ORIGINAL RESEARCH

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Obesogenic Medications and Weight Gain Over 24 Weeks in Patients with Depression: Results from the GUIDED Study

By Jess G. Fiedorowicz, Lisa Brown, James Li, Sagar V. Parikh, Boadie W. Dunlop, Brent P. Forester, Richard C. Shelton, Michael E. Thase, Matthew Macaluso, Kunbo Yu, John F. Greden

ABSTRACT: *Weight gain is a common side-effect of medications used to treat major depressive disorder (MDD). We sought to estimate the frequency of weight gain for obesogenic medications prescribed for MDD and to evaluate if bupropion mitigated risk for weight gain. We analyzed a prospective cohort of patients with weight available at baseline and 12 weeks (n = 1,032) or 24 weeks (n = 871) in a post hoc analysis of the* **G***enomics* **U***sed to* **I***mprove* **DE***pression* **D***ecisions (GUIDED) study of patients with MDD who failed at least one medication trial. We compared weight gain between those on versus not on medications with high risk for weight gain, including a subgroup receiving combination treatment with bupropion. A second analysis evaluated weight gain across traditional medication classes, adjusting for potential confounding variables. Those on medications identified as high risk for weight gain were significantly more likely to experience clinically significant weight gain (≥3%) at 12 weeks (29.3% vs. 16.3%, p < .001) and 24 weeks (33.5% vs. 23.5%, p = .015). No protection from clinically significant weight gain was observed among patients treated with a high-risk medication concomitantly with bupropion (N = 31, 35% and 52% with clinically significant weight gain at 12 and 24 weeks). Antipsychotic medications and tricyclic antidepressants were most often associated with clinically significant weight gain. This study helps quantify the real-world risk of weight gain for patients with MDD on medications with high risk for weight gain, especially for patients taking antipsychotics. Concurrent treatment with bupropion does not appear to mitigate the weight gain risk.*. Psychopharmacology Bulletin. *2021;51(4):8–30.*

Fiedorowicz, University of Ottawa, The Ottawa Hospital, Ottawa Hospital Research Institute; Brown, Li, Yu, Myriad Genetics, Inc.; Parikh, Greden, University of Michigan; Dunlop, Emory University School of Medicine; Forester, McLean Hospital and Harvard Medical School; Shelton, University of Alabama at Birmingham; Thase, University of Pennsylvania, Macaluso, UAB.

To whom correspondence should be addressed: Jess G. Fiedorowicz, University of Ottawa, Canada. E-mail: jess-fiedorowicz@uiowa.edu

Introduction

Major depressive disorder (MDD) is associated with a higher risk of obesity, particularly in women and those with recurrent episodes.[1–3] Longitudinal studies suggest that the temporal relations are bidirectional with stronger associations observed for the direction of depression preceding obesity. In a systematic review of such longitudinal studies ranging from 2–28 years, those who were depressed had a 37% increased risk of developing obesity and those with obesity had an 18% increased risk of becoming depressed.[4] One potential contributor to the increase risk of obesity in those with depression relates to obesogenic effects of medications. Among the many of medications now used to treat MDD, a striking majority are associated with some risk for weight gain.[5] Many antipsychotic medications are especially well-known for their obesogenic potential. Although their use for MDD is declining, antipsychotics are still prescribed to nearly one in five patients with MDD, typically in combination with antidepressants as an augmentation strategy.[6] While increased awareness of side-effects may be one contributor of decreasing use, antipsychotics are not the only medications that can increase weight. Antidepressants also have been associated with varied amounts of weight gain, particularly with long-term use.[7] It is therefore important to view risk for weight gain broadly and across traditional medication classes. Such risk for weight gain can continue over years[8] and can therefore impact obesity-related comorbidities such as diabetes mellitus and cardiovascular disease.[9]

Unlike other medications used to treat MDD, bupropion has been associated with modest weight loss in the treatment of depression in both short-term (8 week)[10] and long-term (52 week) studies.[11] As a consequence, bupropion is often prescribed as an antidepressant either as monotherapy or in combination with another agent for the treatment of MDD when weight gain is deemed a clinical concern.[12,13] Bupropion has been studied in combination with other antidepressants in open label studies[14,15] and STAR*D[16] and differences in weight gain have not been reported or were not assessed. Over the 36-week acute and continuation treatment in the VAST-D trial, the bupropion arms (change or augmentation) showed weight loss of ⩾7% in 18.6–21.6% of participants compared to weight gain of ⩾7% in 7.5–8.5%, much lower than the 30.6% frequency of ⩾7% weight gain with aripiprazole.[17] While a combination of bupropion and naltrexone has been approved by the FDA for the treatment of obesity,[18] bupropion monotherapy has not been approved for this indication.[19]

Utilizing 24-week, prospective data from an initially randomized clinical trial in which clinically-driven, real-world treatment decisions were being made for patients with MDD who were not responsive to at least one medication trial, we sought to estimate the magnitude of weight gain risk for users of high risk obesogenic medications. We also sought to assess whether the common practice of combining bupropion, which is not associated with risk of weight gain as a monotherapy, with these medications had any impact on attenuating weight gain risk. We additionally assessed weight gain with more traditionally defined medication classes and explored potential moderators of weight gain.

Methods

The Genomics Used to Improve DEpression Decisions (GUIDED) study involved a randomized controlled trial of 1,167 patients with MDD who did not respond to at least one medication trial. Participants were randomized to pharmacogenomic testing with the GeneSight Combinatorial Pharmacogenomic test from Assurex Health, Inc. (Mason, OH) versus treatment as usual. Results have been published elsewhere.[20] The study was conducted between April 2014 and February 2017. While the blind was broken at 12 weeks, treatment continued in an open, naturalistic manner for another 12 weeks. The study was approved by the Copernicus Group Independent Review Board and all patients provided written informed consent to participate.

