Commercial Claims Database

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Supplementary eTable 1. List of antidepressant medications by class

Antidepressant medication	Minimum daily adequate dose¹
SSRIs	
Citalopram	20 mg
Escitalopram	10 mg
Fluoxetine	20 mg
Fluvoxamine ²	50 mg
Fluvoxamine, continuous release ²	100 mg
Paroxetine	20 mg
Paroxetine, extended release	12.5 mg
Sertraline	50 mg
NDRI	
Bupropion	150 mg
SNRIs	
Desvenlafaxine	50 mg
Duloxetine	60 mg
Levomilnacipran ²	20 mg
Milnacipran ²	12.5 mg
Venlafaxine	37.5 mg
Serotonin modulators	
Nefazodone	50 mg
Trazodone	150 mg
Vilazodone ²	10 mg
Vortioxetine ²	10 mg

Norepinephrine-serotonin modulator	
Mirtazapine	15 mg
Tricyclics and tetracyclics	
Amitriptyline	25 mg
Amoxapine ²	50 mg
Clomipramine ²	25 mg
Desipramine	25 mg
Doxepin	25 mg
Imipramine	25 mg
Maprotiline	75 mg
Nortriptyline	25 mg
Protriptyline	10 mg
Trimipramine	25 mg
MAOIs	
Isocarboxazid	10 mg
Phenelzine	15 mg
Selegiline transdermal	6 mg
Tranlycypromine	10 mg
Other selected medication³	
Olanzapine-fluoxetine	25 mg

MAOIs = monoamine oxidase inhibitors; NDRI = norepinephrine-dopamine reuptake inhibitors; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

1. Starting doses were based on the recommended starting dose indicated in the American Psychiatric Association (APA) Practice Guidelines for Treatment of Patients with Major Depressive Disorder, 3rd edition, 2010 (https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf).

2. Starting doses for other antidepressant medications not included in the APA Practice Guidelines for Treatment of Patients with Major Depressive Disorder were based on the starting doses indicated in the label (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>).
3. Other selected medications include antidepressant-antipsychotic combination treatments indicated for treatment-resistant depression.

Supplementary eTable 2. List of augmentation medications by class

Augmentation medication
Anxiolytic medication
Buspirone
Anticonvulsant medication
Carbamazepine
Gabapentin
Lamotrigine
Phenytoin
Tiagabine
Topiramate
Valproate
Antipsychotic medication (i.e., second-generation or atypical)
Aripiprazole
Olanzapine
Paliperidone
Quetiapine
Risperidone
Ziprasidone
Lithium medication
Lithium
Psychostimulant medication
Dextroamphetamine ¹
Methamphetamine

Methylphenidate
Modafinil
Pemoline
Thyroid hormone (T3) medication
Liothyronine

1. A combination of amphetamine-dextroamphetamine was also included.

Supplementary eTable 3. Treatment patterns evaluated during follow-up

	TRD cohort	Non-TRD MDD control cohort		Non-MDD control cohort	
	N= 6,411	N= 6,411	P-value	N= 6,411	P-value
Antidepressant medication use, n (%)	6,411 (100.0)	6,411 (100.0)	---	855 (13.3)	---
SSRIs	5,586 (87.1)	5,029 (78.4)	<0.001*	574 (9.0)	<0.001*
NDRIs	3,370 (52.6)	1,477 (23.0)	<0.001*	125 (1.9)	<0.001*
SNRIs	3,109 (48.5)	1,324 (20.7)	<0.001*	145 (2.3)	<0.001*
Serotonin modulators	2,554 (39.8)	966 (15.1)	<0.001*	66 (1.0)	<0.001*
Tricyclics and tetracyclics	1,119 (17.5)	351 (5.5)	<0.001*	95 (1.5)	<0.001*
Norepinephrine-serotonin modulators	887 (13.8)	230 (3.6)	<0.001*	10 (0.2)	<0.001*
Other (i.e., olanzapine-fluoxetine)	24 (0.4)	4 (0.1)	<0.001*	0 (0.0)	<0.001*
MAOIs	15 (0.2)	6 (0.1)	0.050*	0 (0.0)	<0.001*
Duration of antidepressant therapy¹, mean ± SD [median]	235.0 ± 218.1 [156]	170.5 ± 176.7 [91]	<0.001*	22.1 ± 85.6 [0]	<0.001*
Number of unique antidepressant agents received², mean ± SD [median]	3.3 ± 1.2 [3]	1.7 ± 0.9 [1]	<0.001*	0.2 ± 0.5 [0]	<0.001*
Other mental health-related medication use, n (%)	5,826 (90.9)	3,707 (57.8)	<0.001*	949 (14.8)	<0.001*
Anxiolytics	4,406 (68.7)	3,008 (46.9)	<0.001*	663 (10.3)	<0.001*
Anticonvulsants/mood stabilizers ³	2,388 (37.2)	707 (11.0)	<0.001*	222 (3.5)	<0.001*
Antipsychotics	1,994 (31.1)	470 (7.3)	<0.001*	16 (0.2)	<0.001*
Atypical	1,969 (30.7)	458 (7.1)	<0.001*	16 (0.2)	<0.001*
Typical	57 (0.9)	17 (0.3)	<0.001*	0 (0.0)	<0.001*
Psychostimulants	1,716 (26.8)	652 (10.2)	<0.001*	160 (2.5)	<0.001*
Thyroid hormone (T3)	125 (1.9)	27 (0.4)	<0.001*	15 (0.2)	<0.001*
Lithium	122 (1.9)	21 (0.3)	<0.001*	0 (0.0)	<0.001*
Number of unique mental health-related agents received⁴, mean ± SD [median]	5.7 ± 2.2 [5]	2.7 ± 1.6 [2]	<0.001*	0.4 ± 0.8 [0]	<0.001*
Non-pharmacological therapy, n (%)	2,695 (42.0)	1,993 (31.1)	<0.001*	130 (2.0)	<0.001*
Psychotherapy	2,686 (41.9)	1,993 (31.1)	<0.001*	130 (2.0)	<0.001*

