Young Adult Depression, Antidepressant Prescriptions, and Therapy Intensification in People With Incident Depression in the United States

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ABSTRACT

Objective: To evaluate the temporal trend in young adult depression, prescription patterns of first- and second-line antidepressants, and factors influencing therapy intensification for depression stratified by sex.

Methods: A retrospective cohort of people aged ≥ 18 years with incident depression between 2006 and 2017 was extracted from the Centricity Electronic Medical Records.

Results: Among 2,201,086 people with depression (82% on antidepressants), the mean age was 47 years, 29% were male, 40% had cardiometabolic multimorbidity, and 32% were diagnosed at age < 40 years (young adult depression). Prevalence of young adult depression increased significantly from 26% to 36% with a higher proportion in females compared to males (34% vs 26%) between 2006 and 2017. Selective serotonin reuptake inhibitors (SSRIs) were the most prescribed first-line antidepressant (56%), with a prescribing rate increase from 47 per 1,000 person-years to 81 per 1,000 person-years. Among first-line antidepressant recipients, 23% had treatment intensification after a median of 17 months. Compared to those aged 60–70 years, younger males and females had a similar significantly higher treatment intensification risk (range of hazard ratio [HR], 1.09–1.46). Cardiometabolic multimorbidity was associated with a 2% (HR CI, 1.01–1.05) and 7% (HR CI, 1.05–1.09) higher treatment intensification risk in males and females, respectively, while anxiety increased the treatment intensification risk by 63% (HR CI, 1.57–1.68) in males and 57% (HR CI, 1.52–1.62) in females. Non-Whites and SSRI initiators had lower risks of treatment intensification (all HR CI < 1).

Conclusions: More than one-third of US adults with depression are aged < 40 years with an increasing trend among females. The temporal antidepressant prescribing rates were similar between sex, while significant ethnic disparity in therapy intensification was observed between sex.

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The prevalence of depression has been increasing globally, with depressive disorders being one of the leading causes of nonfatal health loss over the last 3 decades.[1] The prevalence of depression among young adults has also been increasing in many countries, including the United States.[2–4] However, the empirical evidence on depression is inconsistent with a high level of heterogeneity due to varying study designs and definitions of the condition in different countries.[5] Globally, the prevalence of mental health disorders remains poorly understood and typically underestimated.[5,6]

National surveys from the United States have reported significantly higher and increasing prevalence of depression among young adults,[2,3,7] while the multimorbidity among this population is also increasing.[8,9] To understand the burden of depression and anxiety, the US National Institute of Mental Health's strategic plan calls for the use of electronic medical records (EMRs) to upscale mental health research.[10]

While increasing prevalence of mental illness coupled with multimorbidity and the associated challenges in therapeutic management has been discussed as one of the most challenging public health issues,[11,12] we are unaware of any study that evaluated the temporal trend in depression onset by age group and sex and the prevalence of cardiometabolic multimorbidity at the time of diagnosis of depression using nationally representative data from the United States.[13] There is also a paucity of large nationally representative data-based studies evaluating the population-based prescriptions of specific antidepressants targeting major depressive disorder (MDD), their changes over time, and the underlying factors driving these changes from the time of depression diagnosis. As practice guidelines in recent years have started to provide more specific recommendations regarding old- and new-generation antidepressant drug classes,[14,15] details of actual prescriptions of antidepressants in the real world could be very informative for clinicians and health policymakers in benchmarking their performance in depression treatment. While claims data were used to evaluate the therapy utilizations in previous studies,[16–18] large EMRs offer unparalleled opportunities to explore risk factors and comorbidities in people with depression to better understand the changing dynamics for successful disease management at the population level.[19] This study

Clinical Points

- More than one-third of US adults with depression are aged < 40 years, with significant increasing trend over the past decade.
- Approximately 1 in 2 adults treated for depression have suboptimal response after first-line antidepressants and would need some form of treatment intensification.
- Age at diagnosis, ethnicity, and cardiometabolic multimorbidity are the major sociodemographic and nonpsychiatric risk factors for antidepressant prescription changes among US adults diagnosed with depression.

addresses the unmet need for real-world evidence to inform the current global debate on the emerging challenges in the efficient management of mental health–related issues.

Using patient-level longitudinal data in people with incident depression from US nationally representative large EMRs, we sought to (1) evaluate the temporal trend in young adult depression, (2) explore the overall trend in antidepressant prescription rates, (3) explore the patterns of first- and second-line antidepressant prescriptions by drug class and generic drug, and (4) identify factors associated with changes to antidepressant prescription stratified by sex. We also compared estimated prevalence rates of depression from the EMRs with those reported in the US national surveys.

METHODS

Data

The Centricity Electronic Medical Records (CEMR) provides patient-level data from over 40,000 ambulatory and primary care medical practices based across all US states. The CEMR is generally representative of the US population with respect to demographics, major disease prevalence, and cardiometabolic risk factors reported in the US national health surveys[20] and has been extensively used for epidemiologic and public health studies.[21–23] The CEMR provides comprehensive longitudinal patient-level information on demographics, anthropometrics, clinical and laboratory measures, medication usage, and diseases. Prescription data include generic ingredients of both inpatient and outpatient medications with their respective prescription start and stop dates.

Cohort Identification

Using a clinically guided machine learning algorithm[24,25] with information from *ICD-CM* disease codes and antidepressant prescriptions for any mental illness, a cohort of people diagnosed with depression was identified (Supplementary Tables 1 and 2). The algorithm is described in the method section of the Supplementary Material and in Supplementary Figure 1. The study cohort of newly identified depression was formed with the following conditions: (1) known age and sex, (2) aged 18–70 years at the time of depression diagnosis by clinical code or prescription use, (3) starting from January 1, 2006, and (4) date of diagnosis at least 12 months after registering in the EMR. The date of depression diagnosis or first prescription date of an antidepressant was defined as the index date (Supplementary Figure 2).

Study Variables

Data on prescriptions, disease diagnoses, demographics, and clinical and laboratory measurements were extracted. A full description and the methodology for demographic, clinical, and medication variable extraction and assessment from the CEMR have been described.[26] Cardiometabolic multimorbidity was defined as having at least 2 cases of atherosclerosis cardiovascular diseases, heart failure, microvascular disease including chronic kidney disease, cancer, type 1 diabetes mellitus, type 2 diabetes mellitus, ≥ class 2 obesity (body mass index ≥ 35 kg/m^2), hypertension, and dyslipidemia. A disease was considered as prevalent at baseline if its first available diagnostic date was on or prior to the index date.

Time to Treatment Intensification

Among people receiving antidepressants and intensified by either adding or switching to a second-line antidepressant, time to treatment intensification was calculated as the number of years between the first prescription date and the first observed date with intensification. Those without intensification during follow-up were "censored," and the time to treatment intensification was calculated as the number of years between the index date and the study observation end date (end date included date of death or date the patient left practice or the last date of data collection). Patients who had dose titration within the same drug could not be identified because of nonavailability of complete data on doses for individual therapies.

Ethics Statement

According to the US Department of Health and Human Services Exemption 4 (CFR 46.101[b][4]), this study is exempt from ethics approval from an institutional review board and informed consent.