For this secondary, *post hoc* analysis of GUIDED data, the sample was restricted to the 1,039 patients with baseline weight and a follow-up weight at 12 or 24 weeks. We identified weight change of ⩾3% at 12 and 24 weeks as clinically significant weight gain, a threshold that has been used in previous research.[21–31] We chose this threshold *a priori* over the more widely-used ⩾5% threshold to improve detection of potentially longer-term clinically deleterious weight gain in this 24 week study.

Medications at "high risk" for weight gain were identified from a recent review of placebo-controlled trials,[5] and included clozapine, olanzapine, iloperidone, chlorpromazine, quetiapine, risperidone, paliperidone, mirtazapine, amitriptyline, amisulpride, valproate, clomipramine, desipramine, doxepin, imipramine, nortriptyline. Thioridazine was added based on clinical trial data showing substantial weight gain relative to the active comparator remoxipride.[32,33] Bupropion was identified as the sole "no risk" medication for weight gain with some propensity to cause weight loss, particularly in patients with obesity.[34,35]

This secondary analysis was performed on the per protocol sample. For the week 12 analyses, use of a given medication or class was categorically operationalized based on whether a participant was on the medication or medication class for at least the final 4 weeks of the treatment period (weeks 8–12). For the week 24 analyses, exposure was based on being on the medication or medication class for at least the final 12 weeks (weeks 12–24). This ensured sufficient time on the medication to see effects on weight. Logistic regression models with the dependent variable consisting of a dichotomous, indicator variable for weight gain, defined as gaining ⩾3%, were analyzed separately at 12 and 24 weeks. We assessed the more popular ⩾5% threshold in a sensitivity analysis. Multivariable models included the potential confounding variables of baseline weight, age (continuous, linear effect), sex, co-occurring generalized anxiety disorder (GAD), co-occurring posttraumatic stress disorder (PTSD), and total number of other medical conditions as covariates. These six covariates were selected from a total of 17 variables considered for the models based on the strength of their association with the primary outcome in logistic regression models through a backward elimination process. Models estimated weight gain by groupings based on propensity for weight gain to test our primary hypothesis, which divided medications into those with and without high risk of weight gain and later by more traditional medication classes: antipsychotics, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and other antidepressants. Estimates were provided for those on any "high risk" medication for weight gain and later stratified for those only on high-risk medications or including a "no risk" medication (bupropion). Differences with a p-value <0.05 were considered statistically significant. Adjustment for multiple comparisons was deferred given the outcome involving an adverse event for which we want to maximize detection, rather than efficacy, where we would prioritize avoiding false claims due to Type I error. In exploratory analyses, we assessed an array of potential moderators of weight gain at week 12 in logistic regression models that included the medication class/grouping of interest, the putative moderator, and a medication class/grouping by moderator interaction with baseline weight as a covariate. Moderators assessed included age (continuous), sex, baseline Hamilton 17-Item Depression Rating Scale (HAM-D17) score, level of gene-drug interactions for the patients prescribed medications (based on GeneSight Psychotropic test report congruence divided into no/moderate (green/yellow) interaction versus significant (red) interaction), polygenic report category of baseline medications (green/yellow/red from GeneSight Psychotropic test), number of medications not responded to at baseline, race (white vs. non-white), ethnicity (Hispanic

vs. non-Hispanic), number of comorbidities, number of cardiovascular comorbidities, and Charlson Comorbidity index.

Results

The sociodemographic and clinical characteristics of the sample are detailed in Table 1, broken down by overlapping medication classes.

TABLE 1

Clinical and Sociodemographic Characteristics for Subsample Prescribed Obesogenic Medications

	Weight Gain Risk			
	Any High Risk (N = 130)	High Risk + Bupropion (N = 31)	High Risk Only (N = 35)	Total (N = 1032)
Age (years)				
Mean (SD)	49.8 (14.4)	48.3 (12.6)	50.4 (14.3)	48.0 (14.5)
Median	52.0	52.0	53.0	50.0
Min, Max	18, 85	23, 74	24, 74	18, 90
Age Group, N(%)				
18 to 34	26 (20.0)	4 (12.9)	9 (25.7)	227 (22.0)
35 to 49	28 (21.5)	10 (32.3)	5 (14.3)	285 (27.6)
50 to 64	53 (40.8)	14 (45.2)	12 (34.3)	379 (36.7)
65 and Over	23 (17.7)	3 (9.7)	9 (25.7)	141 (13.7)
Sex, N(%)				
Female	83 (63.8)	21 (67.7)	23 (65.7)	728 (70.5)
Male	47 (36.2)	10 (32.3)	12 (34.3)	304 (29.5)
Ethnicity, N(%)				
Hispanic or Latino	8 (6.2)	2 (6.5)	4 (11.4)	80 (7.8)
Not Hispanic or Latino	122 (93.8)	29 (93.5)	31 (88.6)	952 (92.2)
Race, N(%)				
White	111 (85.4)	25 (80.6)	29 (82.9)	838 (81.2)
Black	16 (12.3)	5 (16.1)	5 (14.3)	151 (14.6)
Asian	2 (1.5)	1 (3.2)	0	19 (1.8)
Other or Multiple	1 (0.8)	0	1 (2.9)	24 (2.3)
Annual Income ($), N(%)				
0–25,000	47 (36.2)	13 (41.9)	10 (28.6)	442 (42.8)
25,000–50,000	42 (32.3)	11 (35.5)	12 (34.3)	253 (24.5)
50,000–75,000	12 (9.2)	3 (9.7)	5 (14.3)	117 (11.3)
75,000–100,000	7 (5.4)	1 (3.2)	2 (5.7)	52 (5.0)
100,000 and above	5 (3.8)	1 (3.2)	2 (5.7)	35 (3.4)
Refused to answer	17 (13.1)	2 (6.5)	4 (11.4)	133 (12.9)
Highest Level of Education, N(%)				
Less than high school	6 (4.7)	3 (10.0)	0	34 (3.3)
High school diploma or equivalent	23 (18.0)	3 (10.0)	6 (17.6)	212 (20.9)
Some college or postsecondary, no degree	32 (25.0)	11 (36.7)	6 (17.6)	252 (24.8)