ECT

17 (0.3)

1 (0.0)

<0.001*

0 (0.0)

<0.001*

ECT = electroconvulsive therapy; MAOIs = monoamine oxidase inhibitors; MDD = major depressive disorder; NDRIs = norepinephrine-dopamine reuptake inhibitors; SD = standard deviation; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TRD = treatment-resistant depression.

* Significant at the 5% level using Wilcoxon signed-rank tests for continuous variables and McNemar tests for categorical variables.

Notes:

[1] Agents were grouped according to the generic name.

[2] Duration of antidepressant therapy was defined as the number of days with medication available between the first antidepressant claim (i.e., index date) and the last day of supply of antidepressant with no gaps longer than 14 days (gaps were not included in the duration of therapy).

[3] Excludes lithium.

[4] Includes antidepressants as well as anxiolytics, anticonvulsants/mood stabilizers, antipsychotics, psychostimulants, thyroid hormone (T3), and lithium.

Supplementary eTable 4. Comparison of healthcare resource utilization by component among all TRD patients and matched control cohorts, measured from the index date up to 2 years post-index date

HRU per patient per year (PPPY)	TRD cohort (N=6,411)	Non-TRD MDD control cohort (N=6,411)		Non-MDD control cohort (N=6,411)	
		N events/PY	Unadjusted IRR (95%CI) ¹ ; P-value	Adjusted IRR (95%CI) ² ; P-value	Unadjusted IRR (95%CI) ¹ ; P-value
All-cause					
Inpatient visits	0.38	1.85 (1.69 - 2.03); <0.001*	1.96 (1.79 - 2.14); <0.001*	5.24 (4.72 - 5.82); <0.001*	4.71 (4.24 - 5.22); <0.001*
Number of days	1.76	2.18 (1.92 - 2.46); <0.001*	2.34 (2.08 - 2.64); <0.001*	6.30 (5.52 - 7.18); <0.001*	5.80 (5.10 - 6.60); <0.001*
ED visits	1.01	1.50 (1.42 - 1.59); <0.001*	1.47 (1.39 - 1.56); <0.001*	3.13 (2.94 - 3.34); <0.001*	2.94 (2.76 - 3.14); <0.001*
Outpatient visits	25.22	1.46 (1.42 - 1.49); <0.001*	1.44 (1.41 - 1.48); <0.001*	3.67 (3.55 - 3.79); <0.001*	3.57 (3.46 - 3.68); <0.001*
Other visits	3.16	1.58 (1.48 - 1.68); <0.001*	1.52 (1.44 - 1.62); <0.001*	3.03 (2.84 - 3.24); <0.001*	2.74 (2.57 - 2.91); <0.001*
Mental health-related³					
Inpatient visits	0.21	2.77 (2.43 - 3.15); <0.001*	2.71 (2.39 - 3.09); <0.001*	58.15 (41.77 - 80.95); <0.001*	54.28 (38.97 - 75.61); <0.001*
Number of days	1.10	3.08 (2.58 - 3.68); <0.001*	3.10 (2.60 - 3.70); <0.001*	68.24 (54.53 - 85.40); <0.001*	66.62 (53.00 - 83.75); <0.001*
ED visits	0.20	2.10 (1.88 - 2.34); <0.001*	2.08 (1.86 - 2.32); <0.001*	21.97 (17.64 - 27.37); <0.001*	21.32 (17.10 - 26.57); <0.001*
Outpatient visits	12.96	1.65 (1.59 - 1.71); <0.001*	1.65 (1.59 - 1.71); <0.001*	25.87 (24.53 - 27.29); <0.001*	25.78 (24.44 - 27.19); <0.001*
Other visits	0.66	2.44 (2.12 - 2.82); <0.001*	2.39 (2.07 - 2.75); <0.001*	22.50 (18.82 - 26.89); <0.001*	21.12 (17.63 - 25.29); <0.001*
Depression-related⁴					
Inpatient visits	0.14	2.91 (2.52 - 3.35); <0.001*	2.84 (2.46 - 3.27); <0.001*	100.93 (60.11 - 169.45); <0.001*	94.03 (55.96 - 158.00); <0.001*
Number of days	0.75	3.35 (2.74 - 4.09); <0.001*	3.42 (2.80 - 4.17); <0.001*	515.90 (310.60 - 856.91); <0.001*	475.76 (285.18 - 793.71); <0.001*
ED visits	0.10	2.31 (2.01 - 2.66); <0.001*	2.30 (1.99 - 2.64); <0.001*	169.46 (75.61 - 379.80); <0.001*	165.66 (73.90 - 371.35); <0.001*
Outpatient visits	8.58	1.58 (1.52 - 1.65); <0.001*	1.59 (1.53 - 1.65); <0.001*	66.76 (62.40 - 71.42); <0.001*	67.06 (62.67 - 71.76); <0.001*
Other visits	0.26	2.40 (2.04 - 2.82); <0.001*	2.38 (2.02 - 2.80); <0.001*	25.87 (20.20 - 33.13); <0.001*	24.81 (19.36 - 31.79); <0.001*
Suicide-related⁵					
Suicide-related visits (any type)	0.0593	2.82 (2.26 - 3.52); <0.001*	2.76 (2.38 - 3.21); <0.001*	--	--
Inpatient visits	0.0220	3.91 (2.90 - 5.26); <0.001*	3.89 (2.89 - 5.23); <0.001*	--	--
Number of days	0.1430	3.61 (2.35 - 5.53); <0.001*	4.43 (2.89 - 6.80); <0.001*	--	--
ED visits	0.0230	2.60 (2.01 - 3.37); <0.001*	2.61 (2.01 - 3.37); <0.001*	--	--
Outpatient visits	0.0076	2.56 (1.62 - 4.06); <0.001*	2.58 (1.63 - 4.10); <0.001*	--	--
Other visits	0.0066	1.88 (1.10 - 3.22); 0.021*	1.86 (1.08 - 3.19); 0.025*	--	--

