An Electronic Health Records Study of Long-term Weight Gain Following Antidepressant Use

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IMPORTANCE Short-term studies suggest antidepressants are associated with modest weight gain but little is known about longer-term effects and differences between individual medications in general clinical populations.

OBJECTIVE To estimate weight gain associated with specific antidepressants over the 12 months following initial prescription in a large and diverse clinical population.

DESIGN, SETTING, AND PARTICIPANTS We identified 22,610 adult patients who began receiving a medication of interest with available weight data in a large New England health care system, including 2 academic medical centers and affiliated outpatient primary and specialty care clinics. We used electronic health records to extract prescribing data and recorded weights for any patient with an index antidepressant prescription including amitriptyline hydrochloride, bupropion hydrochloride, citalopram hydrobromide, duloxetine hydrochloride, escitalopram oxalate, fluoxetine hydrochloride, mirtazapine, nortriptyline hydrochloride, paroxetine hydrochloride, venlafaxine hydrochloride, and sertraline hydrochloride. As measures of assay sensitivity, additional index prescriptions examined included the antiasthma medication albuterol sulfate and the antiobesity medications orlistat, phentermine hydrochloride, and sibutramine hydrochloride. Mixed-effects models were used to estimate rate of weight change over 12 months in comparison with the reference antidepressant, citalopram.

MAIN OUTCOME AND MEASURE Clinician-recorded weight at 3-month intervals up to 12 months.

RESULTS Compared with citalopram, in models adjusted for sociodemographic and clinical features, significantly decreased rate of weight gain was observed among individuals treated with bupropion (β [SE]: −0.063 [0.027]; \(P = .02\)), amitriptyline (β [SE]: −0.081 [0.025]; \(P = .001\)), and nortriptyline (β [SE]: −0.147 [0.034]; \(P < .001\)). As anticipated, differences were less pronounced among individuals discontinuing treatment prior to 12 months.

CONCLUSIONS AND RELEVANCE Antidepressants differ modestly in their propensity to contribute to weight gain. Short-term investigations may be insufficient to characterize and differentiate this risk.

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multiple prior reports have suggested an association between antidepressant use and weight gain. Because more than 10% of Americans are prescribed antidepressants at any given time, the potential health consequences could be substantial. Obesity has been associated with higher incidence of cardiovascular disease, type 2 diabetes mellitus, hypertension, stroke, dyslipidemia, osteoarthritis, and some cancers, as well as significantly reduced life expectancy and increased all-cause mortality. The prevalence of antidepressant use increases to more than one-third for severely depressed individuals, a group that may be particularly at risk for obesity. In fact, up to a quarter of obesity may be attributable in part to an underlying mood disorder.

Differences between medication classes in their propensity to cause weight gain have been reported; 1 early review suggested older antidepressants, including the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, were more likely to cause weight gain than the selective serotonin reuptake inhibitors or other new antidepressants. The atypical antidepressant mirtazapine and the TCAs amitriptyline hydrochloride and nortriptyline hydrochloride are still widely accepted as contributing to weight gain in patients based on randomized, controlled short-term trials. Among studies examining acute treatment, generally defined as 4 to 12 weeks, the selective serotonin reuptake inhibitors all resulted in average weight loss, as did the serotonin and norepinephrine-reuptake inhibitors venlafaxine hydrochloride and duloxetine hydrochloride, while nortriptyline and mirtazapine resulted in significant weight gain. The only medications with evidence of long-term weight changes (ie, over 4 months or more) were amitriptyline, which caused weight gain, and bupropion hydrochloride, which caused weight loss. Data from long-term treatment with other drugs were either nonexistent or inconclusive and no 12-month data could be identified.

Thus, 2 major questions of clinical importance relating to antidepressants and weight gain remain unanswered. First, what magnitude of weight gain is associated with longer-term antidepressant use in general clinical populations rather than clinical trial populations? Second, are there clinically significant differences between these interventions in terms of weight gain because most studies lack direct head-to-head comparisons? To address these topics, we examined electronic health records from a large New England health care system encompassing more than 4.2 million individuals. By extracting prescribing data and documented patient weights, we assessed the association between specific antidepressants and weight change over the 12 months following medication initiation in more than 22,000 individuals.

