Annals of Internal Medicine ORIGINAL RESEARCH

Medication-Induced Weight Change Across Common Antidepressant Treatments

A Target Trial Emulation Study

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Background: Antidepressants are among the most commonly prescribed medications, but evidence on comparative weight change for specific first-line treatments is limited.

Objective: To compare weight change across common first-line antidepressant treatments by emulating a target trial.

Design: Observational cohort study over 24 months.

Setting: Electronic health record (EHR) data from 2010 to 2019 across 8 U.S. health systems.

Participants: 183 118 patients.

Measurements: Prescription data determined initiation of treatment with sertraline, citalopram, escitalopram, fluoxetine, paroxetine, bupropion, duloxetine, or venlafaxine. The investigators estimated the population-level effects of initiating each treatment, relative to sertraline, on mean weight change (primary) and the probability of gaining at least 5% of baseline weight (secondary) 6 months after initiation. Inverse probability weighting of repeated outcome marginal structural models was used to account for baseline confounding and informative outcome measurement. In secondary analyses, the effects of initiating and adhering to each treatment protocol were estimated.

Results: Compared with that for sertraline, estimated 6-month weight gain was higher for escitalopram (difference, 0.41 kg [95% CI, 0.31 to 0.52 kg]), paroxetine (difference, 0.37 kg [CI, 0.20 to 0.54 kg]), duloxetine (difference, 0.34 kg [CI, 0.22 to 0.44 kg]), venlafaxine (difference, 0.17 kg [CI, 0.03 to 0.31 kg]), and citalopram (difference, 0.12 kg [CI, 0.02 to 0.23 kg]); similar for fluoxetine (difference, −0.07 kg [CI, −0.19 to 0.04 kg]); and lower for bupropion (difference, −0.22 kg [CI, −0.33 to −0.12 kg]). Escitalopram, paroxetine, and duloxetine were associated with 10% to 15% higher risk for gaining at least 5% of baseline weight, whereas bupropion was associated with 15% reduced risk. When the effects of initiation and adherence were estimated, associations were stronger but had wider CIs. Six-month adherence ranged from 28% (duloxetine) to 41% (bupropion).

Limitation: No data on medication dispensing, low medication adherence, incomplete data on adherence, and incomplete data on weight measures across time points.

Conclusion: Small differences in mean weight change were found between 8 first-line antidepressants, with bupropion consistently showing the least weight gain, although adherence to medications over follow-up was low. Clinicians could consider potential weight gain when initiating antidepressant treatment.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. doi:10.7326/M23-2742 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 2 July 2024.

Antidepressants are among the most commonly prescribed medications in the United States (1) and are prescribed for psychiatric conditions like depression, anxiety, chronic pain, and posttraumatic stress disorder (2). In 2017 to 2018, 14% of U.S. adults reported using an antidepressant, up from 11% in 2009 to 2010 (3). Weight gain is a commonly reported side effect of antidepressant use (4–6) that may affect patients' long-term metabolic health given the difficulty of achieving and sustaining weight loss (7, 8). Antidepressant-associated weight gain may additionally lead to increased medication nonadherence, which is associated with poor clinical outcomes, including increased risk for depression relapse and hospitalization (9, 10).

Although antidepressants overall are associated with weight gain, specific antidepressant medications may affect weight differently. For example, selective serotonin reuptake inhibitors (SSRIs) are generally associated with weight gain, and bupropion is associated with small decreases in weight (11). A rigorous comparison of weight change across specific first-line antidepressant

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medications could help guide decision making for patients and providers. However, evidence to support these decisions is limited. Most studies of antidepressant-associated weight gain have included prevalent users instead of new users (6, 12–15), which could bias associations (for example, if the drug has an immediate effect on weight that causes patients to stop adhering). Many studies have also examined entire antidepressant classes (such as SSRIs or tricyclic antidepressants) (13–15), despite potential within-class heterogeneity of effects on weight change (12). Last, many studies have been too small to detect small but clinically meaningful associations (13–16). Additional comparative real-world evidence is needed to help clinicians determine the best antidepressant therapy to initiate for new users, particularly those with weight or metabolic health concerns.

We therefore conducted a large cohort study comparing weight change across common first-line antidepressants using electronic health record (EHR) prescription data. We used a target trial emulation approach (17) in PCORnet, the National Patient-Centered Clinical Research Network, to primarily estimate the effects of initiating each treatment on 6-month weight change. We secondarily estimated the effects of initiating *and adhering to* each treatment. This approach involved first articulating the protocol of the randomized controlled trial (RCT) we would have conducted if it were not prohibitively expensive and challenging to conduct a large trial comparing weight change across antidepressants. We then emulated the protocol by aligning key features of that trial to our observational data (for example, eligibility criteria and treatment strategies) and used causal inference methods to account for differences between the hypothetical RCT and the observational EHR data (such as nonrandom treatment assignment) (17–19).

METHODS

Target Trial

The target trial would include adults aged 20 to 80 years who are initiating a single antidepressant treatment. We would exclude those aged 80 years or older at baseline because weight change after this age is often driven by physiologic adaptations to aging (such as reduced lean body mass) and chronic disease (20, 21). Eligible participants would have no history of antidepressant use and no recent history of cancer, pregnancy, or bariatric surgery, which are associated with large weight changes. They would have no contraindications to any of the medications of interest. Patients would be randomly assigned at baseline to initiate 1 of 8 common first-line antidepressant treatments: sertraline, citalopram, escitalopram, fluoxetine, paroxetine, bupropion, duloxetine, or venlafaxine. Patients would be followed for 2 years and have weight measured at baseline and 6, 12, and 24 months after initiation.