CI = confidence interval; ED = emergency department; HRU = healthcare resource utilization; IRR = incidence rate ratio; PY = person-years; TRD = treatment-resistant depression.

* Significant at the 5% level

Notes:

[1] IRRs, 95% CIs, and p-values were estimated using a generalized linear model (GLM) with a negative binomial or a Poisson distribution based on the results of the overdispersion test.

[2] Adjusted IRRs were adjusted for baseline Quan-Charlson comorbidity index and total healthcare costs.

[3] Mental health-related HRU were identified using the following ICD-9 CM diagnostic codes: 290.xx – 319.xx.

[4] Depression-related HRU were identified using the following ICD-9 CM diagnostic codes: 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, 311.xx.

[5] Suicide-related HRU were identified using the following ICD-9 CM diagnostic codes: E95x, V62.84.

Supplementary eTable 5. Comparison of direct costs by component among all TRD patients and matched control cohorts, measured from the index date up to 2 years post-index date

Healthcare cost (US \$2015) per patient per year (PPPY)	TRD cohort (N=6,411)	Non-TRD MDD control cohort (N=6,411)		Non-MDD control cohort (N=6,411)	
	Mean ± SD [median]	Unadjusted cost difference ¹ (95% CI); P-value	Adjusted cost difference ² (95% CI); P-value	Unadjusted cost difference ¹ (95% CI); P-value	Adjusted cost difference ² (95% CI); P-value
All-cause pharmacy and medical costs	17,261 ± 34,546 [7,609]	7,471 (6,437 ; 8,461) <0.001*	6,709 (5,703 ; 7,663) <0.001*	12,479 (11,516 ; 13,387) <0.001*	9,917 (8,985 ; 10,711) <0.001*
All-cause pharmacy costs	3,466 ± 7,802 [1,655]	1,648 (1,426 ; 1,890) <0.001*	1,537 (1,317 ; 1,767) <0.001*	2,536 (2,311 ; 2,770) <0.001*	2,120 (1,881 ; 2,324) <0.001*
All-cause medical costs	13,795 ± 32,492 [4,782]	5,823 (4,845 ; 6,834) <0.001*	5,172 (4,211 ; 6,143) <0.001*	9,943 (9,080 ; 10,799) <0.001*	7,797 (6,887 ; 8,561) <0.001*
Inpatient costs	4,475 ± 22,622 [0]	2,016 (1,332 ; 2,733) <0.001*	1,737 (1,047 ; 2,462) <0.001*	3,290 (2,643 ; 3,932) <0.001*	2,570 (1,997 ; 3,161) <0.001*
ED costs	1,032 ± 3,126 [62]	470 (381 ; 563) <0.001*	443 (351 ; 532) <0.001*	795 (710 ; 875) <0.001*	697 (608 ; 779) <0.001*
Outpatient costs	7,210 ± 15,100 [3,215]	2,757 (2,268 ; 3,241) <0.001*	2,472 (2,008 ; 2,888) <0.001*	5,046 (4,657 ; 5,445) <0.001*	3,985 (3,555 ; 4,357) <0.001*
Other costs	1,079 ± 4,951 [46]	581 (420 ; 743) <0.001*	520 (342 ; 672) <0.001*	812 (642 ; 966) <0.001*	544 (289 ; 725) <0.001*
Mental health-related pharmacy and medical costs	5,325 ± 18,043 [1,518]	3,306 (2,833 ; 3,798) <0.001*	3,212 (2,695 ; 3,698) <0.001*	5,129 (4,664 ; 5,618) <0.001*	4,908 (4,473 ; 5,364) <0.001*
Psychiatric pharmacy costs³	606 ± 1,613 [48]	480 (438 ; 525) <0.001*	479 (437 ; 524) <0.001*	583 (542 ; 625) <0.001*	577 (535 ; 617) <0.001*
Mental health-related medical costs⁴	4,719 ± 17,946 [1,017]	2,826 (2,366 ; 3,325) <0.001*	2,733 (2,235 ; 3,209) <0.001*	4,546 (4,090 ; 5,062) <0.001*	4,330 (3,883 ; 4,785) <0.001*
Inpatient costs	1,743 ± 13,727 [0]	1,100 (747 ; 1,475) <0.001*	1,021 (614 ; 1,372) <0.001*	1,706 (1,375 ; 2,097) <0.001*	1,564 (1,243 ; 1,955) <0.001*
