Antidepressants and Body Weight: A Comprehensive Review and Meta-Analysis

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Objective: Psychotropic drugs often induce weight gain, leading to discomfort and discontinuation of treatment and, more importantly, increasing the risk of obesity-related illnesses such as diabetes mellitus, hypertension, and coronary heart disease. There is evidence that antidepressant drugs may induce a variable amount of weight gain, but results are sparse and often contradictory.

Data Sources: We performed a literature search using the MEDLINE, ISI Web of Knowledge, and Cochrane research databases for all publications available to January 2009. We used the following keywords: *antidepressant, psychotropic drugs, body weight, weight gain, obesity, overweight, adverse event, side effects, SSRIs, tricyclic antidepressants,* and the name of each antidepressant active compound together with *body weight* or other keywords. Studies reporting body weight changes during treatment with different antidepressants were selected for eligibility. Finally, 116 studies were included in the analysis.

Data Extraction: Weight change mean and standard deviation and size of each group were recorded. Missing means and standard deviations were directly calculated by using information available in the article when possible. Non–placebo-controlled studies were compared to a virtual placebo sample, whose mean and standard deviation were derived by the weighted mean of means and standard deviations of all placebo samples. Methodological quality of studies, heterogeneity, publication bias, and effect of treatment duration were systematically controlled.

Data Synthesis: Quantitative results evidenced that amitriptyline, mirtazapine, and paroxetine were associated with a greater risk of weight gain. In contrast, some weight loss occurs with fluoxetine and bupropion, although the effect of fluoxetine appears to be limited to the acute phase of treatment. Other compounds have no transient or negligible effect on body weight in the short term. However, the effect of each antidepressant may vary greatly depending on an individual's characteristics and generally became more evident in the long term to a variable degree across compounds.

Conclusions: Despite the fact that some analyses were done on only a few studies due to the difficulty of finding reliable information in literature, to our knowledge, this is the first comprehensive meta-analysis to allow comparison of different antidepressants as regards their impact on body weight. Data presented may be helpful for a more accurate treatment selection in patients at risk of obesity or related medical illness.

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Weight gain occurring during drug treatment of psychiatric disorders is a frequent side effect. Indeed, obesity is 2 to 3 times more common among psychiatric patients than in the general population, presumably also because of unhealthy diet and physical inactivity.[1] A study[2] providing epidemiologic data on obesity in patients with bipolar mood disorder has estimated that about 58% of patients are overweight and 26% are from moderately to extremely obese. Moreover, body weight correlated positively with the number of weight-promoting drugs to which the patients had been exposed.

Besides inducing aesthetic problems affecting well-being, overweight frequently leads to discontinuation even if the treatment is effective. Further, it profoundly increases morbidity and mortality: in the United States, obesity is thought to cause between 280,000 and 325,000 deaths per year.[3,4] Some important diseases attributable to obesity are diabetes mellitus type II, osteoarthritis, hypertension, and coronary heart disease. Other associated conditions are ischemic stroke, lower back pain, sleep apnea, and infertility.

Early observations indicated that neuroleptic drugs, tricyclic and heterocyclic antidepressants, monoamine oxidase inhibitors, and lithium increase appetite to a varying degree, stimulating carbohydrate craving and resulting in weight gain over prolonged periods of administration.[5] The exact effect of antidepressant medications on weight is difficult to quantify because depression is often characterized by changes in appetite, energy, and physical activity in itself. Loss of appetite is a common symptom of melancholic depression, and thus weight gain during treatment may be a sign of recovery. On the other hand, some depressive episodes are characterized by increased appetite and carbohydrate craving, and thus increased body weight during short-term treatment may be due to persisting symptoms.