We would primarily estimate intention-to-treat (ITT) effects of 6-month weight gain for each medication versus sertraline (the most commonly prescribed antidepressant in PCORnet), with 12- and 24-month weight change as secondary outcomes. We would also estimate the probability of gaining a clinically meaningful amount of weight, defined as at least 5% of baseline weight, at each time point. We would use a repeated outcomes model with inverse probability weights (IPWs) to adjust for baseline and time-varying measures associated with weight change and with having a weight measurement to account for informative outcome measurement (that is, follow-up visits may be incomplete, resulting in missing outcome measures) (22, 23).

Per protocol effects—the effects of initiating and subsequently adhering to the treatment protocol—would be of secondary interest. The protocol would require patients to continuously take the initiated treatment as prescribed, allowing no more than 1 month to pass without medication at hand (that is, the protocol would allow a 1-month grace period) (24). Patients who became pregnant or received bariatric surgery over follow-up would not be required to remain adherent (24). We would use a repeated outcomes model similar to that of the ITT analysis but with additional IPWs to adjust for protocol nonadherence (25, 26).

In the following sections, we describe how we emulated this target trial using an observational data set (summarized in **Table 1**). The Institutional Review Board of Harvard Pilgrim Health Care approved this study.

Study Population

We obtained EHR data on adult patients who received an antidepressant medication from July 2010 to December 2019 from 8 health systems participating in PCORnet (27, 28) (**Supplement Table 1**, available at Annals.org). We obtained the data using a standardized query of sites' EHRs that specified codes for all data elements to be abstracted from the medical record (https://github.com/PCORnet-DRN-OC/QueryDetails/tree/master/MedWeight%20Project), including demographic information (such as date of birth and sex), prescriptions using RxNorm codes and National Drug Codes (29, 30), diagnoses based on International Classification of Diseases codes, procedures, height, weight, smoking status, and payer type. All data were stored in the PCORnet Common Data Model format, allowing interoperability across sites and easy combination of site data (31). Because person-months was the unit of analysis, we aggregated all EHR data in 30-day intervals (that is, approximate months) relative to the date of patients' first antidepressant prescription.

Eligibility Criteria

A total of 1 081 516 patients received an antidepressant prescription over the study period, and 776 328 received 1 of the 8 medications of interest. Of those, we excluded patients younger than 20 years

Table 1. Specifications of the Target Trial and Emulation With Observational EHR Data

Protocol Component and Target Trial Specification	Emulation
Eligibility criteria	
Age 20–≤80 y	Age 20–≤80 y
No history of antidepressant use	≥1 encounter at least 6 mo before first prescription
Weight measured at baseline	Weight measured within a 3-mo period before initiation
No cancer diagnosis (other than nonmelanoma skin cancer) 1 y before initiation	No cancer diagnosis (other than nonmelanoma skin cancer) 1 y before initiation
No pregnancy 1 y before initiation	No pregnancy 1 y before initiation
No bariatric surgery 3 y before initiation	No bariatric surgery 3 y before initiation
Indicated for monotherapy of 1 of the considered medications	Initiated only 1 of the considered medications
Baseline	
Randomization would occur once all eligibility criteria are met	Baseline is the date of treatment initiation once all eligibility criteria are met
Treatment strategies	
ITT: Initiate treatment with only 1 of the following 8 medications: sertraline, citalopram, escitalopram, fluoxetine, paroxetine, bupropion, duloxetine, or venlafaxine	Date of medication treatment initiation was the date of first prescription
Per protocol: Initiate and adhere to the assigned treatment on a daily basis, allowing for a 1-mo grace period (i.e., allowing the patient to go 1 mo without taking the medication, but no longer)	We estimated the amount of time a patient had medication using information on number of pills, days' supply, and number of refills from the prescription; patients were considered adherent during the time when they had medication on hand based on these calculations; the month after the end of their supply of medicine was the grace period
Treatment assignment	
Randomly assigned to a treatment strategy at baseline	Treatment not assigned randomly
Outcome	
Weight change compared with baseline weight after 6 mo (primary) and after 12 and 24 mo (secondary)	Same as target trial
Follow-up period	
Starts at baseline and ends at the end of available data, death, or 2 y after baseline	Same as target trial
Analysis plan	
ITT: Calculate change in weight from baseline to each time point	ITT: Adjust for baseline covariates and apply IPWs to adjust for informative outcome measurement; predict weight change had each patient initiated and adhered to each medication of interest at each time point *t*
Per protocol: Censor patients when they deviate from their assigned treatment strategy and apply IPWs to adjust for factors associated with adherence/treatment discontinuation	Per protocol: Same as ITT but censor patients when they deviate from their treatment strategy and modify IPWs to additionally adjust for factors associated with adherence/treatment discontinuation
Contrast of interest	
Mean weight change for each antidepressant compared with that for sertraline	Same as target trial

EHR = electronic health record; IPW = inverse probability weight; ITT = intention to treat.

(*n* = 64 077) or 80 years or older (*n* = 35 889) at initiation. We required patients to have had at least 1 encounter with the health system at least 6 months before their first antidepressant prescription, which made it more likely that they had not been previously prescribed an antidepressant and were truly new users. We therefore excluded those without a visit at least 6 months before initiation (*n* = 407 507). A review of 40 total medical records from 3 sites found that 85% of patients meeting this criterion were indeed new users (**Supplement Methods**, available at Annals.org). We excluded persons prescribed more than 1 antidepressant medication at initiation (*n* = 60 825) because the target trial would randomly assign patients to only 1 treatment. We excluded patients without a weight measurement in the 3 months before initiation (*n* = 296 161), which we used to determine their baseline weight. We additionally excluded persons with evidence of cancer (*n* = 51 921) or pregnancy (*n* = 21 104) in the year before initiation and those with evidence of bariatric surgery in the 3 years before initiation (*n* = 2824). Last, we excluded patients missing data on sex (*n* = 22), race (*n* = 49 253), or ethnicity (*n* = 37 892). After all exclusions were applied, the analytic sample comprised 183 118 patients. **Supplement Figure 1** (available at Annals.org) shows a patient eligibility flow chart.