Statistical Methods

Baseline characteristics were summarized by number (%), mean (SD), or median (first quartile, third quartile) as appropriate. To establish clarity on the use of antidepressants with or without a clinical diagnosis code for depression, the study cohorts were divided into 3 groups: (1) individuals with a diagnosis code for depression and prescribed an antidepressant, (2) individuals with a diagnosis code for depression but not prescribed an antidepressant, and (3) individuals taking an antidepressant without a clinical diagnosis for depression. The age groups at the time of diagnosis of depression were categorized as 18–29, 30–39, 40–49, 50–59, and 60–70 years. Representativeness of the data was assessed by computing prevalence of depression and any mental illness using methods described elsewhere[27]

Table 1. Patient Characteristics at Baseline by Status of Incident Depression[a]

Variable	Depression With Antidepressant Prescription	Depression Clinical Code Only	Antidepressant Prescription Only	Total
Patients	931,503 (42)	261,881 (12)	1,007,702 (46)	2,201,086
Years of follow-up, median (Q1–Q3 range)	5.0 (2.5–7.6)	2.1 (0.4–5.1)	3.2 (1.3–6.1)	3.9 (1.5–6.7)
Male	249,007 (27)	81,965 (31)	303,499 (30)	634,471 (29)
Age, mean (SD), y	45 (15)	44 (15)	50 (14)	47 (15)
Ethnicity				
Black	71,188 (8)	34,860 (13)	70,330 (7)	176,378 (8)
White	714,225 (77)	170,880 (65)	740,214 (73)	1,625,319 (74)
Other[b]	15,806 (2)	6,899 (3)	16,482 (2)	39,187 (2)
Unknown	130,284 (14)	49,242 (19)	180,676 (18)	360,202 (16)
Smoking status				
Never	273,730 (29)	77,953 (30)	311,971 (31)	663,654 (30)
Former	88,576 (10)	22,674 (9)	110,314 (11)	221,564 (10)
Current	290,590 (31)	68,694 (26)	226,159 (22)	585,443 (27)
Unknown	278,607 (30)	92,560 (35)	359,258 (36)	730,425 (33)
Weight, kg				
Nonmissing	841,560 (90)	241,621 (92)	878,720 (87)	1,961,901 (89)
Mean (SD)	85 (24)	84 (24)	86 (24)	85 (24)
BMI, kg/m^2				
Nonmissing	673,501 (72)	214,610 (82)	726,870 (72)	1,614,981 (73)
Mean (SD)	31 (8)	30 (8)	31 (8)	31 (8)
Obese	389,526 (42)	101,194 (39)	386,983 (38)	877,703 (40)
SBP, mm Hg				
Nonmissing	850,075 (91)	241,904 (92)	846,897 (84)	1,938,876 (88)
Mean (SD)	123 (14)	123 (15)	125 (15)	124 (15)
Uncontrolled SBP[c]	121,799 (14)	36,713 (15)	151,838 (18)	310,350 (16)
LDL, mg/dL				
Nonmissing	289,571 (31)	80,011 (31)	163,867 (16)	533,449 (24)
Mean (SD)	111 (36)	109 (36)	107 (37)	110 (36)
Uncontrolled LDL[d]	185,042 (64)	49,401 (62)	100,310 (61)	334,753 (63)
Triglycerides, mg/dL				
Nonmissing	359,969 (39)	100,336 (38)	201,196 (20)	661,501 (30)
Median (Q1–Q3 range)	120 (83–176)	111 (77–162)	121 (83–178)	119 (82–174)
Any CVD[e]	66,211 (7)	19,668 (8)	93,945 (9)	179,824 (8)
ASCVD	60,468 (6)	17,715 (7)	85,827 (9)	164,010 (7)
Microvascular[f]	162,286 (17)	49,390 (19)	195,198 (19)	406,874 (18)
Chronic kidney disease	78,083 (8)	23,166 (9)	83,512 (8)	184,761 (8)
Cancer[g]	43,278 (5)	13,577 (5)	52,383 (5)	109,238 (5)
Type 1 diabetes mellitus	10,227 (1)	2,774 (1)	23,725 (2)	36,726 (2)
Type 2 diabetes mellitus	113,326 (12)	31,662 (12)	132,649 (13)	277,637 (13)
Dyslipidemia[h]	302,698 (32)	81,167 (31)	376,428 (37)	760,293 (35)
Hypertension[i]	360,599 (39)	92,848 (35)	488,130 (48)	941,577 (43)
Cardiometabolic multimorbidity[j]	338,966 (36)	92,457 (35)	438,213 (43)	869,636 (40)
Anxiety	177,918 (19)	47,963 (18)	3,897 (0)	229,778 (10)
Other mental illnesses	99,000 (11)	32,311 (12)	3,455 (0)	134,766 (6)

[a]Data are presented as n (%) unless otherwise specified.
[b]Includes Asian, Indian, and Native Hawaiian or other Pacific Islander.
[c]Includes individuals with ASCVD and having SBP of at least 130 mm Hg or individuals without ASCVD and having SBP of at least 140 mm Hg.
[d]Includes individuals with ASCVD and having LDL of at least 70 mg/dL or individuals without ASCVD and having LDL of at least 100 mg/dL.
[e]Includes ASCVD and heart failure.
[f]Includes retinopathy, neuropathy, and nephropathy including chronic kidney disease.
[g]Involves all malignant cancer excluding skin cancer.
[h]Clinical diagnosis and prescription for dyslipidemia.
[i]Clinical diagnosis and prescription for hypertension.
[j]Includes ≥ 2 or more conditions of obesity (BMI ≥ 35 kg/m^2), ASCVD, heart failure, microvascular, cancer, type 1 diabetes mellitus, type 2 diabetes mellitus, dyslipidemia, and hypertension.
Abbreviations: ASCVD = atherosclerosis cardiovascular disease, BMI = body mass index, CVD = cardiovascular disease, LDL = low-density lipoproteins, SBP = systolic blood pressure.

and comparing these estimates with those from national surveys.[28–32]

The rates per 1,000 person-years of initiating individual antidepressant drug classes were estimated using the standard life table technique. Person-years was measured from the date of clinical diagnosis of depression to the earliest of the following: prescription date of the respective antidepressants, date of death, date the patient left the practice, or the last date of data collection from that practice. To evaluate the changing patterns in individual trends for the prescription rates, joinpoint regression based on annual percent change estimates was obtained.[33]

Among those who initiated at least 1 antidepressant monotherapy, the proportion of individuals who initiated second-line therapy and the median time to second-line therapy initiation were calculated overall and by first-line antidepressant drug class. Accounting for potential nonproportionality, the weighted Cox regression model[34] was used to determine factors associated with the risk of antidepressant therapy intensification separately for males

Figure 1. (A) Proportion of People Diagnosed With Depression Aged < 40 Years by Sex and Year of Diagnosis From 2006 to 2017; (B) Proportion of People With Clinical Diagnosis of Depression But Did Not Receive a Prescription for an Antidepressant by Sex and Year of Diagnosis