(*Continued*)

TABLE 1 (*Continued*)

Clinical and Sociodemographic Characteristics for Subsample Prescribed Obesogenic Medications

		WEIGHT GAIN RISK		
	ANY HIGH RISK (N = 130)	HIGH RISK + BUPROPION (N = 31)	HIGH RISK ONLY (N = 35)	TOTAL (N = 1032)
Associate's degree	18 (14.1)	4 (13.3)	4 (11.8)	128 (12.6)
Bachelor's degree	32 (25.0)	7 (23.3)	11 (32.4)	246 (24.2)
Master's degree	15 (11.7)	2 (6.7)	7 (20.6)	109 (10.7)
Doctoral or professional degree	2 (1.6)	0	0	34 (3.3)
Smoker, N(%)				
No	100 (76.9)	27 (87.1)	28 (80.0)	872 (84.5)
Yes	30 (23.1)	4 (12.9)	7 (20.0)	160 (15.5)
Generalized Anxiety Disorder Diagnosis, N(%)				
0	99 (76.2)	22 (71.0)	28 (80.0)	864 (83.8)
1	31 (23.8)	9 (29.0)	7 (20.0)	167 (16.2)
Panic Disorder Diagnosis, N(%)				
0	100 (76.9)	22 (71.0)	32 (91.4)	873 (84.7)
1	30 (23.1)	9 (29.0)	3 (8.6)	158 (15.3)
Posttraumatic Stress Disorder Diagnosis, N(%)				
0	119 (91.5)	27 (87.1)	34 (97.1)	980 (95.1)
1	11 (8.5)	4 (12.9)	1 (2.9)	51 (4.9)
Depression Category, N(%)				
Moderate (HAM-D17 14–18)	25 (19.2)	8 (25.8)	5 (14.3)	289 (28.0)
Severe (HAM-D17 19–22)	45 (34.6)	12 (38.7)	10 (28.6)	373 (36.1)
Very Severe (HAM-D17 > 23)	60 (46.2)	11 (35.5)	20 (57.1)	370 (35.9)
Baseline HAM-D17				
Mean (SD)	22.0 (4.0)	21.2 (3.5)	23.1 (4.5)	21.2 (4.2)
Median	22.0	20.0	24.0	21.0
Min, Max	14, 33	15, 27	14, 33	14, 37
Prior Medication Trials Without Response				
Mean (SD)	3.9 (2.9)	4.5 (3.3)	3.8 (3.4)	3.0 (2.3)
Median	3.0	4.0	3.0	2.0
Min, Max	1, 18	1, 18	1, 13	1, 18
Number of Comorbidities				
Mean (SD)	7.8 (6.0)	8.5 (5.1)	7.6 (7.9)	7.0 (5.5)
Median	7.0	9.0	6.0	6.0
Min, Max	0, 45	2, 24	0, 45	0, 47
Baseline Weight (pounds)				
Mean (SD)	183.2 (40.6)	188.8 (36.0)	171.8 (37.0)	193.3 (49.8)
Median	185.2	190.0	176.0	186.0
Min, Max	103, 300	130, 271	108, 280	95, 387

The following table details features for patients with mdd on "high risk" medications, alone, or with adjunctive "no risk" bupropion to test the hypothesis of whether bupropion appears to mitigate risk of weight gain. As illustrated in figure 1, these groupings are not mutually exclusive as those in the "high risk only" and "high risk + no risk" categories are also included in the "any high risk" group.

The full sample analyzed at 12 weeks (N = 1032) had a median age of about 50 years and was predominantly (70.5%) female. Those on "high risk" medications were more likely to fall in the very severe depression category (46.2% vs. 34.4% in rest of sample), although mean baseline HAM-D-17 scores were similar. They also had more unsuccessful medication trials (mean = 3.9, SD = 2.9 vs. mean = 3.0, SD = 2.3 in entire sample) and weighed less at baseline (mean = 183.2, SD = 40.6 pounds vs. mean = 193.3, SD = 49.8 pounds in entire sample). The sample broken down by overlapping medication classes is shown in Supplemental Table 1.