Treatment Strategies

We classified participants by their first prescribed antidepressant. For the per protocol analysis, protocol adherence was defined as described in the Target Trial section. We estimated when a patient would run out of medication ("prescription length") using information on number of refills and either pill quantity or

days' supply (**Supplement Methods**). Approximately 56% of all prescriptions (from 50% for duloxetine to 62% for bupropion) and 58% at initiation specifically had sufficient data to determine prescription length. If subsequent prescriptions had missing data on the variables required to calculate prescription length, we carried those variables forward from the most recent nonmissing data. Patients with insufficient data to determine prescription length at initiation were assumed to have had a 1-month supply, the minimum possible length of time in our analysis. Pregnancy and bariatric surgery were determined using relevant International Classification of Diseases or procedure codes. Patients were considered nonadherent in the first month their data became inconsistent with the protocol. For patients who did not become pregnant or have bariatric surgery, nonadherence started when more than 1 month passed without medication.

Outcome

We calculated weight change by subtracting weight (in kilograms) in each month from weight at initiation, defined as the weight measurement closest to, but not after, medication initiation and within 3 months before initiation. If a patient had more than 1 weight measurement within a month, we calculated the mean weight for that month. Weight data were cleaned using the R package *growthcleanr*, which removes height and weight data with various errors or inconsistencies from EHRs (32, 33). We also determined whether a patient had gained at least 5% of their baseline weight by dividing weight change by baseline weight. The primary outcome was 6-month weight change. Secondary outcomes included 12- and 24-month weight change, as well as the probability of gaining at least 5% of baseline weight at these time points.

Covariates

Baseline covariates included health conditions (captured with International Classification of Diseases codes), prescriptions for other medications associated with weight change (such as diabetes medications), Medicaid payer type (a marker of socioeconomic status), smoking status, recent health care use, body mass index, and evidence of recent weight change. Patients without a diagnosis, procedure code, or prescription were assumed to not have the disease, procedure, or prescription. We assumed that patients with missing data on smoking were nonsmokers. We derived the same variables over follow-up to address time-varying confounding and additionally adjusted for new antidepressant prescriptions (that is, other than for the initiated treatment) and cancer, pregnancy, and bariatric surgery. **Supplement Table 2** (available at Annals.org) provides details on all covariates.

Statistical Analysis

In the ITT analysis, we followed eligible patients from treatment initiation until the end of 24-month follow-up or death ($n = 3001$), whichever came first. We created stabilized IPWs to adjust for informative outcome measurement because participants had a weight measurement only when they had encounters in the health system (**Supplement Methods**). We truncated IPWs at the 99th percentile to reduce the influence of extreme weights. We then fitted a weighted outcome regression model to the person-month data set using the IPWs. The dependent variable was weight change in a given month, and the independent variables were indicators for initiated treatment, time (modeled as a restricted cubic spline with 4 knots), treatment-by-time interaction terms, and all baseline covariates. We used the parameter estimates from the outcome regression model to predict weight change under adherence to each treatment in each month for every individual. We then averaged across all individuals to obtain "standardized" population-level estimates of average weight change under each treatment strategy in each month (34) (**Supplement Methods**). We estimated differences in average weight change under each strategy compared with sertraline and constructed 95% CIs with 1000 bootstrapped samples. We conducted analyses overall and by sex and baseline obesity status. We used a similar approach to estimate risk ratios (RRs) for gaining at least 5% of baseline weight (**Supplement Methods**).

We followed the same general approach in the per protocol analysis, except that we artificially censored patients when they first became nonadherent to the protocol. When creating the IPWs, we multiplied the IPWs described above by additional IPWs to account for selection bias created by artificial censoring (35) (**Supplement Methods**).

We conducted several sensitivity analyses. First, we required patients to have an encounter at least 12 months before initiation (vs. 6 months in the main analysis) as an alternative definition of new users. Second, we restricted to those with a diagnosis of depression or anxiety (vs. adjusting for these conditions), which may have reduced residual confounding by indication. Third, we excluded patients who initiated treatment after 2017 because their follow-up could have overlapped with the COVID-19 pandemic, which affected weight trajectories (36). Fourth, we excluded people who died during follow-up (vs. censoring them). We compared results using both approaches because there is no universally accepted method to estimate effects when deaths occur, even in RCTs (because weight gain is not defined after death) (37, 38). Fifth, because many patients had missing smoking data, we did an analysis assuming that all persons missing data on smoking were active smokers (vs. assuming they were nonsmokers). Although this is highly unlikely, making the opposite extreme assumption from our main analysis could reveal the potential for bias in our original assumption. Last, we excluded those who at initiation were taking stimulants, steroids, or weight loss medications, which are all associated with weight change (vs. including them