Methods

Overview and Data Set Generation

The Partners HealthCare electronic health record includes sociodemographic data, billing codes, laboratory results, problem lists, medications, vital signs, procedure reports, and narrative notes from Massachusetts General Hospital and Brigham and Women’s Hospital as well as from community and specialty outpatient clinics part of the Partners HealthCare system in Boston, Massachusetts. Adult patients between the ages of 18 and 65 years with at least 1 prescription for an antidepressant between February 1, 1990, and December 1, 2011, were identified. In addition, as measures of assay sensitivity, individuals with a prescription for an antiobesity medication or the antiasthma medication albuterol sulfate in that period were selected for inclusion in a data set (referred to as a data mart), yielding 484,907 individuals drawn from about 4.2 million unique patients in the Partners system. The data mart consists of all electronic records (psychiatric and nonpsychiatric) and can be managed with the i2b2 version 1.6 server software. This system is a scalable computational framework deployed at more than 60 major academic health centers for managing human health data. Medications are documented from electronic prescriptions to patients in the outpatient electronic health record (61%) and medications dispensed by the patient pharmacy (39%). The Partners institutional review board approved all aspects of this study, waiving the requirement for informed consent as detailed by 45 CFR 46.116.

Study Design

The present analysis included adult individuals 18 to 65 years of age who were prescribed 1 of the following antidepressants: amitriptyline, bupropion, citalopram hydrobromide, duloxetine, escitalopram oxalate, fluoxetine hydrochloride, mirtazapine, nortriptyline, paroxetine hydrochloride, venlafaxine, or sertraline hydrochloride. For purposes of understanding assay sensitivity, individuals prescribed the asthma medication albuterol or the antiobesity medications orlistat, phentermine hydrochloride, or sibutramine hydrochloride were also included.

For each patient, the index (initial) prescription was defined as the first study drug prescribed in the patient’s health record. Baseline weight was defined as the nearest weight prior to index prescription within 1 month. Baseline body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was also calculated using the nearest height measurement. Weight measurements closest to 3 months, 6 months, 9 months, and 12 months (within a window of 1 month) after the index prescription were extracted for analysis. Within each window, exposure was defined as 1 or more prescriptions with cumulative days of supply amounting to greater than 80% of days from baseline to time point, corresponding to standard definitions of medication-possession ratio. Confirmation that agents prescribed were actually dispensed to patients is not available for research purposes by prior agreement between the hospital system and the pharmacy data provider. Times when the continuous exposure requirement was not met or a weight measurement was not available were considered to be missing data.

Patients with a medical history of a gastric procedure (eg, weight loss surgery, defined as Current Procedural Terminology 4 [CPT-4] code 43500-43999, or eating disorder prior to or during the study period [International Classification of Diseases Ninth Revision (ICD-9) code 307.1x]) were excluded.
Women who were pregnant within 2 years of the index prescription (CPT-4 codes 59000-59899) were also excluded. Patients with a concomitant prescription of another drug of interest during the study period were also excluded.

To address the role, if any, of concomitant psychotherapy of any type, the presence or absence of such treatment was also assessed based on CPT-4 codes 90804, 90806, and 90808. Likewise, the presence of any concomitant pharmacotherapy with an antipsychotic medication during the study period was identified from prescribing data.

Analysis
Treatment groups were compared in terms of sociodemographic features including age, sex, public vs private insurance, year of index prescription, and self-reported ethnicity. (In this health system, Hispanic or Latino ethnicity is not captured separately from race, so individuals self-reporting as Hispanic were analyzed as a distinct group.) Clinical covariates were also defined, including the presence or absence of a depressive disorder, anxiety disorder, recent tobacco use, or pain disorder, based upon ICD-9 code and/or documentation in the problem list within 1 year of index prescription (see eTable 1 in Supplement for codes used to define these categories). Age-adjusted Charlson Comorbidity Index, a validated measure of overall burden of medical illness, was also calculated.

Primary analysis examined rate of change in weight over 12 months following index prescription using regression with mixed effects. Mixed-effects models represent a well-accepted method for analyzing longitudinal clinical data in which missing or mistimed observations are present and have been previously applied to examine longer-term antidepressant weight gain in clinical trials. The model included main effects for baseline weight, change in weight over the 6 months prior to index prescription, age, sex, race/ethnicity, public vs private insurance, time, diagnosis, pharmacotherapy, and concomitant psychotherapy or antipsychotic treatment. Terms were also included for the interaction of each of these with time. Individual treatments were compared with a reference antidepressant, citalopram; the primary test examined whether weight gain was significantly different from citalopram (P < .05).