However, there is consistent evidence that antidepressant treatment may induce weight gain by interacting with central mechanisms regulating food intake and appetite.[6] Central amines are in fact implicated in the control of feeding.[7] Monoaminergic neurotransmitters interact with neuropeptides and hormones to control satiety mechanisms and eating behavior. The degree of action on serotonergic, dopaminergic, noradrenergic, histaminergic, and cholinergic systems may explain the large differences between antidepressants in their ability to promote weight changes. Given that the estimated incidence of antidepressant prescription is about 2.6%–5.5% each year in the general population,[8] and even higher according to more recent surveys (from 4.3% in males to 10.2% in females[9]), it is of extreme importance to understand the impact of each antidepressant compound on body

For Clinical Use

- Antidepressants are different regarding their potential to induce weight gain.
- An initial weight loss, common to many antidepressants, is very frequently followed by weight gain.

weight, in order to improve the well-being of patients and prevent medical illness associated to obesity. Indeed, antidepressants greatly differ in their ability to induce weight gain, and a better knowledge of the effect of each drug on weight would be extremely helpful. However, while there is good evidence about antipsychotic-induced weight gain,[10] present literature reveals little empirical evidence to compare treatment strategies to manage weight gain associated to treatment with antidepressants, and there are no formal indications, only clinical experience. The existing evidence is heterogeneous, and thus a meta-analytic approach may be useful to investigate discrepant findings.[11,12] For this reason, we conducted a systematic comprehensive and quantitative review of the literature regarding the effect on body weight potentially exerted by the most common antidepressant drugs employed for clinical purposes.

Table 1. Most Common Antidepressants Approved by the US Food and Drug Administration or European Regulatory Agencies

TCAs
Imipramine
Amitriptyline
Clomipramine
Desipramine
Nortriptyline
SSRIs
Citalopram
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
NRI
Reboxetine
SNRIs
Venlafaxine
Duloxetine
NaSSA
Mirtazapine
RIMA
Moclobemide
Others
Nefazodone
Trazodone
Bupropion

Abbreviations: NaSSA = noradrenergic and specific serotonergic antidepressant, NRI = norepinephrine reuptake inhibitor, RIMA = reversible inhibitor of monoamine oxidase A, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

METHOD

Literature Search

To identify eligible studies for this meta-analysis, we searched MEDLINE, ISI Web of Knowledge, and Cochrane research databases for all publications available to January 2009. We used the following keywords: *antidepressant, psychotropic drugs, body weight, weight gain, obesity, overweight, adverse event, side effects, SSRIs, tricyclic antidepressants,* and the name of each antidepressant active compound together with *body weight* or other keywords. We also used reference lists from identified articles and reviews to find additional articles.

The literature search yielded over 3,000 reports, which were then screened for eligibility. To be eligible for this review, a study had to be published in a national/international journal and written in English,[13] include adult patients, investigate at least 1 compound approved for use as an antidepressant agent by US Food and Drug Administration regulations or European regulatory agencies (the most common compounds are listed in Table 1) and administered in monotherapy (with the exception of hypnotics only) at doses not lower than minimal therapeutic dose range for at least 4 weeks, and measure weight before and after initiation of use of the drug or report mean change expressed in kilograms or pounds. Studies reporting only the number of patients stating weight gain or loss (but not the mean change), case reports, review articles, and studies of obese or eating disorders patients (even if dietary advice or program was not part of the intervention) were not considered eligible for our study. The exclusion of studies on obesity and eating disorders was motivated by the choice to consider only studies evaluating the impact of antidepressant on body weight, in which change in weight or eating behavior was not the primary goal. Indeed, even if in some studies dietary advice was not provided to obese and eating disorders patients, these patients were obviously aware of being treated for weight problems, with all the expectations that may go along with being treated for weight or eating disorders and the possibility that they might have made changes in their eating behaviors even if not advised by clinicians.

Finally, the literature search yielded 116 eligible reports (Table 2).

Coding and Data Extraction

Studies were coded by one investigator (L.M.) and spot-checked by another investigator (S. Gibiino, MD, acknowledged). When a discrepancy was found, the coders met to discuss and resolve the discrepancy. When reported directly in the article, the mean and standard deviation of weight change and the size of each group were simply recorded. However, in many cases, they were not reported; in this situation, missing means and standard deviations were directly calculated by using other information available in the article.[14] When standard deviation was not available, we calculated a weighted mean standard deviation on the remaining studies for each drug.[10]

Because the length of evaluation of weight change varied widely between studies, we investigated separately response within 4 to 12 weeks of treatment (acute treatment) and

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Table 2. Studies Selected for the Global Analyses