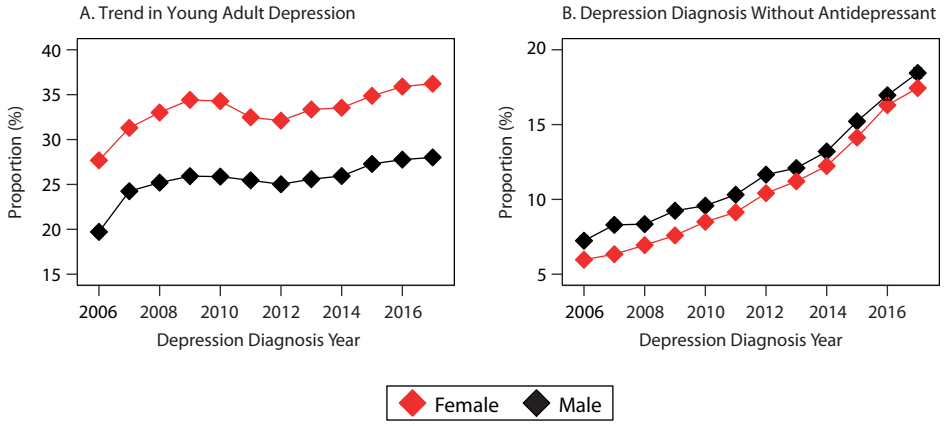
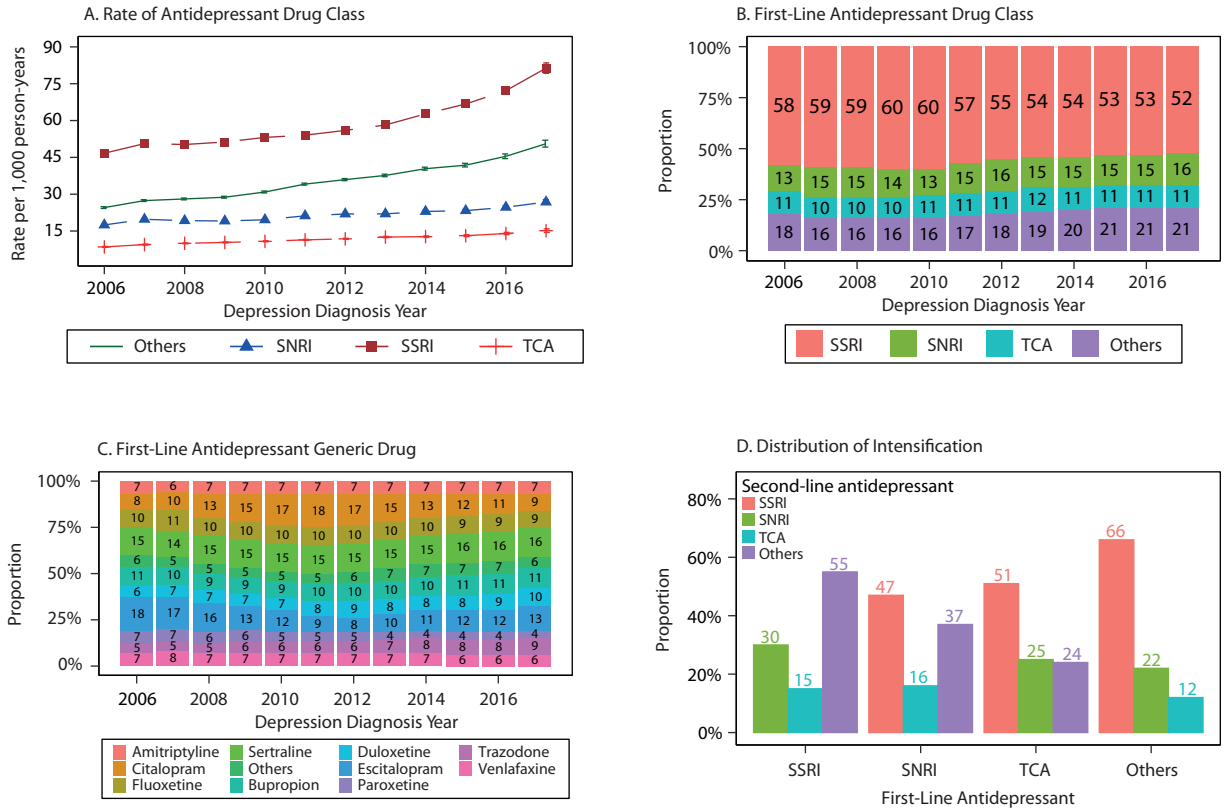
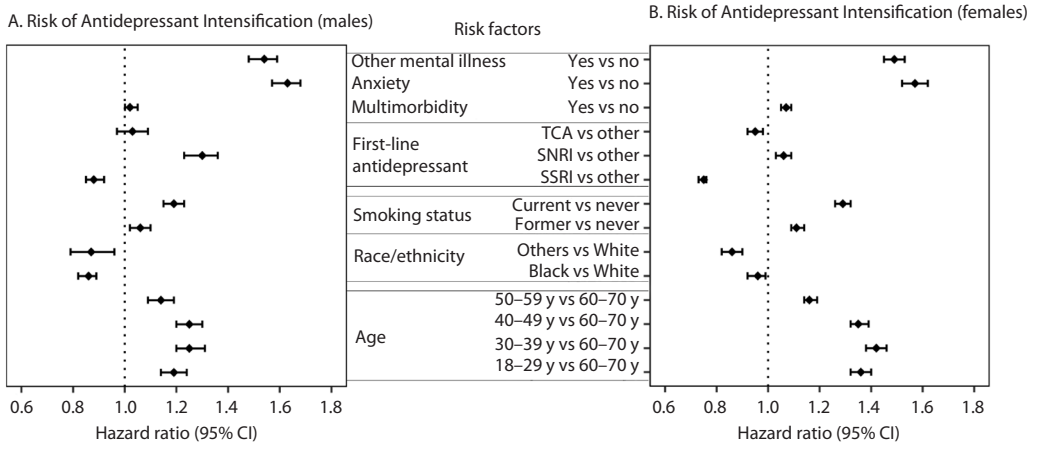


Figure 2. (A) Rates/1,000 Person-Years of Antidepressant Prescriptions by Year of Diagnosis From 2006 to 2017; (B) Proportional Share of First-Line Antidepressant Prescriptions by Drug Class; (C) Proportional Share of First-Line Antidepressant by Generic Drugs; (D) Type of Treatment Intensification From First-Line to Second-Line Antidepressant Drug Class



Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 3. Hazard Ratio Associated With Different Predictors of Treatment Intensification From First-Line to Second-Line Antidepressant Drug Class for (A) Males and (B) Females[a]



[a]The vertical dotted lines represent a hazard ratio of 1 (no difference in risk of treatment intensification).
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

and females, and the results were expressed as hazard ratios (95% CI). Missing covariate data were included as a categorical field to retain sample size.

RESULTS

Representativeness of the EMRs

From all available adult patient–level data from 2006 to 2017 (aged ≥18 years and at least 1 year of being active in the EMRs, n = 19,425,810), the proportions of people with any mental illness/depression were 28.9% (95% CI, 28.8–29.0)/21.4% (95% CI, 21.3–21.5). The overall prevalence of depression during the 2012–2013 study period was 18% (95% CI, 18.1–18.2), which is very close to the 21% reported in the National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) survey during the same period.[28] The prevalence of any mental illness estimated during the periods 2010/2013 was 20.1% (95% CI, 20.1–20.2)/24.3% (95% CI, 24.2–24.3), which is similar to 20%/19% reported in the National Survey on Drug Use and Health survey reports.[29,30] The trends in the prevalence of depression and any mental illness from the CEMR across different demographics were comparable to those from the US national surveys (Supplementary Table 3).

Cohort Characteristics

A total of 2,201,086 patients identified with incidence depression met the study inclusion criteria (Supplementary Figure 2), with a median (Q1, Q3) follow-up of 3.9 (1.5, 6.7) years (Table 1). The mean (SD) age was 47 (15) years, with 29% male, 37% smokers, 40% obese, 15% diabetic, 7% with atherosclerosis cardiovascular disease, 40% with cardiometabolic multimorbidity, and 16% diagnosed with other mental illnesses including anxiety. Approximately 32% of the cohort was diagnosed before age 40 years, and the proportion of young adult depression increased from 26% in 2006% to 36% in 2017, with a significantly higher proportion of females versus males (34% vs 26%, Figure 1A). The baseline cardiometabolic multimorbidity for males/females was 50%/35%.