A challenge in longitudinal clinical data sets is the optimal means of addressing missing data that are not missing at random, in particular, when dropout occurs nonrandomly. In phase 3 randomized clinical trials, multiple methods are typically applied, although recent reviews generally emphasize the appropriateness of mixed-effects models. Here, we used this method for primary analysis, then conducted extensive sensitivity analysis to directly test the role of discontinuation. In addition to models including all subjects, individuals who did or did not complete 12 months of treatment were analyzed separately to allow an analysis of completers and dropouts analogous to clinical trial analyses. In further sensitivity analysis, consistent with the approach described by Fitzmaurice et al, we used logistic regression to develop a model for early (pre-12-month) discontinuation. Then, we examined rates of weight change among completers and dropouts separately and calculated a weighted average between these 2 groups. This result can be interpreted as the rate of weight gain in a given group adjusted for probability of discontinuing treatment.

All analyses used R 3.0.1 (The R Foundation for Statistical Computing). Mixed-effects models were fitted using the R package nleme3.1.

Results
A total of 22,610 patients were included in the analysis (Figure 1) including 19,244 adult patients treated with an antidepressant for at least 3 months and 3,366 patients receiving a nonpsychiatric intervention. Sociodemographic and clinical features of each treatment group are summarized in Table 1 while the interaction of each feature with time in a mixed-effects model of weight is in Table 2. Significant demographic associations with greater weight gain across treatment modalities included younger age and male sex. General medical features associated with greater weight gain included lower baseline BMI and weight loss prior to treatment initiation. Finally, greater weight gain was associated with an anxiety or depression diagnosis and receiving concomitant antipsychotic treatment. Predictors of greater weight gain were similar when analysis was limited to antidepressant-treated patients only (eTable 2 in Supplement).

In linear mixed-effects models comparing individual medications with citalopram, adjusted for sociodemographic and clinical features noted earlier, 3 antidepressant medications exhibited significantly less weight gain than citalopram (Table 3). From greatest to least difference, these included nortriptyline hydrochloride (β [SE]: −0.147 [0.034]; P < .001), amitriptyline (β [SE]: −0.081 [0.025]; P < .001), and bupropion (β [SE]: −0.063 [0.027]; P = .02). Four other medications, duloxetine, was of similar magnitude (β [SE]: −0.093 [0.049]) but not statistically significantly different from citalopram (P = .06). As anticipated, weight loss medications and the asthma treatment albuterol were associated with significantly less weight gain than citalopram. Excluding individuals receiving concomitant antipsychotic treatment did not meaningfully change results (eTable 3 in Supplement).
While mixed-effects models represent a standard means of addressing missing data in longitudinal studies including Food and Drug Administration medication registration trials, they make the assumption that discontinuation is random, which may not be the case. To understand dropout effects in more detail, we considered study completers and dropouts separately, repeating model development in these groups individually (Table 3). For bupropion, nortriptyline, and amitriptyline, observed differences in rate of weight change from citalopram were significant among individuals completing 12 months of treatment (completers). As a further examination of dropout, we explicitly modeled discontinuation risk by developing a logistic regression model of early (prior to 12-month) discontinuation (eTable 4 in Supplement). Probability of discontinuation (and interactions with other terms) was then incorporated in mixed-effects models. This approach effectively allows estimation of coefficients representing a weighted average of dropouts and completers, as recommended for nonignorable dropouts.18 With this approach, the TCAs demonstrated greater difference from citalopram while bupropion effects were somewhat diminished; while not statistically significant, both duloxetine and venlafaxine differences were numerically greater (eTable 5 in Supplement).

For illustrative purposes, Figure 2 depicts weight gain at each point to 12 months based on the best linear unbiased predictor from the mixed-effects model. While the trajectories of most