	Acute Treatment (4–8 wk)			Maintenance Treatment (> 3 mo)		
Drug	Study	Study N and Diagnosis	Quality[a]	Study	Study N and Diagnosis	Quality[a]
Amitriptyline	Sedman, 1973[43]	25 MD	+	Coppen et al, 1978[44,b]	16 MD	+
	Kupfer et al, 1979[45,b]	30 MD	+	Chouinard, 1983[46]	39 MD	–
	Ravaris et al, 1980[47]	50 MD	–	Montgomery et al, 1998[48,b]	86 MD	+
	Remick et al, 1982[49]	11 MD	–	Maggioni et al, 2005[50]	29 Headache	–
	Chouinard, 1985[51]	29 MD	+			
	Hecht Orzack et al, 1986[52,b]	90 MD	+			
	Harris et al, 1986[53]	14 MD	–			
	Fernstrom and Kupfer, 1988[54]	18 MD	+			
	Altamura et al, 1989[55]	10 MD	–			
	Cohn et al, 1990[56]	71 MD	+			
	Reimherr et al, 1990[57,b]	139 MD	+			
	Bakish et al, 1992[58,b]	52 MD	+			
	Beasley et al, 1993[59]	71 MD	+			
	De Ronchi et al, 1998[60]	33 MD	–			
	Sacchetti et al, 2002[61]	29 MD	+			
	Berilgen et al, 2005[62]	19 Migraine	–			
	Altintoprak et al, 2008[63]	20 MD	–			
Imipramine	Bremner, 1984[64]	20 MD	+	Frank et al, 1990[65]	128 MD	+
	Cohn et al, 1990[56]	144 MD	+	Frank et al, 1992[66]	115 MD	+
	Reimherr et al, 1990[57,b]	136 MD	+	Mavissakalian and Perel, 1992[67]	19 Anxiety	+
	Balon et al, 1993[68,b]	14 PD	+	Mavissakalian and Perel, 2000[69]	66 Anxiety	+
	Shioiri et al, 1993[70]	46 MD	–	Mavissakalian et al, 2002[71]	20 Anxiety	+
	Fabre et al, 1995[72,b]	212 MD	+	Mavissakalian, 2003[73]	20 Anxiety	–
	Mavissakalian and Perel, 2000[69]	77 PD	+			
	Silverstone, 2001[74]	75 MD	–			
	Moosa et al, 2003[75]	77 MD	+			
	Mavissakalian, 2003[73]	20 PD	–			
Clomipramine	Beaumont, 1977[76]	61 MD	–	Maina et al, 2004[77]	23 Anxiety	+
	Guelfi et al, 1992[78]	56 MD	–			
	Shioiri et al, 1993[70]	31 MD	–			
Nortriptyline	Fernstrom and Kupfer, 1988[54]	18 MD	+	Miller et al, 1991[79]	30 MD	+
	Weber et al, 2000[80]	12 MD	+	Paradis et al, 1992[81]	29 MD	+
	Gendall et al, 2000[82]	42 MD	–	Reynolds et al, 1999[83]	41 MD	–
	Robinson et al, 2000[84,b]	8 Stroke	–			
Desipramine	Levitt et al, 1987[85]	26 MD	+			
	Stern et al, 1987[86]	31 MD	–			
	Fernstrom and Kupfer, 1988[54]	24 MD	+			
	Shioiri et al, 1993[70]	29 MD	–			
Citalopram	Leinonen et al, 1999[87]	133 MD	+	Allard et al, 2004[88]	75 MD	+
	Lepola et al, 2003[89,b]	160 MD	+	Maina et al, 2004[77]	21 Anxiety	+
	Allard et al, 2004[88]	75 MD	+	Colonna et al, 2005[90]	135 MD	+
				Dannon et al, 2007[91]	34 Anxiety	–
Escitalopram	Lepola et al, 2003[89,b]	160 MD	+	Colonna et al, 2005[90]	144 MD	+
	Montgomery et al, 2004[92]	125 MD	+	Davidson et al, 2005[93]	299 Anxiety	–
	Muller et al, 2008[94,b]	25 Somatoform disorder	+	Kasper et al, 2006[95]	223 MD	+
				Perahia et al,[96,b]	70 MD	+
				Pigott et al, 2007[97]	208 MD	+
Fluoxetine	Altamura et al, 1989[55]	12 MD	–	Levine et al, 1989[98]	15 Anxiety	–
	Bremner, 1984[64]	20 MD	+	Orzack et al, 1990[99]	37 MD	–
	Chouinard, 1985[51]	23 MD	+	Michelson et al, 1999[25,b]	167 MD	+
	Cohn and Wilcox, 1985[100]	35 MD	+	Michelson et al, 1999[25,b]	63 MD	+
	Levine et al, 1987[101]	22 MD	+	Maina et al, 2004[77]	23 Anxiety	+
	Muijen et al, 1988[102,b]	14 MD	+	Keller et al, 2007[103]	177 MD	+
	Corne and Hall, 1989[104]	32 MD	–	Dannon et al, 2007[91]	25 Anxiety	–
	Levine et al, 1989[98]	63 Anxiety	–			
	Orzack et al, 1990[99]	37 MD	–			
	Schweizer et al, 1990[105]	108 MD	–			
	de Jonghe et al, 1991[106]	26 MD	+			
	Feighner et al, 1991[107]	60 MD	+			
	Beasley et al, 1993[59]	65 MD	+			
	Goldstein et al, 1997[108,b]	329 MD	+			
	De Ronchi et al, 1998[60]	32 MD	–			
	Falk et al, 1989[109]	14 MD	–			
	Guelfi et al, 1998[110]	50 MD	–			
	Wheatley et al, 1998[111]	63 MD	–			
	Finkel et al, 1999[112]	33 MD	–			
	Michelson et al, 1999[25]	388 MD	+			
	Gendall et al, 2000[82]	49 MD	–			