Trend in Antidepressant Prescriptions

Among those diagnosed with depression, the proportion not receiving any therapeutic intervention for depression in males/females increased from about 7%/6% in 2006 to 18%/17% in 2017 (Figure 1B). The rates of initiation of different identified classes of antidepressants by the year of diagnosis are provided in Figure 2A. Selective serotonin reuptake inhibitor (SSRI) prescription rates increased significantly (rate [95% CI]/1,000 person-years from 47 [46–48] in 2006 to 81 [79–83] in 2017). The prescribing rates of other antidepressants increased from 24 (95% CI, 23–25) to 51 (95% CI, 49–52)/1,000 person-years, while the prescribing rates of serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) remained relatively unchanged. Similar patterns were observed among males and females (Supplementary Figures 3A and B).

A further evaluation of the overall antidepressant prescription rates by age and sex shows significant higher and recent increases in the rates of antidepressant prescription (mostly SSRIs) among male and female adults aged 18–39 years, while a constant yearly increase in prescription rates for the other age groups was observed since 2006 (Supplementary Figure 4, Supplementary Table 4).

Patterns of First-Line Antidepressant Prescription

In the eligible cohort, 1,797,863 (82%) individuals received at least 2 prescriptions for antidepressants. The most prescribed first-line drug classes were SSRIs (56%: mostly citalopram, escitalopram, and sertraline) followed by "others" (19%: mostly bupropion and trazodone), which were consistent from 2006 to 2017, similar for males and

females (Figures 2B and 2C, Supplementary Figures 3C and 3D).

Patterns of Antidepressant Treatment Intensification

Of those who initiated antidepressants, 405,086 (23%) had a prescription intensification with an overall median (Q1, Q3) of 17 (6, 37) months of duration of first-line antidepressant use before therapy intensification. After a change from SSRI, the most common second-line treatments were 55% other antidepressants followed by 30% SNRIs overall; 60% other antidepressants and 27% SNRIs in males; and 53% other antidepressants and 32% SNRIs in females (Figure 2D, Supplementary Figures 3E and 3F). Among those who initiated SNRIs, TCAs, and other antidepressants, SSRI was the most common second-line choice, with higher percentages of SSRI choice consistently recorded among females. Compared to males, females were 22% more likely to intensify therapy, with the observed trends consistent across all age groups ($P < .01$). Details for all the possible intensification between the drug classes and their respective generic ingredients are presented in Supplementary Table 5.

Factors Associated With Antidepressant Treatment Intensification

Compared to people aged 60–70 years at baseline, the risk of therapy intensification was progressively significantly higher in younger age groups for both sexes (Figure 3, Supplementary Table 6). Overall, compared to those aged 60–70 years, the adjusted hazard ratios (HR) (95% CI) for males/females in the age groups 18–29, 30–39, 40–49, and 50–59 years were 1.19 (1.14–1.24)/1.36 (1.32–1.40), 1.25 (1.20–1.31)/1.42 (1.38–1.46), 1.25 (1.20–1.30)/1.35 (1.32–1.39), and 1.14 (1.09–1.19)/1.16 (1.14–1.19), respectively. Non-White ethnic groups had lower risks of treatment intensification compared to Whites: the adjusted HR (95% CI) for Black/others in males was 0.86 (0.82–0.89)/0.96 (0.92–0.99) and in females was 0.87 (0.79–0.96)/0.86 (0.82–0.90). People with cardiometabolic multimorbidity had higher risk: HR (CI) of therapy intensification for males/females: 1.02 (1.01–1.05)/1.07 (1.05–1.09). Anxiety was associated with higher therapy intensification risk: males/females: 1.63 (1.57–1.68)/1.57 (1.52–1.62). Males and females on SSRIs were significantly less likely to intensify to second-line therapies (range of HR CI, 0.73–0.92), while those on SNRIs had higher risk of therapy intensification (range of HR CI, 1.03–1.36).

DISCUSSION

With global concerns about increasing prevalence of depression among young adults, there is an urgent need to understand the risk dynamics and treatment patterns in people of different ages from the time of diagnosis of depression. The novelty of this study includes the comprehensive evaluation of temporal trends in young adult depression and multimorbidity in males and females, the rates of utilization of different classes of antidepressants, a holistic evaluation of choices of different generic ingredients by the order of initiation, and the factors associated with therapy intensification in more than 2 million people from the United States with incident depression over a decade using large representative EMRs. Our study also highlights sex-based differences in the patterns of treating patients with incident depression in real-life settings.

For a holistic evolution of risk dynamics in people with depression, use of large representative EMRs containing detailed information on risk factors and comorbidities is essential, leading to our ability to conduct robust population-level outcome studies. Fundamental to this is the evaluation of the representativeness of EMRs with survey data in terms of major distribution characteristics. The observed prevalence rates of depression from CEMR during 2006, 2008, and 2012–2013 were similar to those reported in the Behavioral Risk Factor Surveillance System and NESARC-III surveys during the same periods.[28,31,32] Similarities in the trend of any mental illness prevalence by sex, age, and ethnicity were also observed from other US national surveys (Supplementary Table 1).[29,30] With the extensive data mining of the mental illnesses using related clinical diagnoses and prescriptions for antidepressants, the comparability of the proportions of people with depression and the distribution of their clinical characteristics suggest the usability of the EMRs in conjunction with claims and registry–based data for the much-needed population-level evidence generation in mental health, especially to support the US Food and Drug Administration initiative on "Exploring the Use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making."[35,36]

We observed that more than 30% of the cohort were diagnosed with depression at an early age, and the proportion of young adult depression significantly increased by 10% between 2006 and 2017. In addition, 40% of cardiometabolic multimorbidity was recorded in the study cohort with significantly higher proportions in males compared to females (50% vs 35%). In the absence of any population-level study, a detailed exploration of the dynamics of young adult depression and how multimorbidity is playing a role in this context is warranted.

We observed lower earlier and significantly higher recent antidepressant prescriptions rates among young adults compared to older age groups. A possible explanation for the observed trends could be a result of the observed link between SSRIs and increase in suicide rates prior to 2006, which led to a decrease in the use of antidepressants, and the economic downturn in 2008, which led to an increase in MDD and a consequent rise in antidepressant use among young adults.[37–39]

At present, first-line pharmacologic treatment of MDD in adults includes SSRIs, SNRIs, and other new-generation antidepressants.[14,15] In the presence of nonresponse or side effects from the first-line agent, different therapy intensification strategies including modification of the initial drug dosage, switching to a different antidepressant, or augmentation by another drug are recommended. Few

US-based surveys[40,41] and US claims data–based studies[17,18] have evaluated the utilization patterns of antidepressants in people with established depression. Kern and colleagues[17] explored 2014–2019 US claims data and reported that SSRIs were the most common first-line treatment, and 20%–40% of patients had treatment combination after first-line therapies.

As observed in the CEMR, SSRIs with a favorable safety profile remained the most prescribed and increasingly popular antidepressants, while usage of other classes of therapies appeared to remain the same over the last decade. We also found 23% of those who initiated antidepressants intensified to second-line treatments. Although there is no strong evidence for the relative advantages of intensification within or between classes in the management of MDD,[42] in this study we assessed risk factors that could be associated with therapy intensification between therapy classes. Milea and colleagues[16] evaluated factors associated with antidepressant treatment changes using US claims data, reporting 23% treatment change after first-line therapies, and found first-line treatment and other mental illnesses to be associated with treatment change. We found that females, smokers, comorbidities, other mental illnesses, and SNRI initiators were factors significantly associated with higher risk of therapy intensification, with younger adults receiving significantly higher therapy intensification compared to those aged ≥60 years. On the contrary, SSRI initiators and non-Whites were significantly less likely to intensify with a second-line therapy, and this was consistent by sex.