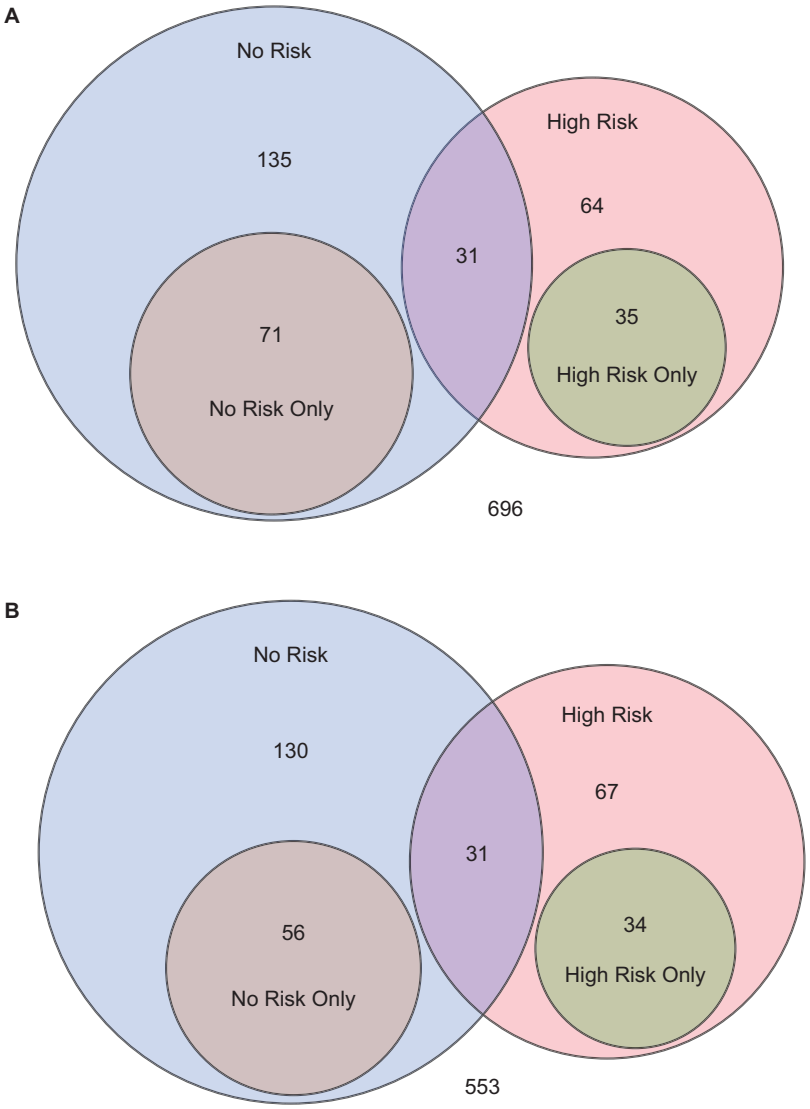
At 12 weeks, a total of 130 (12.6%) patients were on medications classified as "high risk" of weight gain, 24% of those 130 were also on the "no risk" bupropion. At 24 weeks, 132 (15.2%) were on "high risk" medications with a similar proportion on the "no risk" medication as illustrated in Figure 1. The "no risk" medication, bupropion, was used alone or in any combination by 237 patients at 12 weeks and 217 patients at 24 weeks.

Across the entire sample, a total of 186/1032 (18.0%) of patients experienced ⩾3% weight gain by 12 weeks and 220/871 (25.3%) did so at 24 weeks. As shown in Table 2 and consistent with the study hypothesis, those taking "high risk" medications were significantly more likely to experience clinically significant weight gain. Those on any "high risk" medications were more likely to have weight gain at 12 weeks (29.3% vs. 16.3%, $p < .001$) and 24 weeks (33.5% vs. 23.5%, $p = .015$). Those who concurrently used bupropion (high risk and no risk) remained significantly more likely to experience weight gain at 12 weeks (35.1% vs. 17.4%, $p = .014$) and 24 weeks (51.6% vs. 24.0%, $p = .001$). Compared to those on high medications without bupropion, those on high risk medications with bupropion were significantly more likely to experience weigh gain at week 24 ($\chi^2 = 6.09$, $p = .01$), but not at week 12 ($\chi^2 = .77$, $p = .38$). Figure 2 illustrates how these frequencies varied by medication class prescribed. The highest frequency of weight gain was evident for those on antipsychotics and tricyclic antidepressants. Those prescribed antipsychotic medications were significantly more likely to demonstrate weight gain at both 12 weeks ($n = 96$, 28.3% vs. 16.8%, $p = .006$) and 24 weeks ($n = 101$, 39.4% vs. 23.1%, $p < .001$). Patients taking tricyclic antidepressants were also more likely to show weight gain at 12 weeks ($n = 38$, 28.1% vs. 17.5%, $p = .10$) and 24 weeks ($n = 39$, 34.9% vs. 24.6%, $p = .15$), although these differences were not statistically significant in this smaller subsample.

Results that were similar to the univariable models also were observed in multivariable models. These were adjusted for baseline weight, age

FIGURE 1

Patient Groupings Based on Classifications of Medications by Weight Gain Liability



The venn diagrams (a 12 weeks, b 24 weeks) show the frequency at which "no risk" (bupropion) and "high risk" medications were used with the degree of overlap between groups. The remainder of patients (696 at week 12 and 553 at week 24) are on medications that are neither classified as high or no risk.

(continuous, linear effect), sex, co-occurring GAD, co-occurring PTSD, and number of other medical conditions as covariates. All statistically significant findings from univariable models remained statistically significant in multivariable models. Those on "any high risk" medication were more likely to experience weight gain at 12 weeks (29.4% vs. 16.5%,

TABLE 2

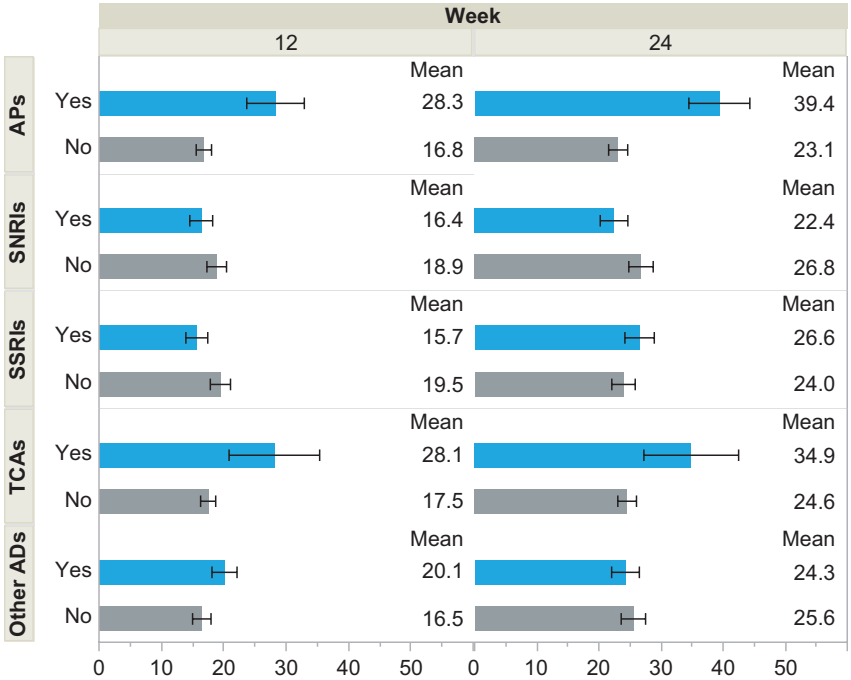
Frequency of Weight Gain by Weight Gain Liability Medication Category