(continued)

Table 2 (continued). Studies Selected for the Global Analyses

	Acute Treatment (4–8 wk)			Maintenance Treatment (> 3 mo)		
Drug	Study	Study N and Diagnosis	Quality[a]	Study	Study N and Diagnosis	Quality[a]
Fluoxetine *(continued)*	Newhouse et al, 2000[113]	119 MD	–			
	Goldstein et al, 2002[114,b]	33 MD	+			
	Moosa et al, 2003[75]	11 MD	+			
	Zanarini et al, 2004[115]	14 BPD	–			
	Papakostas et al, 2005[116]	369 MD	+			
	Versiani et al, 2005[117]	147 MD	–			
	Pollack et al, 2006[118]	12 Anxiety	+			
Fluvoxamine	Davidson et al, 2004[119,b]	73 Anxiety	+	Maina et al, 2004[77]	28 Anxiety	+
	Westenberg et al, 2004[120,b]	92 Anxiety	+	Dannon et al, 2007[91]	25 Anxiety	–
Paroxetine	Benkert et al, 2000[121]	70 MD	–	Dannon et al, 2004[122]	72 Anxiety	+
	Weihs et al, 2000[123]	52 MD	+	Detke et al, 2004[124,b]	70 MD	+
	Hinze-Selch et al, 2000[125,b]	10 MD + others	–	Maina et al, 2004[77]	21 Anxiety	+
	Detke et al, 2004[124,b]	86 MD	+	Aberg-Wistedt, 2000[126]	177 MD	+
	Goldstein et al, 2004[127,b]	87 MD	+	Dannon et al, 2007[91]	38 Anxiety	–
	Perahia et al, 2006[96,b]	96 MD	+			
	Lee et al, 2007[128]	240 MD	–			
Sertraline	Cohn et al, 1990[56]	144 MD	+	Goldberg, 2002[129]	25 MD	–
	Reimherr et al, 1990[57,b]	136 MD	+	Mavissakalian, 2003[73]	16 Anxiety	–
	Fabre et al, 1995[72]	212 MD	–	Maina et al, 2004[77]	22 Anxiety	+
	Coleman et al, 1999[130,b]	115 MD	+	Aberg-Wistedt et al, 2000[126]	176 MD	+
	Finkel et al, 1999[112]	42 MD	–			
	Croft et al, 1999[131]	119 MD	+			
	Newhouse et al, 2000[113]	117 MD	+			
Venlafaxine	Kraus et al, 2002[132]	9 MD	–	Allard et al, 2004[88]	73 MD	+
	Allard et al, 2004[88]	73 MD	+			
	Emslie et al, 2007[133]	69 MD	+			
	Montgomery et al, 2004[92]	124 MD	+			
	Keller et al, 2007[103]	781 MD	+			
	Perahia et al, 2008[134]	270 MD	+			
Duloxetine	Goldstein et al, 2002[114,b]	68 MD	+	Detke et al, 2004[124,b]	145 MD	+
	Nemeroff et al, 2002[135,b]	1118 MD	+	Perahia et al, 2006[96,b]	150 MD	+
	Goldstein et al, 2004[127,b]	177 MD	+	Hardy et al, 2007[136]	685 Diabetes	–