While lack of reliable information on medication adherence is a common problem in all clinical studies, detailed validation studies of US EMRs suggest a high level of agreement between EMR prescription data and pharmacy claims data, especially in chronic diseases.[43] In this study, we found a significant proportion of people who were prescribed antidepressants without a diagnosis code for depression in the EMR. This finding suggests that there is significant undercoding of clinical diagnoses in the primary and ambulatory care systems—a common issue demanding administrative intervention. Also, while we carefully chose antidepressants used for the treatment of depression only, a few people might have received this medication for other conditions as well, which is difficult to tease out from EMRs. Our extensive data-mining approach could guide the future development of dedicated pharmaco-epidemiologic studies using EMRs to generate robust real-world evidence in people with mental illness, while acknowledging the fundamental weaknesses of EMRs in relation to the absence of any therapy use indication, dosing, and general adherence.[20,23] In addition, other selection biases and residual confounding issues inherent in any EMR-based outcome study may remain. Residual bias may be present in the identification of incident depression cases. However, any potential inaccuracies with these input parameters were unlikely to have changed the conclusions of our study.

This study has several strengths including use of large nationally representative population-based data with significant follow-up time, availability of data on patient characteristics, disease events, prescriptions, and laboratory measures. We also validated the representativeness of a US primary care database with the national survey report, establishing suitability of this EMR for clinical and pharmaco-epidemiologic studies. Although antidepressants prescribed in real-world settings do not always conform to practice guidelines,[18] we have addressed the long-term real-world treatment patterns and empirical evidence on identifying high-risk individuals with depression following initiation of first-line therapy.

In conclusion, with increasing prevalence of young adult depression in the United States, cardiometabolic multimorbidity being one of the major factors driving depression incidence, and significant ethnic disparity in therapy management, further exploration is needed in the context of long-term safety in people with depression. This study demonstrates the usability of EMRs to generate the much-needed real-world evidence in people with mental illness in the United States.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

Article Title: Young Adult Depression, Antidepressant Prescriptions, and Therapy Intensification in People With Incident Depression in the United States

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List of Supplementary Material for the article

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Supplementary Material

METHODS

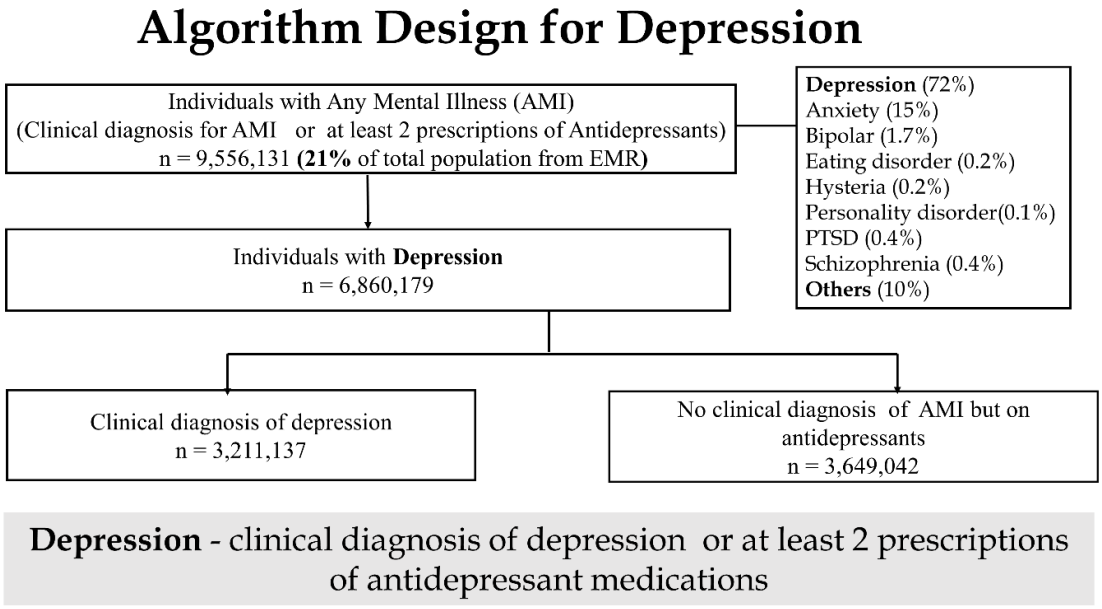
Rule-based Algorithm for identifying individuals with depression.

Background: Depression is the most common type of mental illness and among the leading cause of global disability. People with depression also tend to have other common medical conditions such as diabetes which are linked to worse outcomes. Depression exists in different types and its etiology poorly comprehended; thus, the identification of people with depression is urgently needed to better understand the causes and the course of the disease in order to design new and effective treatment strategies. The algorithm below describes in detail a rule-based approach developed to identify patients with depression from the CEMR database.

Algorithm: Any mental illness (AMI) comprises those mental illnesses that meet the diagnostic criteria specified within the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) excluding developmental and substance use disorder. These include **depression**, anxiety, bipolar, schizophrenia, posttraumatic stress disorder, eating disorder, gender identity disorder, personality disorder, and other unspecified mental illnesses. Patients with AMI were first identified with information from three domains: (1) AMI diagnosis disease codes (ICD 9(10) CM); (2) medications (use of antidepressant drugs for AMI); (3) key-word searching procedures for AMI related diseases from the clinical notes of every patient. Disease codes, search terms and list of antidepressants used for the identification of patients with AMI are indicated in Supplementary Tables 1 & 2. The process for the identification of patients with AMI was executed based on the following rule:

- **Inclusion criteria:** An initial cohort of patients with AMI were identified from the EMRs if the patient has at least one AMI specific diagnosis codes; **OR** use of antidepressants specifically used to treat AMI; **OR** having AMI related diagnostic codes from keywords. A patient was considered to use antidepressant if he / she has at least two prescriptions. The earliest date from either the first date of AMI occurrence or first prescription date was considered as the approximate date of diagnosis of AMI.
- **Classification of AMI and Depression identification:** Within the cohort of patients with AMI, patients with depression and other mental illnesses were formed in the following order:
    a) **Patients with depression:** These include any patient with at least one of the following criteria: (1) has at least one clinical diagnosis code for depression; **OR** (2) has no clinical diagnosis of depression but taking antidepressants specifically used to treat depression; **OR** (3) has no clinical diagnosis of AMI but using other antidepressants used to treat depression (Supplementary Figure 1).
    b) **Other mental illnesses:** These include all other patients not in the pool of patients with depression but have clinical diagnosis codes for anxiety, bipolar, schizophrenia, posttraumatic stress disorder, eating disorder, gender identity disorder, personality disorder, other unspecified mental illnesses or using antidepressant medications.

Among the people considered as having AMI, a total of 6,860,179 (72%) people were identified with depression (Supplementary Figure 1).



Supplementary Figure 1. Methodological design with information to identify people with Depression. The information include ICD 9(10) CM codes and antidepressants mainly prescribed for common mental health disorders such as depression and anxiety.

TABLES

Supplementary Table 1. Antidepressant generic (brand) drugs commonly prescribed for depression in US.