Medication Category	Week	Taking Medication Grouping N	Taking Medication Grouping % of Patients with Wt. Gain	Not Taking Medication Grouping N	Not Taking Medication Grouping % of Patients with Wt. Gain	Δ	P-Value
Any High Risk	12	130	29.3	902	16.3	13.1	**<0.001**
	24	132	33.5	739	23.5	10.0	**0.015**
High Risk Only	12	35	32.8	997	17.4	15.4	**0.022**
	24	34	31.0	837	24.8	6.3	0.41
High Risk & No Risk	12	31	35.1	1001	17.4	17.7	**0.014**
	24	31	51.6	840	24.0	27.6	**0.001**

This table highlights the relative frequencies by which clinically significant weight gain (⩾3%) was observed for those taking "high risk" medications compared to those who were not. The subgroups taking "only high risk" medication or taking a "high risk" medication with a "no risk" medication (i.E., Bupropion) are also shown. The statistical reporting is based on univariable models.

FIGURE 2

Percent of Patients Experiencing Weight Gain by Medication Class



The proportion of patients experiencing clinically significant weight gain (⩾3%) is illustrated by common medication classes. The estimates are based on univariable models.
AD = Antidepressant, AP = antipsychotic, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

$p < .001$) and 24 weeks (36.0% vs. 24.5%, $p = .009$). Individuals on a" high risk" medication with "no risk" bupropion similarly gained significant weight at 12 weeks (35.2% vs. 18.0%, $p = .02$) and 24 weeks (55.3% vs. 25.4%, $p < .001$). Antipsychotic medications were still significantly associated with weight gain at 12 weeks (29.3% vs. 17.3%, $p = .006$) and 24 weeks (43.1% vs. 23.7%, $p < .001$). For the aforementioned multivariable models of "any high risk" medications, baseline weight, age, and number of comorbidities, and sex were found to be statistically significant at week 12. Participants with higher weight at baseline were less likely to gain weight (OR per pound: 0.996, 95% CI: 0.992–0.999); older subjects were less likely to gain weight (OR per year: 0.98, 95% CI: 0.97–0.99); women were less likely to gain weight than men (OR: 0.67, 95% CI: 0.49–0.99); participants with higher number of comorbidities were more likely to gain weight (OR: 1.04, 95% CI: 1.01–1.07 per comorbidity). Baseline weight, age, and number of comorbidities remained statistically significant in models for week 24 while sex was no longer significant. These three variables were also significant for the models including "high risk" medications and "high risk" medication with "no risk" bupropion, and of any individual medication class (antipsychotics, SNRIs, SSRIs, TCAs, other antidepressants). In all of these models, female sex was protective for weight gain at 12 weeks, but not at 24 weeks.

Exploratory analyses looked at interactions between 11 moderator variables and medication groupings/classes in separate models. There was no evidence of moderation for any of the 11 moderator variables with the "high risk" medication grouping, antipsychotics, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, or tricyclic antidepressants. There was evidence of significant moderation by age ($p = .02$) and Charlson Comorbidity Index ($p = .04$) for the disjunctive "other antidepressant" category, which predominantly involved bupropion (54%), vilazodone (13%), mirtazapine (11%), trazodone (11%), and vortioxetine (10%). This moderation was in the direction of greater weight gain with in those taking other antidepressants with more advanced age and more medical comorbidities relative to those taking other antidepressants. In these moderation models with the interaction term, the main effects of age ($p = .79$) and number of comorbidities ($p = .19$) were not significant.

In the sensitivity analysis, using the more conventional ⩾5% threshold, relative differences between groups were similar with, as would be expected, lower frequencies of categorical weight gain. One exception was that those taking SSRIs were significantly less likely to experience ⩾5% weight gain at 12 weeks (4.8% with vs. 9.9% without, $p = .003$).

No differences in frequency of weight gain were seen for SSRIs at 24 weeks (13.5% with vs. 14.8% without, p = .59). Supplemental Table S2 presents the results from the sensitivity analysis related to the medication groupings based on weight gain risk. Supplemental Figure S1 presents the results for more traditional medication classes.

Discussion

In this analysis from the GUIDED study, participants in this trial were prescribed medications with varying weight gain liability. As expected, those on a medication identified as high risk were significantly more likely to experience weight gain at weeks 12 and 24. Importantly, those taking bupropion and high-risk medications had even higher rates of weight gain, in both univariable and multivariable models, and significantly more than those on high-risk medications without bupropion at 24 weeks. Higher frequencies of weight perhaps could have been observed if bupropion was a maker for treatment resistant depression (confounding) or through inhibition of CYP 2D6 metabolism for select high risk medications (iatrogenic weight gain). Regardless, there was certainly no evidence that the addition of bupropion mitigated weight gains. We found that patients taking antipsychotics for at least 4 weeks had significant weight gain compared to those not on antipsychotics.

Overall, this analysis lends further support to the principle that medication treatment selection matters with regard to risk of weight gain. It also fails to lend support for the common, inadequately studied, practice of using bupropion to mitigate risk. While the study was not focused on identifying risk factors for weight gain, multivariate models found older age to generally be protective for weight gain and medical comorbidities to be a risk factor for weight gain. A higher baseline weight was protective although it is worth noting that a greater absolute weight gain was required for those who were higher weight to cross the threshold of our outcome with ⩾3%. Similar results were seen on sensitivity analysis using the ⩾5% weight gain threshold. Interestingly, female gender was protective for weight gain at 12, but not 24 weeks in all models. We did not find evidence of moderation by sex and prior studies have had conflicting results on sex differences in iatrogenic weight gain for these medications.