	Detke et al, 2004[124,b]	93 MD	+	Pigott et al, 2007[97]	188 MD	+
	Wohlreich et al, 2005[137]	249 MD	–	Wohlreich et al, 2007[138]	128 MD	–
	Perahia et al, 2006[96]	195 MD	+	Dunner et al, 2008[139]	175 MD	+
	Lee et al, 2007[128]	238 MD	–			
	Perahia et al, 2008[134]	214 MD	+			
	Raskin et al, 2008[140,b]	207 MD	+			
Mirtazapine	Halikas, 1995[141]	49 MD	+	Montgomery et al, 1998[48,b]	74 MD	+
	Wheatley et al, 1998[111]	60 MD	–	Thase et al, 2001[142]	76 MD	+
	Leinonen et al, 1999[87]	136 MD	+	Goldberg, 2002[129]	25 MD	–
	Benkert et al, 2000[121]	79 MD	–	Walinder et al, 2006[143]	192 MD	–
	Thase et al, 2001[142]	410 MD	+			
	Boshuisen et al, 2001[144]	23 Anxiety	–			
	Kraus et al, 2002[132]	11 MD	–			
	Theobald et al, 2002[145]	20 Cancer	–			
	Nicholas et al, 2003[146]	28 Healthy	+			
	Roose et al, 2003[147]	79 MD	–			
	Versiani et al, 2005[117]	145 MD	–			
	Himmerich et al, 2006[148]	11 MD	–			
	Laimer et al, 2006[149,b]	7 MD	–			
	Schmid et al, 2006[150]	10 MD	+			
	Altintoprak et al, 2008[63]	24 MD	–			
Bupropion	Remick et al, 1982[49]	19 MD	–	Chouinard, 1983[46]	39 MD	–
	Feighner et al, 1991[107]	59 MD	+	Croft et al, 2002[151,b]	103 MD	+
	Weisler et al, 1994[152]	60 MD	+	Maggioni et al, 2005[50]	29 Headache	–
	Reimherr et al, 1998[153,b]	241 MD	+			
	Coleman et al, 1999[130,b]	119 MD	+			
	Croft et al, 1999[131,b]	120 MD	+			
	Settle et al, 1999[154,b]	810 MD	+			
	Weihs et al, 2000[123]	48 MD	+			
	Croft et al, 2002[151]	518 MD	+			
	Jefferson et al, 2006[155,b]	135 MD	+			

(continued)

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Table 2 (continued). Studies Selected for the Global Analyses

	Acute Treatment (4–8 wk)			Maintenance Treatment (> 3 mo)		
Drug	Study	Study N and Diagnosis	Quality[a]	Study	Study N and Diagnosis	Quality[a]
Trazodone	Hecht Orzack et al, 1986[52,b]	90 MD	+			
	Weisler et al, 1994[152]	52 MD	+			
	Falk et al, 1989[109]	13 MD	–			
Moclobemide	Bakish et al, 1992[58,b]	50 MD	+	Moll et al, 1994[156]	928 MD	–
	Guelfi et al, 1992[78]	47 MD	–			
	Gagiano et al, 1994[157]	170 MD	+			
	Silverstone, 2001[74]	81 MD	–			