ED costs	240 ± 985 [0]	134 (109 ; 164) <0.001*	132 (107 ; 162) <0.001*	228 (204 ; 253) <0.001*	218 (196 ; 243) <0.001*
Outpatient costs	2,166 ± 8,008 [750]	1,191 (1,011 ; 1,432) <0.001*	1,182 (1,003 ; 1,417) <0.001*	2,055 (1,838 ; 2,271) <0.001*	1,998 (1,793 ; 2,176) <0.001*
Other costs	570 ± 3,786 [0]	400 (303 ; 509) <0.001*	399 (300 ; 507) <0.001*	558 (466 ; 647) <0.001*	549 (455 ; 644) <0.001*
Depression-related pharmacy and medical costs	3,267 ± 13,176 [1,211]	1,920 (1,583 ; 2,288) <0.001*	1,850 (1,483 ; 2,210) <0.001*	3,198 (2,906 ; 3,604) <0.001*	3,063 (2,777 ; 3,452) <0.001*
Antidepressant pharmacy costs	612 ± 873 [298]	315 (292 ; 339) <0.001*	315 (290 ; 338) <0.001*	572 (547 ; 595) <0.001*	569 (542 ; 591) <0.001*
Depression-related medical costs⁵	2,655 ± 13,140 [540]	1,605 (1,264 ; 1,982) <0.001*	1,535 (1,175 ; 1,926) <0.001*	2,625 (2,331 ; 3,018) <0.001*	2,494 (2,200 ; 2,882) <0.001*
Inpatient visits	1,214 ± 12,458 [0]	828 (513 ; 1,183) <0.001*	767 (414 ; 1,137) <0.001*	1,213 (968 ; 1,617) <0.001*	1,125 (878 ; 1,516) <0.001*
ED visits	113 ± 540 [0]	67 (53 ; 82) <0.001*	66 (52 ; 81) <0.001*	112 (100 ; 127) <0.001*	107 (94 ; 120) <0.001*
Outpatient costs	1,125 ± 2,542 [420]	554 (487 ; 623) <0.001*	549 (483 ; 616) <0.001*	1,098 (1,029 ; 1,163) <0.001*	1,070 (986 ; 1,140) <0.001*
Other costs	204 ± 1,545 [0]	155 (115 ; 196) <0.001*	153 (113 ; 191) <0.001*	202 (168 ; 242) <0.001*	193 (159 ; 228) <0.001*
Suicide-related medical costs⁶	266 ± 1,806 [0]	199 (154 ; 247) <0.001*	196 (152 ; 244) <0.001*	266 (223 ; 310) <0.001*	254 (207 ; 299) <0.001*
Inpatient visits	191 ± 1,619 [0]	149 (106 ; 194) <0.001*	146 (103 ; 191) <0.001*	191 (154 ; 227) <0.001*	181 (142 ; 219) <0.001*
ED visits	42 ± 321 [0]	26 (17 ; 36) <0.001*	26 (17 ; 36) <0.001*	42 (35 ; 50) <0.001*	41 (34 ; 49) <0.001*

Outpatient costs	5 ± 114 [0]	3 (-1 ; 7) 0.092	3 (-1 ; 7) 0.108	5 (3 ; 9) <0.001*	5 (3 ; 8) <0.001*
Other costs	28 ± 396 [0]	21 (10 ; 32) <0.001*	21 (10 ; 32) <0.001*	28 (19 ; 38) <0.001*	27 (19 ; 37) <0.001*

CI = confidence interval; ED = emergency department; SD = standard deviation; TRD = treatment-resistant depression.

* Significant at the 5% level

Notes:

[1] Unadjusted cost differences were estimated using an ordinary least squares regression model and 95% CIs and p-values were estimated using a non-parametric bootstrap procedure (N=499).

[2] Adjusted cost differences were estimated using an ordinary least squares regression model adjusted for baseline Quan-Charlson comorbidity index and total healthcare costs; 95% CIs and p-values were estimated using a non-parametric bootstrap procedure (N=499).

[3] Psychiatric pharmacy costs include the following classes of agents (generic product identifier [GPI] prefix): anxiolytics ('57'), antipsychotics/antimanics ('59'), anticonvulsants ('7299', '721', '726'), and other mood stabilizers (e.g., lithium).

[4] Mental health-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: 290.xx – 319.xx.

[5] Depression-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, 311.xx.

[6] Suicide-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: E95x, V62.84.