Table 2. Baseline Characteristics of the Study Population

Characteristic	Overall (*n* = 183 118)	Sertraline (*n* = 37 351)	Citalopram (*n* = 30 184)	Escitalopram (*n* = 24 993)	Fluoxetine (*n* = 23 169)	Paroxetine (*n* = 7675)	Bupropion (*n* = 27 054)	Duloxetine (*n* = 20 435)	Venlafaxine (*n* = 12 257)
Mean age (SD), *y*	48.2 (15.7)	46.8 (16.7)	48.0 (16.1)	46.2 (16.1)	46.0 (15.9)	50.9 (14.8)	47.6 (14.1)	54.3 (14.1)	50.2 (14.1)
Sex, %									
Male	35	36	35	33	32	34	42	34	24
Female	65	64	65	67	68	66	58	66	76
Race, %									
Asian American/ Pacific Islander	2	2	2	2	2	1	2	1	1
Black/African American	15	16	12	14	12	17	14	19	13
White	79	77	80	81	80	77	80	76	81
Other or >1 race	5	5	5	4	6	5	4	4	5
Ethnicity, %									
Hispanic	7	6	7	7	7	8	5	7	6
Not Hispanic	93	94	93	93	93	92	95	93	94
Mean body mass index (SD), *kg/m²*	29.4 (7.4)	29.0 (7.4)	28.8 (7.1)	29.0 (7.3)	29.1 (7.5)	29.2 (7.1)	30.1 (7.7)	31.1 (7.9)	29.8 (7.3)
Mean weight (SD), *kg*	84.0 (23.0)	82.9 (22.8)	82.2 (22.2)	82.6 (22.7)	82.9 (22.9)	83.0 (22.1)	87.2 (23.7)	88.4 (24.2)	83.7 (22.4)
Overweight/obesity status, %									
Overweight	30	30	30	29	29	31	30	28	30
Obesity	40	37	36	37	38	39	43	49	42
Diagnoses, %									
Depression	36	39	43	33	47	28	32	23	32
Anxiety	39	47	47	48	41	41	22	22	33
Neuropathic pain	16	12	13	11	12	14	13	40	19
Mental health disorder	2	3	2	2	3	2	2	2	2
Obsessive compulsive disorder	1	1	<1	<1	1	1	<1	<1	<1

and adjusting for this medication use). All analyses were conducted using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

The National Institutes of Health had no role in the design of the study; collection, analysis, or interpretation of the data; writing of the report; or decision to submit the report for publication.

RESULTS

The most common antidepressant treatments initiated were sertraline (*n* = 37 351 [20%]), citalopram (*n* = 30 184 [16%]), and bupropion (*n* = 27 054 [15%]). The least common was paroxetine (*n* = 7675 [4%]). At baseline, the mean age across all medications was 48.2 years and the mean body mass index was 29.4 kg/m^2. Approximately 35% of patients were male (65% female); 7% were Hispanic; and 79% were White, 15% were Black or African American, and 2% were Asian American/Pacific Islander. Approximately 36% had a documented diagnosis of depression, and 39% had a diagnosis of anxiety. We observed several differences in the covariate distribution by treatment (**Table 2**; the distribution of all baseline covariates by treatment is in **Supplement Table 3**, available at Annals.org). The median time that patients adhered to the medication treatment, according to our criteria, was 4 months for sertraline, citalopram, escitalopram, fluoxetine, bupropion, and venlafaxine and 3 months for paroxetine and duloxetine. The percentage of patients who remained adherent to the treatment protocol ranged from 28% to 41% at 6 months, 16% to 21% at 12 months, and 4% to 5% at 24 months (**Table 3**). Across treatments and time points, 5% to 13% of patients who stopped adhering to the treatment protocol switched medications within 3 months, and 7% to 10% of those who were adherent added an additional medication. The percentage of patients with a weight measurement exactly at the 6-, 12-, and 24-month time points ranged from 15% to 30% across medications; 40% to 50% had a weight measurement at 1 or more time points. Few patients were prescribed stimulants, steroids, or weight loss medications over follow-up (**Supplement Table 4**, available at Annals.org).

The **Figure** shows adjusted population-level estimates of average weight change for each treatment over every month of follow-up in the ITT analyses (estimates at 6, 12, and 24 months are in **Supplement Table 5**,

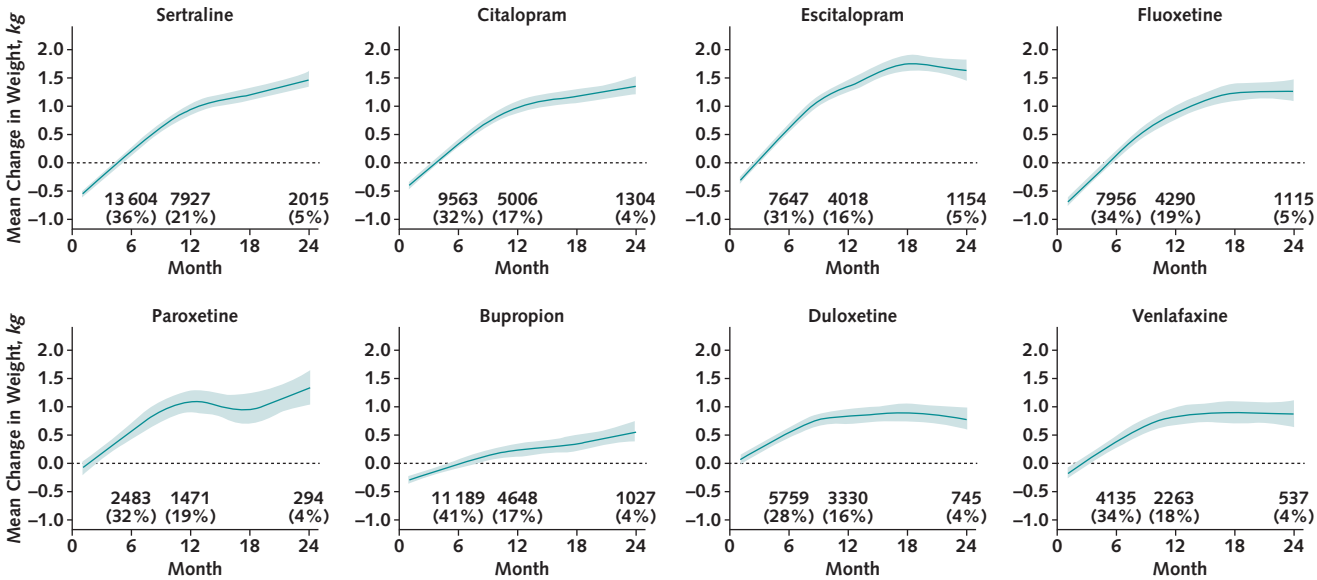
Table 3. Descriptive Statistics of Weight and Adherence Measures, by Treatment, at 6, 12, and 24 Months After Initiation