### Table 1. Baseline Patient Demographic and Clinical Features by Study Drug

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Female, %</th>
<th>Age, Mean (SD), y</th>
<th>White, %</th>
<th>Public Insurance, %</th>
<th>Prescription, Median (IQR), y</th>
<th>Baseline BMI, mean (SD)</th>
<th>ACCI, Median (IQR)</th>
<th>Depression*, Anxiety*, Pain*, Smoking*, Antipsychotic Concomitant, Psychotherapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressant</strong></td>
<td></td>
<td></td>
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<tr>
<td>SSRI</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram hydrobromide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67</td>
<td>45.0 (11.9)</td>
<td>78</td>
<td>21</td>
<td>2008 (2006-2009)</td>
<td>28.2 (6.6)</td>
<td>0 (0-1)</td>
<td>42</td>
</tr>
<tr>
<td>Escitalopram oxalate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66</td>
<td>45.0 (12.4)</td>
<td>87</td>
<td>16</td>
<td>2006 (2005-2008)</td>
<td>27.5 (6.2)</td>
<td>0 (0-3)</td>
<td>42</td>
</tr>
<tr>
<td>Paroxetine hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70</td>
<td>44.2 (11.9)</td>
<td>66</td>
<td>30</td>
<td>2007 (2005-2008)</td>
<td>28.6 (6.7)</td>
<td>0 (0-3)</td>
<td>52</td>
</tr>
<tr>
<td>Sertraline hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65</td>
<td>44.9 (12.2)</td>
<td>77</td>
<td>23</td>
<td>2006 (2004-2008)</td>
<td>28.1 (6.1)</td>
<td>0 (0-3)</td>
<td>38</td>
</tr>
<tr>
<td>Non-SSRI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68</td>
<td>44.6 (12.2)</td>
<td>78</td>
<td>21</td>
<td>2007 (2005-2009)</td>
<td>28.1 (6.5)</td>
<td>0 (0-3)</td>
<td>42</td>
</tr>
<tr>
<td>Amitriptyline hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71</td>
<td>45.0 (11.9)</td>
<td>61</td>
<td>33</td>
<td>2007 (2006-2009)</td>
<td>28.4 (6.4)</td>
<td>1 (0-3)</td>
<td>18</td>
</tr>
<tr>
<td>Bupropion hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60</td>
<td>44.9 (11.4)</td>
<td>80</td>
<td>23</td>
<td>2007 (2005-2009)</td>
<td>29.0 (6.9)</td>
<td>0 (0-3)</td>
<td>36</td>
</tr>
<tr>
<td>Duloxetine hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65</td>
<td>51.1 (9.6)</td>
<td>80</td>
<td>28</td>
<td>2007 (2007-2009)</td>
<td>29.8 (6.8)</td>
<td>2 (0-4)</td>
<td>39</td>
</tr>
<tr>
<td>Mirtazapine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54</td>
<td>49.4 (10.8)</td>
<td>68</td>
<td>38</td>
<td>2007 (2005-2009)</td>
<td>26.9 (6.9)</td>
<td>3 (0-6)</td>
<td>57</td>
</tr>
<tr>
<td>Nortriptyline hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65</td>
<td>44.8 (11.6)</td>
<td>55</td>
<td>42</td>
<td>2008 (2006-2009)</td>
<td>28.1 (6.1)</td>
<td>2 (0-4)</td>
<td>24</td>
</tr>
<tr>
<td>Venlafaxine hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>85</td>
<td>48.3 (10.4)</td>
<td>83</td>
<td>21</td>
<td>2007 (2005-2008)</td>
<td>28.3 (6.5)</td>
<td>2 (0-4)</td>
<td>32</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
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<tr>
<td>Weight loss</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61</td>
<td>46.6 (10.8)</td>
<td>66</td>
<td>25</td>
<td>2007 (2004-2008)</td>
<td>38.5 (6.2)</td>
<td>2 (0-3)</td>
<td>16</td>
</tr>
<tr>
<td>Phentermine hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70</td>
<td>41.3 (12.1)</td>
<td>80</td>
<td>14</td>
<td>2008 (2007-2009)</td>
<td>38.8 (7.4)</td>
<td>1 (0-3)</td>
<td>22</td>
</tr>
<tr>
<td>Sibutramine hydrochloride&lt;sup&gt;a&lt;/sup&gt;</td>
<td>74</td>
<td>43.3 (11.8)</td>
<td>79</td>
<td>14</td>
<td>2007 (2005-2008)</td>
<td>36.5 (5.8)</td>
<td>0 (0-2)</td>
<td>12</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol sulfate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61</td>
<td>46.2 (12.5)</td>
<td>74</td>
<td>24</td>
<td>2008 (2006-2009)</td>
<td>30.2 (7.3)</td>
<td>2 (0-4)</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SSRI, selective serotonin reuptake inhibitor.

* Selected diagnosis within 1 year of index prescription.

Concomitant treatment with an antipsychotic or psychotherapy during the study period.