Supplementary eTable 6. Healthcare costs among TRD patients¹ measured from the TRD start date to 2 years post-TRD, stratified by number of antidepressant/augmentation lines of therapy of adequate dose and duration²

Healthcare cost (US \$2015) PPPY, mean ± SD [median]	Stratifications by number of lines of therapy of adequate dose and duration ²					
	<u>Overall TRD cohort</u>	2 lines	3 lines	4 lines	5 lines	≥6 lines
	N=6,411	N= 438	N= 1,041	N= 1,215	N= 1,061	N= 2,656
All-cause pharmacy and medical costs	17,261 ± 34,546 [7,609]	12,047 ± 25,421 [4,430]	14,699 ± 53,630 [5,181]	15,073 ± 35,933 [5,272]	16,699 ± 45,862 [5,988]	18,667 ± 41,486 [8,177]
All-cause pharmacy costs	3,466 ± 7,802 [1,655]	2,678 ± 7,056 [850]	3,033 ± 9,590 [990]	3,167 ± 7,986 [1,323]	3,470 ± 10,746 [1,434]	4,894 ± 10,466 [2,334]
All-cause medical costs	13,795 ± 32,492 [4,782]	9,370 ± 24,009 [2,556]	11,666 ± 52,481 [2,925]	11,906 ± 33,723 [3,073]	13,229 ± 43,841 [3,625]	13,773 ± 38,375 [4,374]
Inpatient costs	4,475 ± 22,622 [0]	2,047 ± 9,303 [0]	4,159 ± 48,454 [0]	3,696 ± 22,763 [0]	5,018 ± 36,584 [0]	4,182 ± 22,601 [0]
ED costs	1,032 ± 3,126 [62]	1,023 ± 4,860 [0]	949 ± 5,444 [0]	770 ± 2,725 [0]	791 ± 2,418 [0]	988 ± 3,924 [0]
Outpatient costs	7,210 ± 15,100 [3,215]	5,665 ± 16,111 [1,793]	5,709 ± 11,565 [2,161]	6,510 ± 17,604 [2,277]	6,702 ± 17,560 [2,756]	7,491 ± 20,314 [3,156]
Other costs	1,079 ± 4,951 [46]	635 ± 3,374 [0]	849 ± 6,712 [0]	930 ± 6,432 [0]	719 ± 3,467 [0]	1,110 ± 5,920 [36]
Mental health-related pharmacy and medical costs	5,325 ± 18,043 [1,518]	3,819 ± 13,535 [684]	3,761 ± 13,480 [798]	4,155 ± 17,030 [840]	5,653 ± 34,501 [938]	5,739 ± 22,023 [1,525]
Psychiatric pharmacy costs³	606 ± 1,613 [48]	516 ± 1,889 [8]	467 ± 1,810 [3]	490 ± 1,502 [10]	616 ± 2,292 [23]	1,111 ± 3,708 [130]
Mental health-related medical costs⁴	4,719 ± 17,946 [1,017]	3,303 ± 13,408 [429]	3,294 ± 13,295 [568]	3,665 ± 16,906 [565]	5,037 ± 34,302 [655]	4,627 ± 21,642 [808]
Inpatient costs	1,743 ± 13,727 [0]	706 ± 4,994 [0]	881 ± 5,284 [0]	1,070 ± 7,040 [0]	2,537 ± 32,768 [0]	1,437 ± 10,919 [0]
ED costs	240 ± 985 [0]	124 ± 870 [0]	252 ± 3,236 [0]	145 ± 1,307 [0]	160 ± 789 [0]	193 ± 1,044 [0]
Outpatient costs	2,166 ± 8,008 [750]	2,058 ± 8,136 [350]	1,707 ± 5,672 [448]	2,061 ± 12,572 [480]	1,972 ± 7,565 [533]	2,463 ± 15,584 [645]
Other costs	570 ± 3,786 [0]	415 ± 3,251 [0]	455 ± 6,187 [0]	390 ± 3,415 [0]	370 ± 3,107 [0]	535 ± 4,896 [0]
Depression-related pharmacy and medical costs	3,267 ± 13,176 [1,211]	1,728 ± 4,235 [447]	2,204 ± 8,356 [628]	2,108 ± 6,082 [795]	3,698 ± 32,270 [897]	3,171 ± 10,235 [1,200]
Antidepressant pharmacy costs	612 ± 873 [298]	358 ± 1,090 [53]	498 ± 1,054 [127]	559 ± 921 [181]	617 ± 1,433 [211]	759 ± 1,148 [350]
Depression-related medical costs⁵	2,655 ± 13,140 [540]	1,370 ± 4,075 [187]	1,706 ± 8,132 [252]	1,549 ± 5,962 [306]	3,081 ± 32,261 [318]	2,412 ± 10,173 [447]
Inpatient visits	1,214 ± 12,458 [0]	238 ± 2,276 [0]	369 ± 3,274 [0]	534 ± 4,795 [0]	1,976 ± 32,084 [0]	1,026 ± 9,328 [0]

ED visits	113 ± 540 [0]	33 ± 250 [0]	187 ± 3,201 [0]	58 ± 509 [0]	84 ± 548 [0]	80 ± 550 [0]
Outpatient costs	1,125 ± 2,542 [420]	1,009 ± 2,578 [163]	989 ± 3,763 [229]	853 ± 2,156 [263]	905 ± 2,420 [267]	1,158 ± 3,217 [376]
Other costs	204 ± 1,545 [0]	90 ± 1,241 [0]	161 ± 2,747 [0]	104 ± 1,459 [0]	117 ± 1,559 [0]	149 ± 1,075 [0]