Drug class	Generic name	Brand name	Indications
Tricyclic antidepressants (TCAs)	amitriptyline	ALAVIL(Elavil), ENTRAVIL, LIMBITROL, TRIAVIL, VANATRIP, ETRAFON	major depressive disorder (MDD), anxiety disorders, and less commonly attention deficit hyperactivity disorder (ADHD) and bipolar disorder,
	amoxapine	ASENDIN	anxiety, depression
	clomipramine	ANAFRANIL	depression, anxiety, panic disorder
	doxepin	SILENOR, SINEQUAN	insomnia (low dose of doxepin), depression, anxiety
	trimipramine, desipramine, imipramine	SURMONTIL, NORPRAMIN, TOFRANIL,	depression
	nortriptyline	PAMELOR, AVENTYL	depression, ADHD
	protriptyline	VIVACTIL	depression, ADHD
Monoamine -oxidase inhibitors (MAOIs)	isocarboxazid	MARPLAN	depression
	Phenelzine	NARDIL	depression
	tranylcypromine	PARNATE	depression
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	Prozac, SYMBYAX, SARAFEM, SELFEMRA	MDD, obsessive compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder (PMDD), depression associated with

			bipolar, anxiety, Anorexia Nervosa, Posttraumatic Stress Syndrome (PTSD), Binge Eating Disorder
	sertraline	ZOLOFT	depression, OCD, panic disorder, PTSD, social anxiety disorder, and PMDD
	paroxetine	PAXIL, PEXEVA	depression, OCD, panic attacks, anxiety disorders, PTSD, and PMDD
	citalopram	CELEXA, CIPRAMIL	depression, anxiety, OCD, panic disorder, PTSD, and PMDD
	escitalopram	LEXAPRO, CIPRALEX	anxiety in adults and MDD
	fluvoxamine	LUVOX	OCD, depression
	vortioxetine	BRINTELLIX, TRINTELLIX	major depressive disorder
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine, desvenlafaxine	EFFEXOR, PRISTIQ, KHEDEZLA	anxiety, depression
	duloxetine	CYMBALTA, IRENKA	depression, anxiety
	levomilnacipran	FETZIMA	depression
Other antidepressants	buproprion	BUDEPRION¸ BUPROBAN, WELLBUTRIN, APLENZIN, APPBUTAMONE, FORFIVO, APLENZIN	depression
	trazodone	OLEPTRO, DESYREL	depression
	mirtazapine	REMERON	depression
	nefazodone	SERZONE	depression
	maprotiline	LUDIOMIL	depression, anxiety
	vilazodone	VIIBRYD, TIANEPTINE	depression, anxiety

Supplementary Table 2. Clinical codes and terms used for the identification of patients with Any mental illness.

Disease	ICD09 CM	ICD10 CM	Search terms
Depression	290.13x, 290.2x, 290.21x, 290.43x, 296.[23]x, 96.82x, 298.0x, 300.4x, 301.12x, 309.[01]x, 309.28x, 311x	f3[23]x, 34.1x, f43.2[13]x, 25.1x, f41.8x	depressive, depression, Seasonal affective disorder, dysthymic, dysthymia
Anxiety	300.[023]x,	f4[01]x	anxiety, phobia, phobic, anxious, fear, obsess, panic, hypochondria
Bipolar	296.[01]x,	f3[01]x	bipolar, manic, mania
Schizophrenia	295x	f20x	Schizophrenia
Posttraumatic stress disorder	309.81x	f43.1x	Posttraumatic stress disorder, PTSD
Personality disorder	301x	f60x	personality disorder
Hysteria	300.[18]x	f45x	hysteria, somatization
Eating disorder	307.5x	f50	Eating disorder, bulimia nervosa, pica, anorexia nervosa, bulimia, anorexia
Other mental illness #	295-98, 300-302, 306-311	f20-f48, f50, f60, f63-f69, f99	paranoid, nerve pain, neuropathic pain mental disorder, mental illness, cyclothymic, delusion, cataplexy

All other mental illnesses in the list of disease codes specified for the row; **[]** = square bracket signifies either of the number or letter within, for example, f3[23] =f32, f33; **x** = represents a list of missing letter or number that completes the pattern of a particular disease codes.

Supplementary Table 3. Among all research-ready validated individuals registered in the EMR during the study periods, the prevalence of any mental illness (AMI) and depression are compared with diagnoses reported in the US National surveys.

Disease	Source	Size	Study period	Prevalence, % (95% CI)									
				Overall	Gender		Age					Race	
					Male	Female						Black	White
Depression							**18-29 yrs.**	**30-44 yrs.**	**45-64 yrs.**	**65+ yrs.**			
	NESARC-III [1]	36,309	2012-2013	20.6	14.7	26.1	20.2	22.0	22.9	14.4		15.2	23.1
	CEMR	14,818,513	2012-2013	18.2 (18.1, 18.2)	12.9 (12.8, 12.9)	22.0 (21.9, 22.0)	12.7 (12.6, 12.7)	17.7 (17.7, 17.8)	20.7 (20.6, 20.8)	18.6 (18.5, 18.6)		13.5 (13.4, 13.5)	21.7 (21.7, 21.8)
							18-24 yrs.	**25-34 yrs.**	**35-44 yrs.**	**44-54 yrs.**	**55+ yrs.**		
	BRFSS[2, 3]	91,377	2008	16.1	11.2	20.7	14.8	14.4	16.7	19.9	14.9	12.3	17.3
	CEMR	4,670,863	2008	12.2 (12.1, 12.2)	8.3 (8.3, 8.4)	14.9 (14.8, 15.0)	7.5 (7.4, 7.6)	10.1 (10.0, 10.2)	12.5 (12.4, 12.6)	14.0 (13.9, 14.1)	13.1 (13.0, 13.1)	7.7 (7.6, 7.8)	14.3 (14.2, 14.4)
	BRFSS[2, 3]	306,953	2006 & 2008	15.9	11.2	20.5	14.7	14.4	16.7	19.6	14.7	11.8	17.3
	CEMR	6,217,384	2006 & 2008	13.0 (12.4, 13.0)	8.4 (8.5)	15.3 (15.3, 15.4)	7.8 (7.7, 7.8)	10.4 (10.3, 10.5)	12.8 (12.7, 12.9)	14.4 (14.3, 14.4)	13.2 (13.1, 13.2)	8.1 (7.9, 8.2)	15.2 (15.1, 15.2)

AMI							**18-25 yrs.**	**26-49 yrs.**	**50+ yrs.**				
	NSDUH [4]	68,487	2010	20.0	16.8	23.0	29.9	22.1	14.3			19.7	20.6
	CEMR	8,171,102	2010	20.1 (20.1, 20.2)	16.1 (16.0, 16.1)	23.0 (22.9, 23.0)	14.6 (14.5, 14.6)	20.8 (20.7, 20.9)	20.8 (20.8, 20.9)			15.5 (15.4, 15.6)	23.7 (23.6, 23.8)
	NSDUH[5]	~ 67,500	2013	18.5	14.4	22.3	19.4	21.5	15.3			16.9	19.3
	CEMR	14,594,364	2013	24.3 (24.2, 24.3)	19.1 (19.0, 19.2)	27.9 (27.9, 28.0)	18.2 (18.1, 18.2)	25.3 (25.2, 25.3)	24.8 (24.8, 24.9)			19.9 (19.9, 20.1)	28.9 (28.9, 29.0)

NESARC -III: National Epidemiologic Survey on Alcohol and Related Conditions-III; BRFSS: Behavioral Risk Factor Surveillance System; NSDUH: National Survey on Drug Use and Health

Supplementary Table 4. Rates 1000 person-years (95% CI) of antidepressant drug class intensification from first-line AD monotherapy to second-line drugs by age groups and gender.