Treatment	Percentage With a Weight Measurement	Percentage Adherent	Among Nonadherent Participants		Among Adherent Participants	
			Percentage Switching Medications in 3 Months	Top 3 Most Commonly Replaced Medications*	Percentage With Additional Medications†	Top 3 Most Commonly Added Medications*
6 months						
Sertraline	24	36	9	1) Other, 2) bupropion, 3) venlafaxine	9	1) Other, 2) bupropion, 3) citalopram
Citalopram	22	32	9	1) Other, 2) bupropion, 3) sertraline	9	1) Other, 2) bupropion, 3) sertraline
Escitalopram	23	31	8	1) Other, 2) bupropion, 3) sertraline	9	1) Other, 2) bupropion, 3) sertraline
Fluoxetine	20	34	9	1) Other, 2) sertraline, 3) bupropion	9	1) Other, 2) bupropion, 3) sertraline
Paroxetine	24	32	9	1) Other, 2) bupropion, 3) venlafaxine	9	1) Other, 2) sertraline, 3) bupropion
Bupropion	22	41	8	1) Other, 2) fluoxetine 3) citalopram	7	1) Other, 2) sertraline, 3) escitalopram
Duloxetine	30	28	8	1) Other, 2) venlafaxine, 3) bupropion	9	1) Other, 2) venlafaxine, 3) bupropion
Venlafaxine	24	34	10	1) Other, 2) bupropion, 3) escitalopram	8	1) Other, 2) bupropion, 3) citalopram
12 months						
Sertraline	22	21	9	1) Other, 2) bupropion, 3) escitalopram	9	1) Other, 2) bupropion, 3) escitalopram
Citalopram	21	17	10	1) Other, 2) sertraline, 3) bupropion	10	1) Other, 2) bupropion, 3) sertraline
Escitalopram	23	16	13	1) Bupropion, 2) duloxetine, 3) other	10	1) Bupropion, 2) other, 3) sertraline
Fluoxetine	20	19	10	1) Other, 2) bupropion, 3) escitalopram	10	1) Other, 2) bupropion, 3) sertraline
Paroxetine	23	19	9	1) Escitalopram, 2) sertraline, 3) duloxetine	10	1) Other, 2) sertraline, 3) bupropion
Bupropion	21	17	9	1) Other, 2) fluoxetine 3) venlafaxine	10	1) Other, 2) sertraline, 3) escitalopram
Duloxetine	27	16	10	1) Other, 2) bupropion, 3) venlafaxine	10	1) Other, 2) bupropion, 3) escitalopram
Venlafaxine	24	18	7	1) Other, 2) sertraline, 3) bupropion	10	1) Other, 2) bupropion, 3) duloxetine
24 months						
Sertraline	16	5	7	1) Other, 2) bupropion, 3) duloxetine	7	1) Other, 2) bupropion, 3) escitalopram
Citalopram	17	4	10	1) Other, 2) sertraline, 3) venlafaxine	10	1) Other, 2) sertraline, 3) bupropion
Escitalopram	16	5	6	1) Bupropion, 2) other, 3) venlafaxine	10	1) Bupropion, 2) other, 3) sertraline
Fluoxetine	15	5	5	1) Bupropion, 2) duloxetine, 3) other	9	1) Other, 2) bupropion, 3) sertraline
Paroxetine	17	4	10	1) Citalopram, 2) venlafaxine, 3) bupropion	10	1) Sertraline, 2) other, 3) bupropion
Bupropion	16	4	8	1) Other, 2) fluoxetine, 3) escitalopram	10	1) Other, 2) sertraline, 3) escitalopram
Duloxetine	19	4	6	1) Other, 2) fluoxetine, 3) sertraline	9	1) Other, 2) bupropion, 3) sertraline
Venlafaxine	18	4	7	1) Sertraline, 2) bupropion, 3) other	9	1) Other, 2) bupropion, 3) sertraline

* Other includes antidepressants that were not analyzed as part of the main analysis (e.g., tricyclic antidepressants).
† Other than the originally initiated medication treatment.

available at Annals.org). Compared with that for sertraline, 6-month weight change was lower for bupropion (difference, −0.22 kg [95% CI, −0.33 to −0.12 kg]) and higher for escitalopram (difference, 0.41 kg [CI, 0.31 to 0.52 kg]), duloxetine (difference, 0.34 kg [CI, 0.22 to 0.44 kg]), paroxetine (difference, 0.37 kg [CI, 0.20 to 0.54 kg]), and venlafaxine (difference, 0.17 kg [CI, 0.03 to 0.31 kg]) (Table 4). The pattern of results was similar for the probability of gaining at least 5% of baseline weight. We found an RR of 0.85 (CI, 0.81 to 0.89) for initiation of treatment with bupropion compared with sertraline, indicating an estimated 15% reduced risk for gaining at least 5% of baseline weight for bupropion initiators versus sertraline initiators after

Figure. Associations of antidepressant treatment initiation with weight change over 24 mo.