There has been limited study of weight gain related to treatment of MDD in large clinical research and real-world samples. In an analysis of the Canadian National Population Health Survey, those under age 65 on antidepressants were found to have significantly more weight gain over the 12-year follow-up. The weight gain attributed to antidepres-

sants was modest (1.1 kg/12 years) although this estimate should be interpreted cautiously given the limitations in assessment of exposure to medications (recorded use for past two days in interviews conducted every two years) and outcome (self-reported height and weight).[36] Risk for weight gain with antidepressants may persist over many years and was found especially prominent in years two and three,[8] beyond the follow-up length of this analysis. In a large, prospective occupational cohort in Finland followed for a mean of 4.8 years, incident antidepressant use, defined as at least 200 daily doses, was significantly associated with self-reported weight gain. In this study, incident users of any antidepressants (n = 910) experienced significantly greater relative weight change of 4.5% vs. 2.2% in propensity-score matched controls. This difference was most pronounced for incident users of tricyclic antidepressants compared to propensity score matched controls (n = 27, 7.9% vs. 1.5%, p = .0004).[37] In a slightly larger subsample on tricyclic antidepressants, our analysis similarly showed a higher frequency of clinically significant weight gain for users of tricyclic antidepressants although this difference was not statistically significant. In the Netherlands Study of Depression and Anxiety, after one year of follow-up, self-reported weight gain was 29% in users of mirtazapine, 22% in users of tricyclic antidepressants, and 19% in users of selective serotonin reuptake inhibitors.[38] Using electronic medical record data in the Northeastern United States, weight change was assessed in 19,244 patients receiving an antidepressant for varied indications. As expected, bupropion was associated with significantly less weight gain than the referent comparator citalopram although unexpectedly so too were the tricyclic antidepressants nortriptyline and amitriptyline, although these may have been used at lower doses (e.g., for pain) and with less frequent concomitant antipsychotic use[39] or used in lower doses for indications such as pain. Clinical trials have shown greater weight gain with tricyclic antidepressants over comparator selective serotonin reuptake inhibitors.[40,41]

Weight gain can occur quickly and dramatically for some patients with mood disorders.[42] Better understanding and consideration of the factors that influence weight gain will improve precision-medicine decisions. With antipsychotic medications, weight gain of ⩾5% in the first month was found to be the best predictor of intermediate (3 month) and long-term (1 year) weight gain.[43] Early changes in weight (1 week) also have been associated with intermediate (6 week) weight gain with antidepressants.[44] The mortality risks associated with weight gain likely are most relevant for those with obesity. Increases in body mass index of 3–5 kg/m^2 over 2 years in those with Class II or greater obesity are associated with a 33–53% increase in mortality.[45] It is therefore important for clinicians to recognize weight gain early and intervene appropriately

for at risk patients. Clinicians should also be aware of the considerable individual differences in vulnerability to weight gain with obesogenic psychotropic medications.[5]

Strengths of the study included the large and reasonably generalizable sample with MDD. The results are also generally consistent with existing evidence and are biologically plausible. One notable exception to generalizability is an underrepresentation of Asian participants, which may be of particular importance given a tendency for more adiposity and related metabolic factors at a given body mass index in this population.[46]

This prospective cohort study has several limitations. While this was a randomized controlled trial, participants were randomized to whether their provider would have an additional tool for clinical decision making. Participants were not randomized to specific medications or medication groupings such as the "high risk" grouping used in our analysis or to adjuvant "low risk" bupropion. The analyses therefore effectively rely on an observational study design and weight gain was not a prespecified outcome. The study design dictated that our analyses had to use generic, previously-established medication groupings that did not fully take dose or duration (beyond four weeks) of medications into consideration. We also did not take specific prior medication trials into account. Those prescribed antipsychotics had more prior medication trials without response. In schizophrenia, lack of prior obesogenic medication exposure, is associated with greater weight gain.[47] Assuming this also holds for MDD, our results would be biased toward the null and away from the observed weight gain seen with antipsychotics. It is possible that providers discontinued medications that were causing weight gain prior to a given assessment. If anything, this reasonable practice might bias our results toward the null hypothesis and diminish our assay sensitivity. Our thresholds for medication exposure also carry some risk of misclassification with, for example, those being on medications less than 4 week for the 12-week analysis not being included. Any resultant bias from this exposure misclassification would again be in the direction of the null hypothesis. With data being collected as part of a clinical trial and weights regularly collected, it is also likely that providers may have displayed less therapeutic inertia than is commonly seen in real-world.[48,49] and even trial settings.[50] As noted, greater changes in medications would be expected to bias this analysis toward not finding differences between medication groups and some clear differences were nonetheless observed. This study also was not designed to assess weight changes; thus, some predictors of medication-induced weight gain were not available. For instance, family history of obesity has also been found to a be a risk factor for weight gain with both antidepressants[51] and

antipsychotics.[52] Our multivariable models adjusted for comorbidities, but not the severity of the comorbidities or depression. None of the Genesight-associated genes in the combinatorial test have been demonstrated to be strongly associated with weight gain, so were not evaluated in this analysis. Nevertheless, this is an area that could be explored in future studies. For example, the T allele of the 102T/C polymorphism of *HRT2A* has been associated with weight gain,[53] but was not tested in Genesight.

Conclusions

This study conveys three important messages for clinical providers. First, it illustrates the real-world risk of weight gain with obesogenic medications used to treat MDD. Findings largely replicate those seen in clinical trials with these medications and hopefully call attention to this known, but still under-studied and under-appreciated phenomenon. Second, our findings do not support the practice of adding bupropion to mitigate any risk of high-risk medications although the overall study was not directly designed to test this question. The combination of bupropion and naltrexone is well-established for weight loss[54–56] and may be better suited for any such study using a randomized controlled trial design. Third, the high observed frequencies of weight gain underscore the importance of monitoring weight in patients being treated for MDD, addressing weight gain early in treatment, and undertaking evidence-based strategies to manage this risk. ✤

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Mr. Li owns stock in Myriad Genetics, Inc. where he was an employee from January 2016 to November 2020. He now works for PTC Therapeutics.