CI = confidence interval; ED = emergency department; SD = standard deviation; TRD = treatment-resistant depression

Notes:

[1] The TRD cohort was defined as MDD patients for whom 2 antidepressant treatment courses (including augmentation therapy with anticonvulsant, anxiolytic, antipsychotic, lithium, psychostimulant, and thyroid hormone medications; see Supplementary eTables 1 and 2 at Psychiatrist.com for lists of antidepressant and augmentation medications, respectively) with adequate dose and duration failed to improve their depression. Failure of a treatment course was defined as a switch of antidepressant (no more than 180 days after the end of the previous treatment), the addition of an antidepressant, or the initiation of an augmentation therapy. The initiation of the third antidepressant or augmentation medication defined TRD.

[2] Adequate dose was defined as the minimum starting dose recommended by the American Psychiatric Association treatment guidelines. Adequate duration was defined as at least 6 weeks of continuous therapy with no gaps longer than 14 days.

[3] Psychiatric pharmacy costs include the following classes of agents: anxiolytics, antipsychotics/antimanics, anticonvulsants, and other mood stabilizers (e.g., lithium).

[4] Mental health-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: 290.xx – 319.xx.

[5] Depression-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, 311.xx.

Supplementary eTable 7. Comparison of indirect work loss-related resource utilization by component among all TRD patients and matched control cohorts, measured from the index date up to 2 years post-index date

Resource use PPPY	TRD cohort (N=1,908)	Non-TRD MDD control cohort (N=1,908)		Non-MDD control cohort (N=1,908)	
	N events/PY	Unadjusted IRR (95%CI) ¹ ; P-value	Adjusted IRR (95%CI) ² ; P-value	Unadjusted IRR (95%CI) ¹ ; P-value	Adjusted IRR (95%CI) ² ; P-value
All-cause					
Total work loss days	35.77	1.72 (1.55 - 1.90); <0.001*	1.74 (1.57 - 1.93); <0.001*	6.02 (5.26 - 6.90); <0.001*	6.16 (5.38 - 7.04); <0.001*
Medical-related absenteeism days ⁴	10.02	1.49 (1.35 - 1.64); <0.001*	1.47 (1.34 - 1.62); <0.001*	4.71 (4.16 - 5.34); <0.001*	4.74 (4.19 - 5.36); <0.001*
Inpatient-related days	0.25	1.34 (0.70 - 2.57); 0.381	2.02 (1.06 - 3.85); 0.034*	9.21 (4.38 - 19.38); <0.001*	9.22 (4.32 - 19.65); <0.001*
ED-related days	0.11	1.53 (1.08 - 2.16); 0.016*	1.53 (1.08 - 2.17); 0.016*	3.13 (2.06 - 4.76); <0.001*	3.17 (2.08 - 4.82); <0.001*
Outpatient days	7.34	1.50 (1.35 - 1.68); <0.001*	1.50 (1.35 - 1.68); <0.001*	4.57 (3.98 - 5.26); <0.001*	4.64 (4.04 - 5.33); <0.001*
Other days	2.32	1.44 (1.12 - 1.87); 0.005*	1.37 (1.06 - 1.77); 0.017*	4.99 (3.74 - 6.65); <0.001*	4.86 (3.66 - 6.47); <0.001*
Disability days	25.75	1.82 (1.39 - 2.38); <0.001*	1.87 (1.43 - 2.44); <0.001*	6.69 (4.95 - 9.05); <0.001*	6.92 (5.13 - 9.35); <0.001*
Mental health-related⁴					
Total work loss days	17.61	2.23 (1.95 - 2.56); <0.001*	2.23 (1.94 - 2.55); <0.001*	82.01 (69.93 - 96.18); <0.001*	82.54 (70.35 - 96.84); <0.001*
Medical-related absenteeism days ³	4.83	1.62 (1.43 - 1.84); <0.001*	1.62 (1.43 - 1.84); <0.001*	28.05 (24.12 - 32.62); <0.001*	27.96 (24.04 - 32.52); <0.001*
Inpatient-related days	0.20	3.06 (1.37 - 6.85); 0.006*	3.06 (1.37 - 6.84); 0.007*	34.79 (13.96 - 86.68); <0.001*	57.92 (20.21 - 165.96); <0.001*
ED-related days	0.01	2.82 (0.98 - 8.16); 0.056	2.76 (0.95 - 8.04); 0.062	--	--
Outpatient days	3.68	1.63 (1.42 - 1.87); <0.001*	1.63 (1.42 - 1.87); <0.001*	23.79 (20.13 - 28.10); <0.001*	23.75 (20.10 - 28.07); <0.001*
Other days	0.95	1.44 (0.94 - 2.20); 0.095	1.43 (0.93 - 2.19); 0.103	69.63 (42.18 - 114.96); <0.001*	69.60 (42.06 - 115.17); <0.001*
Disability days	12.78	2.56 (1.74 - 3.75); <0.001*	2.58 (1.76 - 3.78); <0.001*	236.18 (156.66 - 356.06); <0.001*	273.29 (177.88 - 419.89); <0.001*
Depression-related⁵					
Total work loss days	12.08	2.22 (1.90 - 2.60); <0.001*	2.22 (1.90 - 2.60); <0.001*	151.54 (124.75 - 184.08); <0.001*	153.14 (125.99 - 186.15); <0.001*
Medical-related absenteeism days ³	3.42	1.59 (1.39 - 1.83); <0.001*	1.59 (1.39 - 1.83); <0.001*	64.72 (53.19 - 78.74); <0.001*	65.23 (53.57 - 79.44); <0.001*
Inpatient-related days	0.16	3.16 (1.30 - 7.65); 0.011*	3.20 (1.32 - 7.76); 0.010*	39.81 (14.30 - 110.86); <0.001*	158.02 (32.46 - 769.31); <0.001*
ED-related days	0.00	2.01 (0.48 - 8.45); 0.339	2.00 (0.48 - 8.33); 0.341	--	--
Outpatient days	2.57	1.62 (1.40 - 1.89); <0.001*	1.62 (1.40 - 1.89); <0.001*	55.34 (44.75 - 68.44); <0.001*	56.05 (45.28 - 69.37); <0.001*
Other days	0.69	1.34 (0.84 - 2.15); 0.222	1.33 (0.83 - 2.13); 0.241	259.64 (118.37 - 569.53); <0.001*	258.60 (117.45 - 569.39); <0.001*
Disability days	8.66	2.60 (1.59 - 4.24); <0.001*	2.63 (1.61 - 4.29); <0.001*	255.96 (151.26 - 433.12); <0.001*	348.64 (194.25 - 625.75); <0.001*