The figure shows adjusted population-level estimates of average weight change (*dark green line*) and 95% CIs from 1000 bootstrapped samples (*light green bands*) for initiating each of the 8 antidepressant treatments over 24 mo from initiation. The null (0 kg mean weight change) is depicted with a dashed horizontal line. The curves begin at month 1 because the model estimates effects on weight change only after baseline. Numbers (percentages) within each graph at the 6-, 12-, and 24-month marks are numbers of adherent participants (percentage of total) at each time point.

6 months. We observed positive associations for escitalopram (RR, 1.15 [CI, 1.10 to 1.20]), duloxetine (RR, 1.10 [CI, 1.04 to 1.15]), and paroxetine (RR, 1.14 [CI, 1.06 to 1.22]) versus sertraline.

Weight gain was lower for bupropion than for sertraline at 12 and 24 months after initiation (difference, −0.71 kg [CI, −0.87 to −0.55 kg] and −0.91 kg [CI, −1.14 to −0.66 kg], respectively). Escitalopram was associated with weight gain versus sertraline after 12 months (difference, 0.41 kg [CI, 0.25 to 0.56 kg]) but not after 24 months (difference, 0.16 kg [CI, −0.08 to 0.40 kg]). In contrast to the 6-month outcomes, duloxetine and venlafaxine were associated with less 24-month weight gain than sertraline (difference, −0.69 kg [CI, −0.93 to −0.43 kg] and −0.59 kg [CI, −0.87 to −0.32 kg], respectively). Risk ratios for gaining at least 5% of baseline weight were consistent with relative weight change results (**Table 4**).

The ITT results were robust in all sensitivity analyses (**Supplement Table 6**, available at Annals.org), although when restricting to those with baseline depression or anxiety, we estimated 0.25 kg greater weight reduction for bupropion versus sertraline than in the main analysis at all time points (for example, 6 months: difference, −0.47 kg [CI, −0.61 to −0.32 kg]). We found few differences in associations by sex or baseline obesity status (**Supplement Table 7**, available at Annals.org).

Associations were generally stronger across time points in per protocol analyses, which accounted for medication adherence (**Table 5**; **Supplement Figure 2** and **Supplement Table 5**, available at Annals.org). For example, 6-month weight change was lower for bupropion versus sertraline (difference, −0.80 kg [CI, −1.26 to −0.42 kg]) and higher for escitalopram versus sertraline (difference, 1.03 kg [CI, 0.52 to 1.45 kg]) than in ITT analyses. Several per protocol associations were stronger than ITT associations for 12- and 24-month weight change, but the 95% CIs were wide and included the null for all medications except bupropion.

Discussion

In this study of 183 118 new antidepressant users, we found small differences in short- and longer-term weight change between 8 first-line medications. Six months after initiation, we estimated that approximately 1 in 3 patients was still adherent to their initially prescribed medication. Users of escitalopram, paroxetine, and duloxetine gained approximately 0.3 to 0.4 kg more weight and were 10% to 15% more likely to gain at least 5% of their baseline weight than sertraline users. Conversely, bupropion users gained 0.22 kg less weight and were 15% less likely to gain at least 5% of their baseline weight than sertraline users. Fluoxetine use was not associated with 6-month weight change compared with sertraline use. We observed the same general patterns in per protocol analyses, which accounted for adherence, but the associations were stronger and less precisely estimated.

This study found differences in medication-induced weight gain over 6 months both within and between

Table 4. Weight Change Difference and Relative Risk for Gaining ≥5% of Baseline Weight at 6, 12, and 24 Months After Initiating Antidepressant Treatment Compared With Sertraline: Intention-to-Treat Analysis*

Treatment	6 Months	12 Months	24 Months
Mean weight change (95% CI), *kg*			
Sertraline	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
Citalopram	0.12 (0.02 to 0.23)	0.03 (−0.12 to 0.19)	−0.11 (−0.33 to 0.11)
Escitalopram	0.41 (0.31 to 0.52)	0.41 (0.25 to 0.56)	0.16 (−0.08 to 0.40)
Fluoxetine	−0.07 (−0.19 to 0.04)	−0.06 (−0.22 to 0.10)	−0.20 (−0.45 to 0.05)
Paroxetine	0.37 (0.20 to 0.54)	0.15 (−0.08 to 0.37)	−0.14 (−0.46 to 0.21)
Bupropion	−0.22 (−0.33 to −0.12)	−0.71 (−0.87 to −0.55)	−0.91 (−1.14 to −0.66)
Duloxetine	0.34 (0.22 to 0.44)	−0.11 (−0.29 to 0.04)	−0.69 (−0.93 to −0.43)
Venlafaxine	0.17 (0.03 to 0.31)	−0.12 (−0.30 to 0.08)	−0.59 (−0.87 to −0.32)
Risk ratio for gaining ≥5% of baseline weight (95% CI)			
Sertraline	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Citalopram	1.01 (0.97 to 1.06)	1.02 (0.98 to 1.06)	1.00 (0.96 to 1.05)
Escitalopram	1.15 (1.10 to 1.20)	1.10 (1.06 to 1.15)	1.01 (0.96 to 1.06)
Fluoxetine	0.98 (0.93 to 1.03)	0.96 (0.92 to 1.01)	0.96 (0.92 to 1.01)
Paroxetine	1.14 (1.06 to 1.22)	1.03 (0.95 to 1.09)	0.96 (0.90 to 1.03)
Bupropion	0.85 (0.81 to 0.89)	0.78 (0.75 to 0.82)	0.86 (0.81 to 0.90)
Duloxetine	1.10 (1.04 to 1.15)	1.00 (0.95 to 1.04)	0.92 (0.87 to 0.97)
Venlafaxine	1.02 (0.96 to 1.08)	0.95 (0.89 to 1.00)	0.90 (0.85 to 0.96)