<sup>a</sup> N = 5215.

<sup>b</sup> N = 758.

<sup>c</sup> N = 1758.

<sup>d</sup> N = 167.

<sup>e</sup> N = 112.

<sup>f</sup> N = 3000.

<sup>g</sup> N = 2205.

<sup>h</sup> N = 2153.

<sup>i</sup> N = 326.

<sup>j</sup> N = 251.

<sup>k</sup> N = 937.

<sup>m</sup> N = 944.

<sup>n</sup> N = 87.

<sup>o</sup> N = 167.

<sup*p> N = 112.

<sup>q</sup> N = 3000.
Antidepressants are qualitatively similar, the relatively diminished slope for TCAs and bupropion is apparent (eFigure in Supplement shows results limited to observed cases only and is generally similar to the predicted curves). Both figures also illustrate the weight loss observed with orlistat, phentermine, and sibutramine as well as the general weight-neutrality of albuterol. Finally, while analyses and figures focus on percentage of weight gain per month, for maximal clinical interpretability observed and predicted, absolute weight change in kilograms is also depicted at 3 months, 6 months, 9 months, and 12 months in eTables 6-9 in Supplement.

**Discussion**

In this electronic health record study using data from 22,610 individuals, including 19,244 antidepressant-treated patients, we identified statistically significant differences in trajectory of weight gain for multiple antidepressants, with bupropion and the TCAs nortriptyline and amitriptyline demonstrating significantly less weight gain than citalopram. Conversely, SSRIs were similar in rate of weight gain; escitalopram, the S enantiomer of citalopram, did not differ significantly from the racemic mixture. While not statistically significantly different from citalopram, the serotonin-norepinephrine reuptake inhibitors, particularly duloxetine, yielded somewhat less weight gain.

It is difficult to compare these results with prior investigations, which are almost entirely shorter-term outcomes derived from randomized, controlled efficacy trials in specific disorders. Nonetheless, our results are generally consistent with those presented in a recent meta-analysis, which suggested greatest weight gain with mirtazapine and paroxetine hydrochloride, similar in magnitude to citalopram. This analysis also suggested least weight gain with bupropion.

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**Table 2. Association of Sociodemographic, Health Status, and Concomitant Treatment Variables With Weight Change in Mixed-Effects Model**

<table>
<thead>
<tr>
<th>Feature</th>
<th>β (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.002 (0.001)</td>
<td>.001</td>
</tr>
<tr>
<td>Female</td>
<td>−0.030 (0.014)</td>
<td>.03</td>
</tr>
<tr>
<td>White</td>
<td>−0.020 (0.015)</td>
<td>.19</td>
</tr>
<tr>
<td>Public insurance</td>
<td>0.004 (0.015)</td>
<td>.79</td>
</tr>
<tr>
<td>Health status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>−0.010 (0.001)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prebaseline weight trend</td>
<td>−4.109 (0.812)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Index prescription, y</td>
<td>−0.005 (0.003)</td>
<td>.08</td>
</tr>
<tr>
<td>Comorbidity index (ACCI)</td>
<td>0.005 (0.008)</td>
<td>.48</td>
</tr>
<tr>
<td>Depression diagnosis</td>
<td>0.057 (0.014)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anxiety diagnosis</td>
<td>0.093 (0.016)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pain diagnosis</td>
<td>−0.004 (0.014)</td>
<td>.75</td>
</tr>
<tr>
<td>Recent smoker</td>
<td>0.043 (0.023)</td>
<td>.06</td>
</tr>
<tr>
<td>Concomitant treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>0.025 (0.023)</td>
<td>.29</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>0.118 (0.033)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Values are estimates (and standard error) of interaction of each variable with time in mixed-effect models.