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Supplementary Material

TABLE S1

Clinical and Sociodemographic Characteristics of Full Sample

	Drug Class					
	Antipsychotic (N = 96)	SNRI (N = 409)	SSRI (N = 430)	TCA (N = 38)	Other AD (N = 399)	Total (N = 1032)
Age (years)						
Mean (SD)	49.1 (12.8)	49.1 (14.3)	47.2 (14.9)	51.8 (14.1)	47.8 (14.4)	48.0 (14.5)
Median	53.0	51.0	49.0	54.0	50.0	50.0
Min, Max	18, 74	18, 83	18, 90	23, 73	18, 85	18, 90
Age Group, N(%)						
18 to 34	15 (15.6)	80 (19.6)	103 (24.0)	7 (18.4)	90 (22.6)	227 (22.0)
35 to 49	23 (24.0)	115 (28.1)	119 (27.7)	6 (15.8)	109 (27.3)	285 (27.6)
50 to 64	49 (51.0)	154 (37.7)	151 (35.1)	16 (42.1)	146 (36.6)	379 (36.7)
65 and Over	9 (9.4)	60 (14.7)	57 (13.3)	9 (23.7)	54 (13.5)	141 (13.7)
Sex, N(%)						
Female	71 (74.0)	296 (72.4)	297 (69.1)	26 (68.4)	277 (69.4)	728 (70.5)
Male	25 (26.0)	113 (27.6)	133 (30.9)	12 (31.6)	122 (30.6)	304 (29.5)
Ethnicity, N(%)						
Hispanic or Latino	8 (8.3)	33 (8.1)	39 (9.1)	2 (5.3)	19 (4.8)	80 (7.8)
Not Hispanic or Latino	88 (91.7)	376 (91.9)	391 (90.9)	36 (94.7)	380 (95.2)	952 (92.2)
Race, N(%)						
White	78 (81.3)	347 (84.8)	333 (77.4)	34 (89.5)	327 (82.0)	838 (81.2)
Black	16 (16.7)	45 (11.0)	78 (18.1)	2 (5.3)	57 (14.3)	151 (14.6)
Asian	0	7 (1.7)	9 (2.1)	1 (2.6)	9 (2.3)	19 (1.8)
Other or Multiple	2 (2.1)	10 (2.4)	10 (2.3)	1 (2.6)	6 (1.5)	24 (2.3)

Annual Income ($), N(%)						
0–25,000	46 (47.9)	174 (42.5)	198 (46.0)	7 (18.4)	176 (44.1)	442 (42.8)
25,000–50,000	21 (21.9)	94 (23.0)	105 (24.4)	17 (44.7)	104 (26.1)	253 (24.5)
50,000–75,000	8 (8.3)	53 (13.0)	45 (10.5)	6 (15.8)	38 (9.5)	117 (11.3)
75,000–100,000	10 (10.4)	20 (4.9)	7 (4.0)	1 (2.6)	26 (6.5)	52 (5.0)
100,000 and above	2 (2.1)	19 (4.6)	7 (1.6)	3 (7.9)	13 (3.3)	35 (3.4)
Refused to answer	9 (9.4)	49 (12.0)	58 (13.5)	4 (10.5)	42 (10.5)	133 (12.9)
Highest Level of Education, N(%)						
Less than high school	5 (5.2)	13 (3.3)	18 (4.2)	1 (2.7)	14 (3.5)	34 (3.3)
High school diploma or equivalent	15 (15.6)	66 (16.5)	103 (24.3)	6 (16.2)	80 (20.3)	212 (20.9)
Some college or postsecondary, no degree	25 (26.0)	100 (25.0)	106 (25.0)	8 (21.6)	110 (27.8)	252 (24.8)
Associate's degree	14 (14.6)	60 (15.0)	42 (9.9)	2 (5.4)	50 (12.7)	128 (12.6)
Bachelor's degree	20 (20.8)	99 (24.8)	103 (24.3)	12 (32.4)	94 (23.8)	246 (24.2)
Master's degree	12 (12.5)	47 (11.8)	43 (10.1)	7 (18.9)	30 (7.6)	109 (10.7)
Doctoral or professional degree	5 (5.2)	15 (3.8)	9 (2.1)	1 (2.7)	17 (4.3)	34 (3.3)
Smoker, N(%)						
No	79 (82.3)	347 (84.8)	356 (82.8)	31 (81.6)	344 (86.2)	872 (84.5)
Yes	17 (17.7)	62 (15.2)	74 (17.2)	7 (18.4)	55 (13.8)	160 (15.5)
Generalized Anxiety Disorder Diagnosis, N(%)						
0	71 (74.0)	326 (79.7)	367 (85.5)	31 (81.6)	330 (82.9)	864 (83.8)
1	25 (26.0)	83 (20.3)	62 (14.5)	7 (18.4)	68 (17.1)	167 (16.2)
Panic Disorder, Diagnosis, N(%)						
0	68 (70.8)	337 (82.4)	366 (85.3)	33 (86.8)	334 (83.9)	873 (84.7)
1	28 (29.2)	72 (17.6)	63 (14.7)	5 (13.2)	64 (16.1)	158 (15.3)
Posttraumatic Stress Disorder Diagnosis, N(%)						
0	87 (90.6)	382 (93.4)	413 (96.3)	36 (94.7)	379 (95.2)	980 (95.1)
1	9 (9.4)	27 (6.6)	16 (3.7)	2 (5.3)	19 (4.8)	51 (4.9)

(*Continued*)

TABLE S1 (*Continued*)