[a]Good quality was defined by a score of at least 3 on the Jadad scale and/or by at least 4 stars on the Newcastle-Ottawa Scale. A plus sign (+) indicates that the study met criteria for good quality, and a minus sign (–) indicates that it did not.
[b]Placebo controlled.
Abbreviations: BPD = borderline personality disorder, MD = major depression, PD = panic disorder.

during longer periods (maintenance, > 4 months). Of 116 selected trials, only 30 included a comparison between 1 or more antidepressant drugs with placebo. Thus, non–placebo-controlled studies were compared to a virtual placebo sample, for which the mean and standard deviation were derived by the weighted mean of means and standard deviations of all placebo samples. Size of the virtual placebo sample was set equal to that of treated patients for each compared study in order to avoid significance inflation. The same procedure has been employed in a previous work.[15]

Assessment of Methodological Quality of Studies

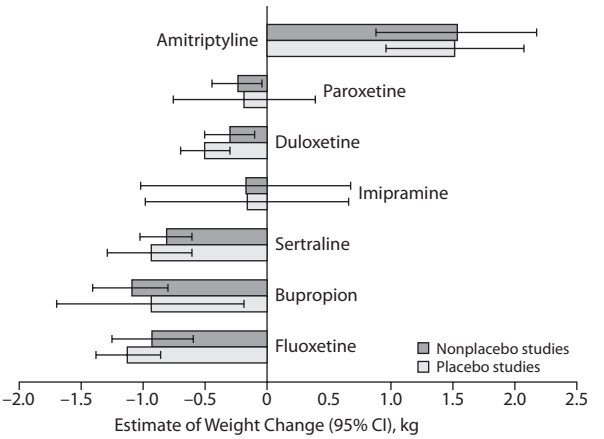
Methodological quality of the studies was evaluated by an independent rater (S. Gibiino, MD) employing the Jadad scale for quality of randomized controlled trials[16] and a modified version of the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford_web.ppt). Good quality was defined by a score of at least 3 on the Jadad scale or at least 4 stars on the Newcastle-Ottawa Scale.

Data Analysis

To test the reliability of the estimates derived from our analyses (performed on both placebo-controlled and non–placebo-controlled studies), we performed a preliminary analysis of placebo-controlled studies only. In fact, lumping together placebo-controlled and observational nonplacebo studies including different kind of treated patients may be criticized. Indeed, the creation of "virtual controls" may artificially increase the number of unexposed subjects in the meta-analysis, thereby potentially increasing the amount of evidence. Estimates derived from placebo-controlled studies were therefore compared with those obtained by other studies, and significance of the difference was tested by the Student *t* test.

Data were then entered into the Cochrane Collaboration review manager software (RevMan version 5; Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen, Denmark) and analyzed by RevMan analysis 1.01. A random-effect model was used in all analyses to take into account between-studies variations. Individual and global mean differences and 95% CIs were calculated. Heterogeneity between studies was assessed with the χ^2 test. Moreover, we systematically tested for publication bias by the Egger test,[17] which is considered more powerful than the rank correlation test.[18] The effect of methodological quality of studies and diagnosis of treated patients (major depression, anxiety, or other) was systematically tested by regression analysis. Further, since maintenance treatment duration varied widely from 4 to more than 12 months, we regressed mean body weight change on treatment duration. In the event that an effect of treatment duration on results was observed, or when sufficient studies allowed such analysis, we separately analyzed studies of medium-term (4–7 months) and long-term (≥ 8 months) treatment periods.

Figure 1. Estimates (with 95% CIs) of Weight Change Associated With Antidepressant Treatments Derived From Placebo-Controlled Studies and Nonplacebo/Observational Studies



RESULTS

Reliability of Estimates of Body Weight Change Associated to Antidepressant Treatment

To test the efficacy of our methodology to produce reliable estimates of weight changes associated to treatment with antidepressants, we compared the estimates derived from placebo-controlled studies with those obtained from observational non–placebo-controlled studies. Estimates derived from randomized placebo-controlled studies of drugs for which a sufficient number of placebo-controlled

Table 3. Effect of Each Antidepressant on Weight Change During Acute Treatment (4–12 wk)