**Table 3. Association of Medication Prescription With Weight Change Over Time Compared With Citalopram in Mixed-Effects Model**

<table>
<thead>
<tr>
<th>Class</th>
<th>Treatment</th>
<th>Mixed-Effects Model All Patients</th>
<th>Compliers</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>Citalopram hydrobromide</td>
<td>0 (Reference)</td>
<td>0 (Reference)</td>
<td>0 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Escitalopram oxalate</td>
<td>−0.071 (0.038)</td>
<td>.06</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine hydrochloride</td>
<td>−0.003 (0.022)</td>
<td>.90</td>
<td>.99</td>
</tr>
<tr>
<td></td>
<td>Paroxetine hydrochloride</td>
<td>−0.046 (0.026)</td>
<td>.08</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Sertraline hydrochloride</td>
<td>−0.044 (0.026)</td>
<td>.09</td>
<td>.27</td>
</tr>
<tr>
<td>Non-SSRI</td>
<td>Amitriptyline hydrochloride</td>
<td>−0.081 (0.025)</td>
<td>.01</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Bupropion hydrochloride</td>
<td>−0.063 (0.027)</td>
<td>.02</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Duloxetine hydrochloride</td>
<td>−0.093 (0.049)</td>
<td>.06</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>−0.054 (0.056)</td>
<td>.34</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline hydrochloride</td>
<td>−0.147 (0.034)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine hydrochloride</td>
<td>−0.044 (0.033)</td>
<td>.19</td>
<td>.76</td>
</tr>
<tr>
<td>Controls</td>
<td>Weight loss</td>
<td>−0.230 (0.105)</td>
<td>.03</td>
<td>.31</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
<td>−0.128 (0.126)</td>
<td>.31</td>
<td>.249 (0.197)</td>
</tr>
<tr>
<td></td>
<td>Phentermine hydrochloride</td>
<td>−0.525 (0.074)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Sibutramine hydrochloride</td>
<td>0.146 (0.112)</td>
<td>.19</td>
<td>.291 (0.185)</td>
</tr>
<tr>
<td></td>
<td>Bronchodilator</td>
<td>−0.123 (0.025)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

Values are covariate-adjusted estimates (and standard error) of interaction of drug and time with citalopram in a mixed-effects model. Compliers include only patients who had a weight measured at the 12-month point; dropouts include patients with no weight measurement at the 12-month point.
Figure 2. Mean Change in Weight After Index Prescription by Percentage of Baseline Body Mass Index Estimated by Best Linear Unbiased Prediction (BLUP)

A

SSRI, citalopram

SSRI, escitalopram

SSRI, fluoxetine

SSRI, paroxetine

SSRI, sertraline

Bronchodilators, albuterol

Other AD, amitriptyline

Other AD, bupropion

Other AD, duloxetine

Other AD, mirtazapine

Other AD, nortriptyline

Other AD, venlafaxine

B

Antiobesity, orlistat

Antiobesity, phentermine

Antiobesity, sibutramine

Patient, No. 5215 3056 2369 1917 1996

Patient, No. 758 434 327 256 289

Patient, No. 2824 1697 1293 995 1078

Patient, No. 1758 1052 792 634 649

Patient, No. 1873 1109 819 661 678

Patient, No. 3000 2171 1285 706 667

Patient, No. 2265 1388 1047 828 751

Patient, No. 2153 1326 935 675 599

Patient, No. 326 222 179 142 115

Patient, No. 251 192 133 103 83

Patient, No. 937 588 471 363 313

Patient, No. 944 584 432 337 350

Patient, No. 87 57 46 30 23

Patient, No. 167 139 100 62 52

Patient, No. 112 80 36 37 32

A, Antidepressents and albuterol sulfate. B, Weight loss medications. There is a difference in scale between parts A and B, corresponding to weight gain (A) vs weight loss (B). AD indicates antidepressants and SSRI, selective serotonin reuptake inhibitors.
and fluoxetine. One area of discordance is weight gain with amitriptyline, which we find to be significantly less than citalopram. However, that meta-analysis categorized 4 or more months of treatment as long term and suggested significant heterogeneity between individual studies for some TCAs. Previous investigation of amitriptyline focused on individuals with major depressive disorder, characterized as acute responders\(^{11}\) with less apparent medical comorbidity.

Caution is also warranted in comparing the present results with a prior randomized investigation of nortriptyline and escitalopram in major depressive disorder. In that 26-week study, greater weight gain was observed with nortriptyline at end point among 195 patients, while we observed less weight gain at 12 months among approximately 1700 patients (β: −0.071 vs −0.147; Table 3). Apart from differences in antidepressant indication (ie, this study includes all indications, not major depression alone), we note that as a clinical cohort, the present group had a substantially greater burden of comorbidity and greater age at entry, which may help to explain the differences in observed weight gain. Moreover, we note that recent systematic reviews also observed no significant difference in weight gain between escitalopram and nortriptyline.\(^{10,19}\) Extensive sensitivity analyses suggest the observed effects of nortriptyline are not explained by biased study discontinuation.