Suicide-related⁶

Total work loss days	0.0276	2.82 (0.57 - 13.90); 0.203	2.47 (0.49 - 12.54); 0.274	--	--
Medical-related absenteeism days ³	0.0276	2.82 (0.57 - 13.90); 0.203	2.47 (0.49 - 12.54); 0.274	--	--
Inpatient-related days	0.0276	2.82 (0.57 - 13.90); 0.203	2.47 (0.49 - 12.54); 0.274	--	--
ED-related days	0.0000	--	--	--	--
Outpatient days	0.0000	--	--	--	--
Other days	0.0000	--	--	--	--
Disability days	0.0000	--	--	--	--

CI = confidence interval; ED = emergency department; HRU = healthcare resource utilization; IRR = incidence rate ratio; PY = patient-years; TRD = treatment-resistant depression.

* Significant at the 5% level

Notes:

[1] IRRs, 95% CIs, and p-values were estimated using a generalized linear model (GLM) with a negative binomial or a Poisson distribution based on the results of the overdispersion test.

[2] Adjusted IRRs were adjusted for baseline Quan-Charlson comorbidity index and total healthcare costs.

[3] The number of medical-related absenteeism days was imputed based on length of stay for inpatient visits or a half day each for ED, outpatient, and other visits.

[4] Mental health-related HRU were identified using the following ICD-9 CM diagnostic codes: 290.xx – 319.xx.

[5] Depression-related HRU were identified using the following ICD-9 CM diagnostic codes: 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, 311.xx.

[6] Suicide-related HRU were identified using the following ICD-9 CM diagnostic codes: E95x, V62.84.

Supplementary eTable 8. Comparison of indirect costs by component among all TRD patients and matched control cohorts, measured from the index date up to 2 years post-index date