CLINICAL AND SOCIODEMOGRAPHIC CHARACTERISTICS OF FULL SAMPLE

	DRUG CLASS					
	ANTIPSYCHOTIC (N = 96)	SNRI (N = 409)	SSRI (N = 430)	TCA (N = 38)	OTHER AD (N = 399)	TOTAL (N = 1032)
Depression Category, N (%)						
Moderate (HAM-D17 14–18)	16 (16.7)	111 (27.1)	134 (31.2)	9 (23.7)	102 (25.6)	289 (28.0)
Severe (HAM-D17 19–22)	43 (44.8)	145 (35.5)	155 (36.0)	13 (34.2)	152 (38.1)	373 (36.1)
Very Severe (HAM-D17 > 23)	37 (38.5)	153 (37.4)	141 (32.8)	16 (42.1)	145 (36.3)	370 (35.9)
Baseline HAM-D17						
Mean (SD)	21.9 (3.7)	21.3 (4.2)	21.0 (4.3)	21.4 (4.0)	21.3 (4.1)	21.2 (4.2)
Median	21.0	21.0	21.0	21.0	21.0	21.0
Min, Max	15, 33	14, 35	14, 37	14, 30	14, 35	14, 37
Number of Medication Trials Without Response						
Mean (SD)	4.5 (3.0)	3.1 (2.2)	2.8 (2.1)	4.2 (3.1)	3.3 (2.5)	3.0 (2.3)
Median	4.0	2.0	2.0	3.0	3.0	2.0
Min, Max	1, 18	1, 16	1, 18	1, 13	1, 18	1, 18
Number of Comorbidities						
Mean (SD)	8.3 (6.4)	7.5 (5.6)	7.0 (5.4)	8.2 (4.5)	6.8 (5.5)	7.0 (5.5)
Median	7.0	6.0	6.0	8.0	6.0	6.0
Min, Max	1, 45	0, 47	0, 38	0, 21	0, 45	0, 47
Baseline Weight (pounds)						
Mean (SD)	197.2 (41.8)	196.3 (49.8)	193.2 (49.1)	182.4 (48.1)	192.4 (48.4)	193.3 (49.8)
Median	191.2	191.8	185.2	177.9	185.5	186.0
Min, Max	112, 320	98, 363	102, 387	108, 300	95, 380	95, 387

The following table details a variety of features for the full sample used in this analysis stratified by five broad medication classes (n = 1032). These strata are not mutually exclusive. For example, someone on both a selective serotonin reuptake inhibitor and an antipsychotic would be included in both relevant columns.
Snri = serotonin-norepinephrine reuptake inhibitor, ssri = selective serotonin reuptake inhibitor, tca = tricyclic antidepressant, ad = antidepressan.

TABLE S2

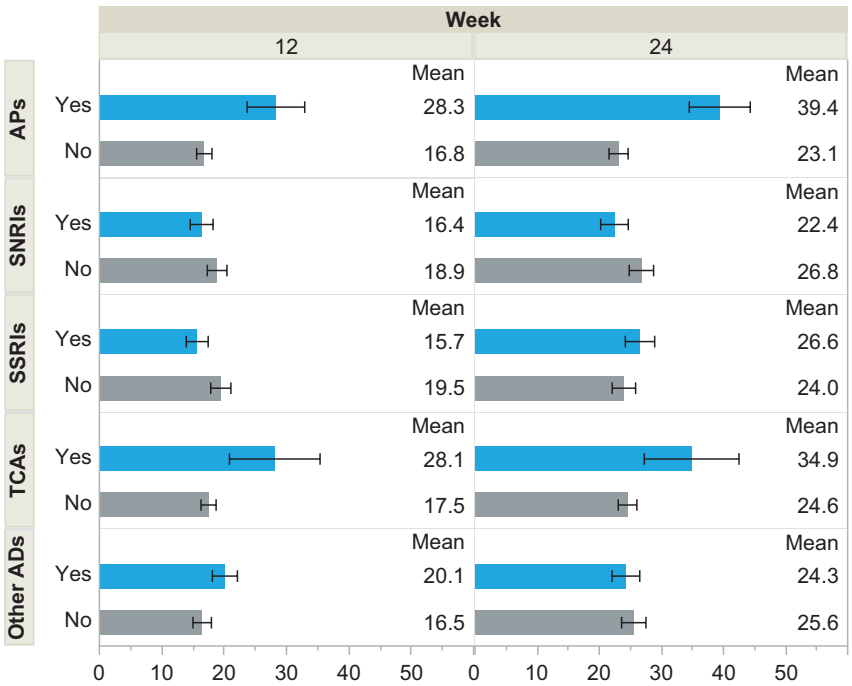
Frequency of Weight Gain by Weight Gain Liability Medication Category

		Taking Medication Grouping		Not Taking Medication Grouping			
Medication Category	Week	N	% of Patients with Wt. Gain	N	% of Patients with Wt. Gain	Δ	P-Value
Any High Risk	12	130	16.8	902	6.4	10.4	<**0.001**
	24	132	22.5	739	12.8	9.7	**0.004**
High Risk Only	12	35	17.0	997	7.4	9.6	**0.034**
	24	34	24.4	837	13.8	10.6	0.084
High Risk & No Risk	12	31	18.4	1001	7.4	10.9	**0.029**
	24	31	28.7	840	13.7	15.0	**0.024**

This table highlights the relative frequencies from sensitivity analyses, wherein clinically significant weight gain was based on the ⩾5% threshold, was observed for those taking "high risk" medications compared to those who were not. The subgroups taking "only high risk" medication or taking a "high risk" medication with a "no risk" medication (i.E., Bupropion) are also shown. The statistical reporting is based on univariable models. This table is the sensitivity analysis version of table 2.

FIGURE S1

Percent of Patients Experiencing Weight Gain by Medication Class



The proportion of patients experiencing clinically significant weight gain from the sensitivity analysis, , wherein clinically significant weight gain was based on the ⩾5% threshold, is illustrated by common medication classes. The estimates are based on univariable models.
AD = Antidepressant, AP = antipsychotic, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.