As a naturalistic study, the risk for confounding in our results is substantial; that is, particular patient subgroups might be more likely to be prescribed 1 medication vs another. For example, if physicians tended to prescribe mirtazapine only to patients who are underweight, a mirtazapine-associated weight gain might be spuriously elevated. A recent report underscores the relevance of weight gain in antidepressant-prescribing practices.\(^{19}\) This study addressed that possibility by adjusting for a range of sociodemographic and clinical features including diagnoses and concomitant treatment. Those at greatest risk for weight gain, independent of treatment type, included individuals who were younger men with lower BMI and who had experienced weight loss during the prior 6 months. Presence of an anxiety or depression diagnosis (but not a pain-related diagnosis) was associated with greater weight gain.

The potential impact of depressive symptoms on weight change bears particular comment. For a subset of patients, initial weight loss resulting from depression-associated reduction in appetite may be reversed as symptoms diminish, giving the appearance of treatment-associated weight gain. For others in whom depression is associated with increase in appetite, symptom reduction may contribute to weight loss. It is difficult to predict the net effect on observed weight change without a means of distinguishing these phenomena. However, the overall differences in rate of weight gain reported were adjusted for all of these potential differences. Apart from their role in addressing confounders, these variables may also be applied to identify individuals at greatest risk for weight gain when initiating antidepressant treatment.

We note several additional caveats in interpreting these results. While weight is routinely documented in primary care visits, some ascertainment bias may result if, for example, overweight individuals are more likely to have their weight measured more frequently. The present cohort could therefore over-sample overweight individuals (the mean BMI at baseline, approximately 28.3, falls in the overweight range where ≤30 is considered to be obese). Another key source of bias is likely to be treatment discontinuation as a result of weight gain, which should cause underestimation of true weight gain. To address this possibility, we conducted extensive sensitivity analysis, analyzing and presenting completers and dropouts separately, as well as modeling dropout explicitly. Reassuringly, the predicted and observed results are quite similar. Still, we cannot exclude the possibility that more modest differences between interventions are missed because individuals with greater weight gain preferentially discontinue treatment.

Another limitation is the possibility that our results systematically overrepresent or underrepresent treatment effects because adherence is not confirmed. In this, our study is like the large majority of other studies where blood levels are not routinely measured. In general, by misclassifying patients as treated, the lack of robust confirmation of adherence would tend to bias our results toward failing to detect real differences or underestimating the magnitude of weight gain. Further limitations include a lack of direct examination of antidepressant dose-response effects or treatment-by-clinical feature effects, both of which would require larger data sets for adequate statistical power.

In fact, only very large-scale randomized clinical trials can assess the relatively modest effects we observed with adequate statistical power while fully excluding confounding. Moreover, even a large randomized trial would be vulnerable to the effects of nonrandom dropout and poor adherence. Among alternative strategies, meta-analysis is hindered by heterogeneous study designs along with other limitations such as inconsistency in data collection, inclusion of mixed groups of drug-naïve and nonnaïve patients, monotherapy vs combination therapy, variable duration of treatment, and uncontrolled baseline features.\(^{20}\) Postmarketing surveillance systems, such as that represented by the Food and Drug Administration’s Adverse Effect Reporting System, do not capture quantitative and nonepisodic changes over time. Electronic health records therefore represent a powerful tool for evaluating longitudinal association in sample sizes that cannot be readily achieved in individual clinical trials. In addition to large sample sizes, they allow quantification of longer-term changes than the typical acute randomized trial. Results should also be more generalizable owing to the extensive inclusion criteria often required in randomized trials.

Conclusions

Taken together, our results clearly demonstrate significant differences between several individual antidepressant strategies in their propensity to contribute to weight gain. While the absolute magnitude of such differences is relatively modest, these differences may lead clinicians to prefer certain treatments according to patient preference or in individuals for whom weight gain is a particular concern, such as those with the other weight gain risk factors we report here. Estimates of absolute weight gain (eTables 6-9 in Supplement) may also be useful in clinical discussions with patients on this topic. In light of the marked elevation in mortality observed with depres-
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sive and related disorders,21 interventions to diminish weight gain merit further investigation. Moreover, this study illustrates the role of electronic health records investigations to systematically detect and quantify adverse effects, complementing traditional approaches including randomized trials, meta-analysis, and postmarketing surveillance.

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REFERENCES