Indirect cost (US \$2015) PPPY	TRD cohort (N=1,908)	Non-TRD MDD control cohort (N=1,908)		Non-MDD control cohort (N=1,908)	
	Mean ± SD [median]	Unadjusted cost difference (95% CI) ¹ ; P-value	Adjusted cost difference (95% CI) ² ; P-value	Unadjusted cost difference (95% CI) ¹ ; P-value	Adjusted cost difference (95% CI) ² ; P-value
All-cause					
Total work loss-related costs	4,576 ± 11,043 [1,094]	1,890 (1,278 ; 2,499); <0.001*	1,811 (1,168 ; 2,410); <0.001*	3,671 (3,193 ; 4,179); <0.001*	3,460 (2,996 ; 3,930); <0.001*
Medical-related absenteeism costs ³	831 ± 776 [653]	40 (-14 ; 91); 0.140	39 (-15 ; 88); 0.156	344 (301 ; 389); <0.001*	331 (287 ; 375); <0.001*
Inpatient-related costs	23 ± 105 [0]	5 (-2 ; 13); 0.112	5 (-2 ; 12); 0.136	15 (10 ; 21); <0.001*	13 (8 ; 19); <0.001*
ED-related costs	20 ± 55 [0]	0 (-4 ; 3); 0.922	0 (-4 ; 3); 0.962	4 (1 ; 7); 0.028	3 (0 ; 7); 0.048
Outpatient costs	638 ± 717 [477]	11 (-38 ; 56); 0.689	10 (-38 ; 56); 0.693	245 (199 ; 285); <0.001*	241 (195 ; 280); <0.001*
Other costs	150 ± 381 [0]	25 (3 ; 48); 0.024	23 (1 ; 47); 0.032	81 (60 ; 101); <0.001*	73 (52 ; 93); <0.001*
Disability costs	3,745 ± 11,089 [0]	1,850 (1,223 ; 2,465); <0.001*	1,773 (1,146 ; 2,363); <0.001*	3,326 (2,839 ; 3,818); <0.001*	3,129 (2,649 ; 3,609); <0.001*
Mental health-related⁴					
Total work loss-related costs	2,430 ± 8,167 [371]	1,444 (1,047 ; 1,863); <0.001*	1,442 (1,060 ; 1,843); <0.001*	2,398 (2,051 ; 2,790); <0.001*	2,415 (2,057 ; 2,808); <0.001*
Medical-related absenteeism costs ³	414 ± 557 [253]	56 (19 ; 92); <0.001*	57 (20 ; 94); <0.001*	388 (362 ; 413); <0.001*	392 (365 ; 416); <0.001*
Inpatient-related costs	17 ± 96 [0]	8 (3 ; 14); 0.004	8 (3 ; 14); 0.004	16 (12 ; 21); <0.001*	15 (11 ; 20); <0.001*
ED-related costs	4 ± 20 [0]	1 (0 ; 2); 0.076	1 (0 ; 2); 0.080	3 (2 ; 4); <0.001*	3 (2 ; 4); <0.001*
Outpatient costs	334 ± 525 [174]	33 (-3 ; 66); 0.080	34 (-2 ; 68); 0.064	311 (286 ; 334); <0.001*	315 (290 ; 338); <0.001*
Other costs	59 ± 212 [0]	14 (2 ; 27); 0.016	14 (2 ; 27); 0.012	57 (48 ; 67); <0.001*	58 (48 ; 67); <0.001*
Disability costs	2,016 ± 8,153 [0]	1,389 (1,001 ; 1,797); <0.001*	1,386 (1,005 ; 1,797); <0.001*	2,011 (1,652 ; 2,403); <0.001*	2,024 (1,675 ; 2,415); <0.001*
Depression-related⁵					
Total work loss-related costs	1,580 ± 6,788 [210]	892 (585 ; 1,233); <0.001*	887 (585 ; 1,237); <0.001*	1,570 (1,299 ; 1,922); <0.001*	1,570 (1,306 ; 1,906); <0.001*
Medical-related absenteeism costs ³	301 ± 472 [157]	41 (10 ; 70); 0.012	42 (11 ; 71); 0.008	294 (275 ; 314); <0.001*	298 (277 ; 318); <0.001*
Inpatient-related costs	13 ± 80 [0]	6 (1 ; 10); 0.020	6 (1 ; 10); 0.016	12 (9 ; 16); <0.001*	13 (9 ; 17); <0.001*
ED-related costs	2 ± 14 [0]	1 (0 ; 2); 0.004	1 (0 ; 2); 0.004	2 (2 ; 3); <0.001*	2 (2 ; 3); <0.001*
Outpatient costs	242 ± 439 [100]	25 (-4 ; 53); 0.104	26 (-4 ; 54); 0.092	236 (216 ; 254); <0.001*	239 (219 ; 257); <0.001*
Other costs	44 ± 183 [0]	9 (-2 ; 21); 0.104	9 (-2 ; 22); 0.104	44 (35 ; 52); <0.001*	44 (35 ; 52); <0.001*

Disability costs	1,280 ± 6,763 [0]	851 (548 ; 1,188); <0.001*	845 (546 ; 1,190); <0.001*	1,276 (1,002 ; 1,629); <0.001*	1,272 (1,009 ; 1,608); <0.001*
Suicide-related⁶					
Total work loss-related costs	4 ± 37 [0]	1 (-1 ; 4); 0.244	1 (-1 ; 4); 0.240	4 (2 ; 5); <0.001*	4 (2 ; 5); <0.001*
Medical-related absenteeism costs ³	4 ± 37 [0]	1 (-1 ; 4); 0.244	1 (-1 ; 4); 0.240	4 (2 ; 5); <0.001*	4 (2 ; 5); <0.001*
Inpatient-related costs	3 ± 36 [0]	1 (-1 ; 3); 0.273	1 (-1 ; 3); 0.273	3 (2 ; 5); <0.001*	3 (2 ; 5); <0.001*
ED-related costs	0 ± 4 [0]	0 (0 ; 0); 0.641	0 (0 ; 0); 0.637	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*
Outpatient costs	0 ± 0 [0]	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*
Other costs	0 ± 3 [0]	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*
Disability costs	0 ± 0 [0]	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*	0 (0 ; 0); <0.001*

CCI = Charlson comorbidity index; CI = confidence interval; ED = emergency department; SD = standard deviation; TRD = treatment-resistant depression.

* Significant at the 5% level

Notes:

[1] Unadjusted cost differences were estimated using an ordinary least squares regression model and 95% CIs and p-values were estimated using a non-parametric bootstrap procedure (N=499).

[2] Adjusted cost differences were estimated using an ordinary least squares regression model adjusted for baseline Quan-Charlson comorbidity index and total healthcare costs; 95% CIs and p-values were estimated using a non-parametric bootstrap procedure (N=499).

[3] The medical-related absenteeism costs were imputed based on the time absent from work related to full day wage equivalent for inpatient visits and a half day wage equivalent each for ED, outpatient, and other visits.

[4] Mental health-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: 290.xx – 319.xx.

[5] Depression-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, 311.xx.

[6] Suicide-related costs were defined as all costs during a visit with any of the following ICD-9 CM diagnostic codes: E95x, V62.84.