	Male				**Female**			
Age groups	**SSRI**	**SNRI**	**TCA**	**Others**	**SSRI**	**SNRI**	**TCA**	**Others**
18 to 29 years	67.4 (65.9 – 68.9)	15.9 (15.4 – 16.4)	8.1 (7.7 – 8.4)	36.6 (35.8 – 37.4)	84.2 (83.2 – 85.1)	20.2 (19.9 - 20.5)	11.3 (11.1 – 11.5)	35.9 (35.6 – 36.4)
30 to 39 years	59.5 (58.3 – 60.8)	18.8 (18.3 – 19.3)	9.8 (9.4 – 10.1)	37.7 (36.9 – 38.4)	71.9 (71.1 – 72.8)	23.8 (23.5 – 24.1)	12.8 (12.6 – 13.1)	37.9 (37.6 – 38.4)
40 to 49 years	49.8 (48.9 – 50.7)	18.7 (18.3 – 19.1)	10.8 (10.5 – 11.1)	36.4 (35.8 – 37.0)	59.7 (59.1 – 60.3)	25.9 (25.6 – 26.2)	13.4 (13.2 – 13.6)	36.2 (35.8 – 36.6)
50 to 59 years	42.4 (41.8 – 43.1)	17.6 (17.3 – 17.9)	10.1 (9.9 – 10.3)	32.2 (31.7 – 32.7)	50.5 (49.9 – 50.9)	23.4 (23.1 – 23.7)	11.8 (11.7 – 12.0)	30.8 (30.5 – 31.1)
60 to 70 years	37.2 (36.6 – 37.9)	13.6 (13.3 – 13.9)	7.4 (7.2 – 7.6)	25.5 (25.1 – 25.9)	45.7 (45.2 – 46.2)	171.7 (17.5 – 17.9)	9.2 (9.0 – 9.4)	25.1 (24.8 – 25.4)
Total	46.9 (46.5 – 47.31)	16.6 (16.5 – 16.8)	9.2 (9.1 – 9.3)	32.3 (32.0 – 32.5)	58.8 (58.6 – 59.1)	22.2 (22.0 – 22.3)	11.7 (11.6 – 11.7)	32.6 (32.4 – 32.7)

Supplementary Table 5. Intensification between antidepressant drug classes, by generic drugs. Only those generic drugs with a minimum of 10% change within each of the second-line antidepressant classes are presented.

First-line Antidepressants	**Second-line Antidepressants**			
	SNRI	**TCA**	**Others**	**SSRI**
SSRI (1,003,822 (56))† >	62,925 (30)	30,522 (15)	114,299 (55)	**Not needed**
time (in months) to second-line for SSRI, *median (q1, q3)*	19 (8, 39)	18 (6, 39)	17 (6, 39)	
	citalopram > duloxetine 7,630 (12)	citalopram > amitriptyline 5,116 (**17**)	citalopram > buproprion 15,486 (**14**)	
	citalopram > venlafaxine 8,096 (13)	escitalopram > amitriptyline 3,545 (**12**)	citalopram > trazodone 11,230 (**10**)	
	escitalopram > duloxetine 7,698 (12)	fluoxetine > amitriptyline 3,737 (**12**)	escitalopram > buproprion 13,980 (**12**)	
	escitalopram > venlafaxine 7,479 (**12**)	sertraline > amitriptyline 5,055 (**17**)	fluoxetine > buproprion 10,991 (**10**)	
	sertraline > duloxetine 7,325 (**12**)		sertraline > buproprion 14,605 (**13**)	
	Sertraline > venlafaxine 7,532 (**12**)		sertraline > trazodone 10,995 (**10**)	
SNRI (265,875 (15))† >	**Not needed**	10,992 (16)	25,298 (37)	32,595 (47)

time (in months) to second-line for SNRI, *median (q1, q3)*		14 (5, 32)	16 (5, 36)	18 (7, 37)
		duloxetine > amitriptyline 4,643 (**42**)	duloxetine > buproprion 5,607 (**22**)	venlafaxine > sertraline 3,622 (**11**)
		duloxetine > nortriptyline 1,601 (**15**)	duloxetine > trazodone 5,847 (**23**)	duloxetine > citalopram 3,996 (**12**)
		venlafaxine > amitriptyline 2,251 (**20**)	venlafaxine > buproprion 5,580 (**22**)	duloxetine > escitalopram 3,708 (**11**)
			venlafaxine > trazodone 4,887 (**19**)	duloxetine > fluoxetine 3,207 (**10**)
				venlafaxine > escitalopram 3,562 (**11**)
				venlafaxine > citalopram 4,015 (**12**)
				duloxetine > sertraline 3,749 (**12**)
TCA (191,981 (11))[†] >	10,809 (25)	**Not needed**	10,037 (24)	21,903 (51)
time (in months) to second-line for TCA, *median (q1, q3)*	15 (6, 34)		18 (7, 39)	17 (6, 37)
				amitriptyline > citalopram 4,046 (**18**)
				amitriptyline > escitalopram 2,667 (**12**)

				amitriptyline > fluoxetine 2,606 (**12**)
				amitriptyline > sertraline 3,967 (**18**)
Others (336,185 (19))† >	17,743 (22)	10,065 (12)	**Not needed**	53,158 (66)
time (in months) to second-line for Others, *median (q1, q3)*	14 (5, 32)	15 (6, 34)		14 (5, 32)
	buproprion > duloxetine 4,833 (**27**)	buproprion > amitriptyline 2,668 (**27**)		buproprion > citalopram 7,256 (**14**)
	buproprion > venlafaxine 4,281 (**24**)	trazodone > amitriptyline 2,930 (**29**)		buproprion > escitalopram 6,735 (**13**)
	trazodone > duloxetine 4,083 (**23**)			buproprion > fluoxetine 5,533 (**10**)
	trazodone > venlafaxine 2,515 (**14**)			buproprion > sertraline 7,402 (**14**)
				trazodone > citalopram 5,068 (**10**)
				trazodone > sertraline 5,122 (**10**)

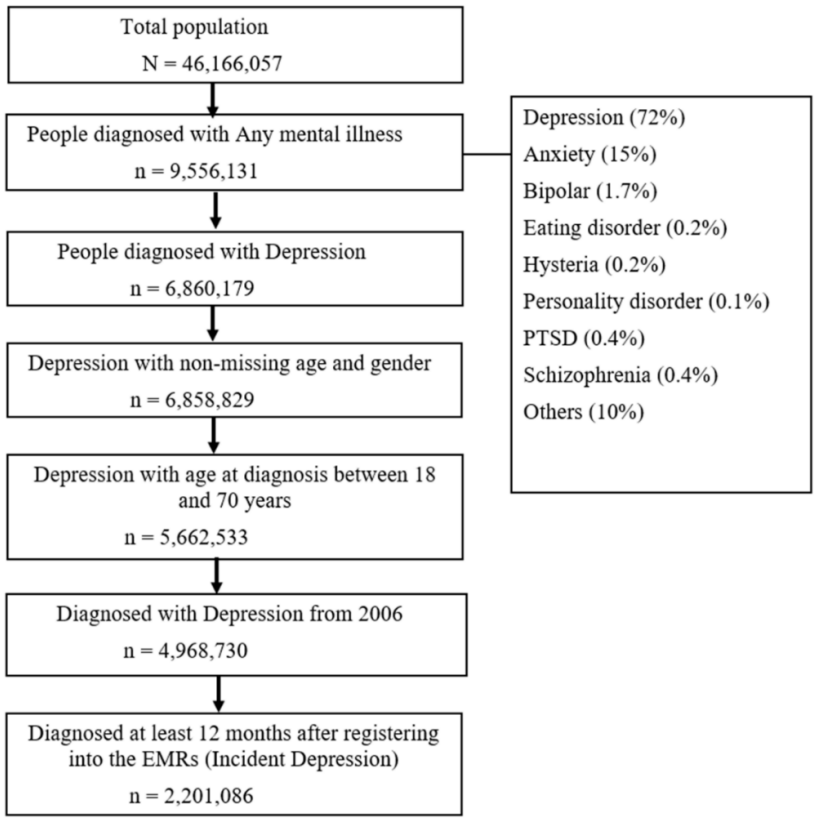
Data values in count (%) unless otherwise specified, **SNRI**: serotonin noradrenaline reuptake inhibitor, **TCA**: tricyclic antidepressant, **SSRI**: selective serotonin reuptake inhibitor, †: represents count (%) of first-line AD drug class from all those who initiated at least one AD drug class, > shows direction of intensification.