* Mean weight change was estimated from models adjusting for time and baseline covariates. Time-varying covariates were adjusted for by applying inverse probability weights. 95% CIs were calculated from 1000 bootstrapped samples.

antidepressant subclasses. Across all analyses, bupropion was associated with the least weight gain. This finding has been previously documented (5, 11) and may be due to bupropion's inhibition of dopamine and norepinephrine reuptake, as well as its activation of the hypothalamic melanocortin system (5, 39). Weight gain was 0.25 kg lower among bupropion users with baseline depression or anxiety than among all bupropion users, possibly because that analysis removed patients taking bupropion solely for smoking cessation (40), who might be more likely to gain weight. Duloxetine and venlafaxine, both serotonin–norepinephrine reuptake inhibitors (SNRIs), showed greater 6-month weight gain than sertraline, although weight gain under these SNRIs was similar to that of some other SSRIs. Serotonin–norepinephrine reuptake inhibitors are expected to have slightly stronger anorexigenic effects than SSRIs through norepinephrine reuptake (5), although weight gain has still been documented (5, 39). Among SSRIs, escitalopram and paroxetine were associated with the greatest 6-month weight gain, which may be important for clinicians to consider for patients at risk for nonadherence due to short-term, weight-related side effects. Of note, although patients' absolute weight increased under all treatments, our lack of a control group of nonusers makes comparative weight change estimates the most unbiased outcome. These results highlight an opportunity for clinicians to alter their prescribing patterns when multiple antidepressant treatment options exist, especially for patients with weight and metabolic health concerns (41, 42).

We also examined 12- and 24-month weight change, but the results were limited by low adherence. Across medications, adherence was 28% to 41% at 6 months, 16% to 21% at 12 months, and 4% to 5% at 24 months. Adherence differed little between medications except at 6 months, when it was slightly higher for bupropion (41%) than the other medications (28% to 36%). This low adherence did not lead to bias in the ITT analysis, given that that analysis estimated only the effects of treatment initiation, but it made it more difficult to attribute relative weight change at the 12- and 24-month time points to the specific medications of interest. At the same time, we likely underestimated adherence because of limitations of the data. For the approximately 40% of prescriptions missing data on duration, we conservatively assumed a 1-month prescription, the shortest possible time. This assumption could have misclassified some patients as nonadherent if their prescriptions were for longer. We also could have missed prescriptions if patients switched health systems. Keeping the limitations of low adherence in mind, 24-month weight gain was lower for duloxetine and venlafaxine than for sertraline, which was due to plateauing weight gain around 12 to 18 months for the SNRIs (vs. a continual increase in weight gain for the SSRIs). We also observed a narrowing of the initial differences in weight change between SSRIs after 24 months. Bupropion continued to be associated with the least weight gain at 12 and 24 months after initiation.

The per protocol analysis aimed to address the low levels of adherence in this study by artificially censoring patients when they became nonadherent and adjusting for common causes of adherence and weight gain. However, residual confounding could have been present if we failed to properly adjust for some of these common causes. Also, because of the low adherence rates, many fewer patients were included in the per protocol analysis at later time points, which reduced precision. Our results were consistent with expectations: The point estimates from the per protocol analysis were generally farther from the null with wider

Table 5. Weight Change Difference and Relative Risk for Gaining ≥5% of Baseline Weight at 6, 12, and 24 Months After Initiating Antidepressant Treatment Compared With Sertraline: Per Protocol Analysis*

Treatment	6 Months	12 Months	24 Months
Mean weight change (95% CI), *kg*			
Sertraline	0.00 (Reference)	0.00 (Reference)	0.00 (Reference)
Citalopram	0.16 (−0.30 to 0.60)	−0.15 (−1.00 to 0.60)	−0.11 (−2.08 to 1.59)
Escitalopram	1.03 (0.52 to 1.45)	0.96 (0.16 to 1.68)	0.48 (−1.32 to 2.11)
Fluoxetine	−0.33 (−0.81 to 0.09)	−0.05 (−0.97 to 0.75)	0.94 (−1.22 to 2.62)
Paroxetine	0.63 (−0.13 to 1.38)	−0.02 (−1.39 to 1.11)	−2.40 (−9.78 to 2.92)
Bupropion	−0.80 (−1.26 to −0.42)	−1.09 (−1.99 to −0.25)	−2.30 (−4.37 to −0.40)
Duloxetine	0.45 (−0.28 to 1.03)	1.21 (−0.11 to 2.07)	2.85 (−0.42 to 5.47)
Venlafaxine	−0.36 (−1.08 to 0.23)	0.83 (−0.64 to 2.29)	0.61 (−2.07 to 2.65)
Risk ratio for gaining ≥5% of baseline weight (95% CI)			
Sertraline	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Citalopram	0.92 (0.77 to 1.10)	1.06 (0.82 to 1.32)	1.27 (0.89 to 1.78)
Escitalopram	1.34 (1.11 to 1.60)	1.32 (1.06 to 1.63)	1.00 (0.68 to 1.41)
Fluoxetine	0.74 (0.59 to 0.90)	1.03 (0.80 to 1.30)	1.55 (1.08 to 2.16)
Paroxetine	1.36 (1.03 to 1.74)	1.27 (0.82 to 1.77)	1.30 (0.70 to 2.08)
Bupropion	0.57 (0.46 to 0.70)	0.70 (0.49 to 0.92)	0.63 (0.38 to 0.96)
Duloxetine	1.25 (0.97 to 1.49)	1.28 (0.94 to 1.61)	1.31 (0.83 to 1.85)
Venlafaxine	0.94 (0.74 to 1.19)	1.24 (0.93 to 1.60)	1.48 (0.90 to 2.21)