Supplementary Table 6. Rates per 1000 person-years (95% CI) of antidepressant drug class intensification from first-line AD monotherapy to second-line drugs by age groups and gender.

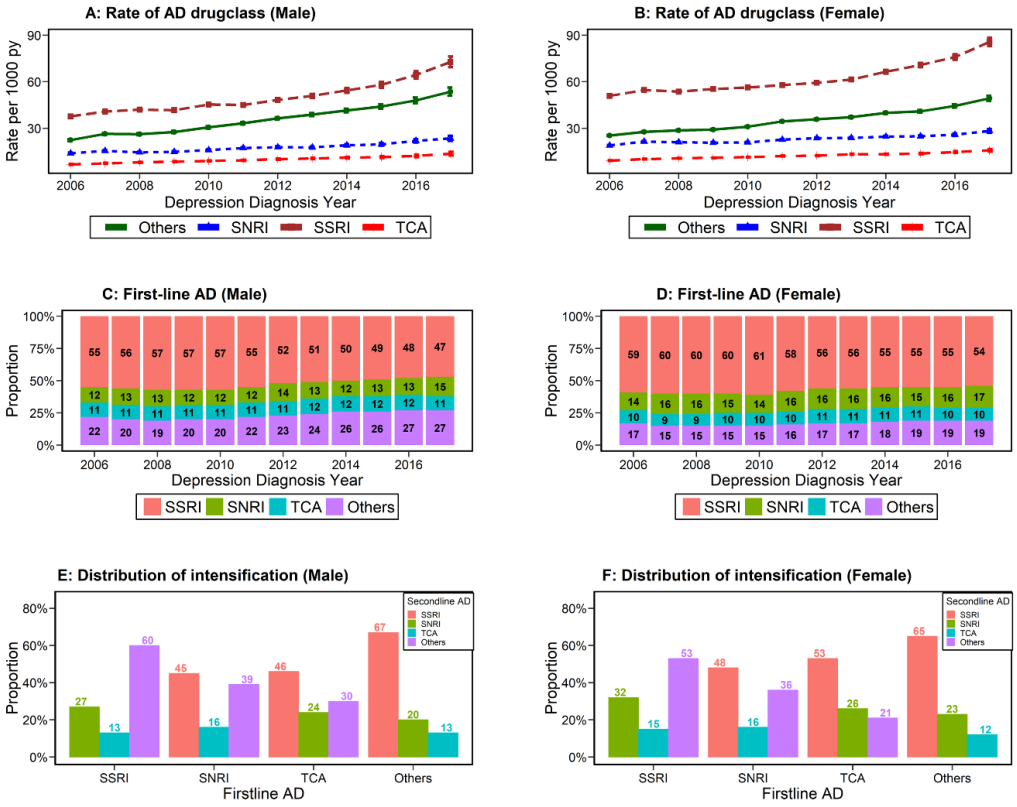
Age groups	Male	Female
18 to 29 years	62.14 (61.01 - 63.27)	71.97 (71.34 - 72.61)
30 to 39 years	65.66 (64.63 - 66.71)	75.53 (74.91 - 76.16)
40 to 49 years	63.77 (62.94 - 64.61)	73.48 (72.93 - 74.04)
50 to 59 years	56.90 (56.24 - 57.57)	63.84 (63.37 - 64.30)
60 to 70 years	45.36 (44.80 - 45.92)	52.26 (51.83 - 52.70)
Overall	56.37 (56.02 - 56.71)	66.21 (65.97 - 66.45)

FIGURES

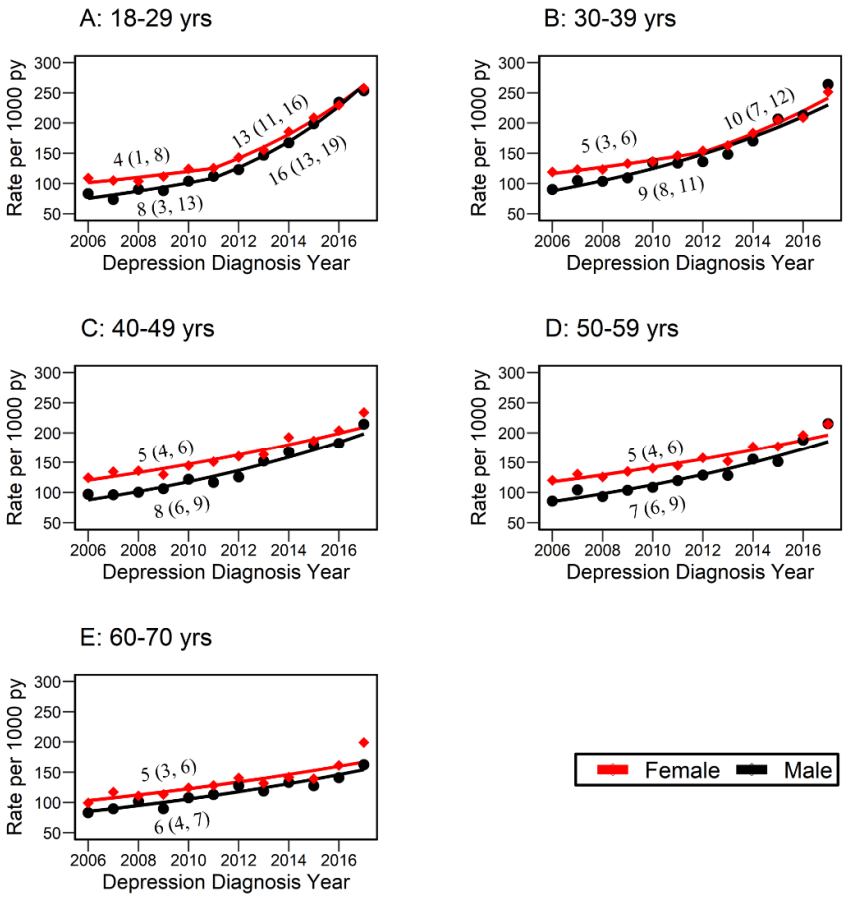
Supplementary Figure 2. Flow chart for the selection of study cohort of patients with incident depression.



Supplementary Figure 3. Distribution of Antidepressant drug class prescriptions and intensifications by gender: (A) and (B) The rates / 1000 person-years of antidepressant drug class prescriptions; (C) and (D) Proportional share of first-line antidepressant (AD) prescriptions by drug class; (E) and (F) type of treatment intensification from first-line to second-line AD drug class.



Supplementary Figure 4. Observed and modelled trend in the overall antidepressant prescription rates (per 1000 person-years) among US adults with incident depression. The trends are represented separately by age (18-29, 30-39, 40-49, 50-59 and 60-70 years at diagnosis of depression) and gender. The dots and squares represent observed rates while the lines are the estimates from Join-Point Regression model. The numbers within the plots are the annual percent change (95% CI) of the trends.



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