* Mean weight change was estimated from models adjusting for time and baseline covariates. Time-varying covariates were adjusted for by applying inverse probability weights. 95% CIs were calculated from 1000 bootstrapped samples.

CIs than those obtained from ITT analyses. However, both analyses showed a similar pattern of results in both magnitude and direction.

Previous EHR-based studies have observed overall similar patterns of weight change associated with these antidepressant treatments. None to our knowledge have used a target trial emulation approach. Arterburn and colleagues (16) had generally similar findings to the present study in ITT and per protocol analyses, although they found greater 2-year weight gain for sertraline than fluoxetine treatment initiators. However, many of their estimates had large CIs, likely due to their small sample size. They also found that approximately 4% of patients were adherent to their initiated treatment after 2 years, similar to the present study. Blumenthal and colleagues (12) found less weight gain for bupropion and SNRIs than for citalopram, and similar weight gain between SSRIs, also similar to our study. Gafoor and colleagues (6) estimated similar long-term weight change between SSRIs and SNRIs, with slightly less weight gain for paroxetine users, but they did not directly estimate differences in weight change between specific medications. Other studies also tended to observe weight gain for SSRIs generally but did not compare weight gain between treatments, making direct comparison with our study challenging (13–15). Unlike the present study, most previous studies included prevalent users at baseline, adjusted for fewer clinical and demographic factors, and did not account for adherence over follow-up (6, 12–15). Other than Arterburn and colleagues (16), previous studies did not report the percentage of patients who adhered to their initiated treatment over time.

Our study has several limitations compared with the RCT that we sought to emulate. First, we could not verify that patients were new antidepressant users (that is, if they had a previous prescription not listed in the EHR). However, we required at least 6 months of lead time before initiation, and our findings were similar when requiring at least 12 months of lead time. Second, as in any observational study, because our study did not randomly assign participants to treatment, baseline confounding was likely present to some degree, including confounding by indication because some medications are used for reasons other than treatment of mental health conditions. We adjusted for many baseline confounders and ran analyses restricted to those with baseline depression or anxiety, which yielded similar results (except slightly stronger associations for bupropion). Third, we did not have consistent information on medication dose and could not examine dose–response effects. Thus, although this study had more limitations than RCTs for causal inference, we mitigated many of these with our analytic approach and interrogated our assumptions with sensitivity analyses. This allowed us to draw important insights on antidepressant-associated weight gain with observational data, which was the most appropriate way to answer this research question given the logistic constraints of an analogous RCT.

Our study has other limitations that are shared with RCTs. First, time-varying confounding by new diagnoses, prescriptions, or health behaviors that predict adherence was likely present. Estimating per protocol effects requires adjustment for these variables, even in RCTs, as we did. Second, we had data only on prescriptions and could not verify whether the medications were dispensed or taken as prescribed, although an RCT would likely also have difficulty verifying that patients took the prescribed medication. Third, because most patients did not encounter the health system at exactly 6, 12, and 24 months, only 15% to 30% had weight measurements in those months. Missingness of outcome data is a well-documented issue in RCTs (43, 44), although an RCT might measure more patients'

weights at fixed follow-up time points. We addressed this with IPWs that adjusted for demographics, health behaviors, diagnoses, and prescriptions that predict having a weight measurement, as also recommended for RCTs with incomplete outcome ascertainment (45). Last, some patients were prescribed antidepressants other than their initiated treatment over follow-up, which could have affected weight. However, only 7% to 10% of people added an antidepressant at any point over follow-up (consistent across medications), and we adjusted for these adjunctive therapies.

In summary, this study found greater 6-month weight gain for patients newly prescribed escitalopram, paroxetine, duloxetine, and venlafaxine compared with sertraline, but less 6-month weight gain for those newly prescribed bupropion. Clinicians and patients could consider these differences when making decisions about specific antidepressants, especially given the complex relationships of obesity and depression with health, quality of life, and stigma (46–49).

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Grant Support: By grant 5R01DK120598 from the National Institute of Diabetes and Digestive and Kidney Diseases (Dr. Block).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M23-2742.

Reproducible Research Statement: *Study protocol and statistical code:* Contact Dr. Petimar (e-mail, jsp778@mail.harvard.edu). *Data set:* Not available.

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Final approval of the article: J.P. Block, M.F. Daley, W.J. Heerman, D.M. Janicke, W.S. Jones, K.H. Lewis, P.-I.D. Lin, J.W. Merriman, J. Petimar, C. Prentice, S.L. Rifas-Shiman, S. Toh, J.G. Young, H. Yu.
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Statistical expertise: J.G. Young.
Obtaining of funding: J.P. Block, D.M. Janicke.
Administrative, technical, or logistic support: J.P. Block, J. Petimar, J.G. Young, H. Yu.
Collection and assembly of data: J.P. Block, M.F. Daley, D.M. Janicke, W.S. Jones, S.L. Rifas-Shiman.