Drug	Cases (n)	Controls (n)	Mean Difference, kg [95% CI]	Z	*P*	Heterogeneity I^2 (%)	Heterogeneity *P*	Publication Bias (Egger test *P*)
Amitriptyline	710	697	1.52 [1.08 to 1.95]	6.88	<.0001	87	<.0001	<.0001
Imipramine	751	619	−0.20 [−0.77 to 0.38]	0.67	NS	88	<.0001	NS
Nortriptyline	80	78	2.00 [0.74 to 3.25]	3.12	.002	63	.04	NS
Clomipramine	148	148	1.00 [−0.44 to 2.43]	1.36	NS	93	<.0001	NS
Desipramine	110	110	0.82 [−0.77 to 2.42]	1.01	NS	94	<.0001	NS
Citalopram	368	362	−0.64 [−0.89 to −0.38]	4.94	<.0001	0	NS	NS
Escitalopram	310	305	−0.33 [−0.58 to −0.07]	2.49	.01	1	NS	NS
Fluoxetine	2219	2260	−0.94 [−1.24 to −0.65]	6.26	<.0001	87	<.0001	NS
Fluvoxamine	165	194	−0.02 [−0.49 to 0.45]	0.09	NS	71	.06	…[a]
Paroxetine	631	643	−0.28 [−0.46 to −0.09]	2.92	.004	12	NS	NS
Sertraline	885	895	−0.87 [−1.04 to −0.70]	10.06	<.0001	14	NS	NS
Venlafaxine	1326	1326	−0.50 [−0.74 to −0.27]	4.26	<.0001	59	.03	.0079
Duloxetine	2652	1973	−0.55 [−0.77 to −0.33]	4.93	<.0001	76	<.0001	.0078
Mirtazapine	1173	1173	1.74 [1.28 to 2.20]	7.39	<.0001	83	<.0001	NS
Bupropion	2129	1553	−1.13 [−1.41 to −0.84]	7.68	<.0001	81	<.0001	.011
Trazodone	155	155	−0.20 [−0.94 to 0.54]	0.53	NS	73	.03	NS
Moclobemide	348	351	−0.21 [−0.30 to −0.13]	4.98	<.0001	0	NS	NS

[a]Egger test could not be performed because only 2 studies were entered into the analysis.
Abbreviation: NS = nonsignificant.

Table 4. Effect of Each Antidepressant on Weight Change During Medium- and Long-Term Treatment (≥4 mo)

Drug	Cases (n)	Controls (n)	Mean Difference, kg [95% CI]	Z	*P*	Heterogeneity I^2 (%)	Heterogeneity *P*	Publication Bias (Egger test *P*)
Amitriptyline	170	141	2.24 [1.82 to 2.66]	10.47	<.0001	0	NS	NS
Imipramine	368	368	−0.04 [−1.36 to 1.28]	0.06	NS	70	.005	NS
Nortriptyline	100	100	1.24 [−0.51 to 2.99]	1.39	NS	0	NS	NS
Citalopram	286	286	1.69 [−0.97 to 4.34]	1.24	NS	83	<.0001	NS
Escitalopram	944	944	0.65 [−0.16 to 1.45]	1.58	NS	66	.02	NS
Fluoxetine	616	418	−0.31 [−1.04 to 0.43]	0.81	NS	43	NS	NS
Paroxetine	399	387	2.73 [0.78 to 4.68]	2.75	.006	69	.007	.0085
Sertraline	239	239	−0.12 [−1.65 to 1.42]	0.15	NS	0	NS	NS
Duloxetine	1471	1304	0.71 [−0.23 to 1.65]	1.47	NS	88	<.0001	NS
Mirtazapine	559	542	2.59 [−0.23 to 5.41]	1.80	.07	96	<.0001	NS
Bupropion	637	637	−1.87 [−2.37 to −1.37]	7.33	<.0001	0	NS	NS

Abbreviation: NS = nonsignificant.

studies were available are reported in Figure 1. As shown in the figure, estimates derived from placebo-controlled studies were similar to those derived from observational nonplacebo studies. Indeed, no significant difference could be observed for any drug (fluoxetine $P = .59$, bupropion $P = .30$, sertraline $P = .50$, imipramine $P = .99$, duloxetine $P = .15$, paroxetine $P = .83$, amitriptyline $P = .98$).

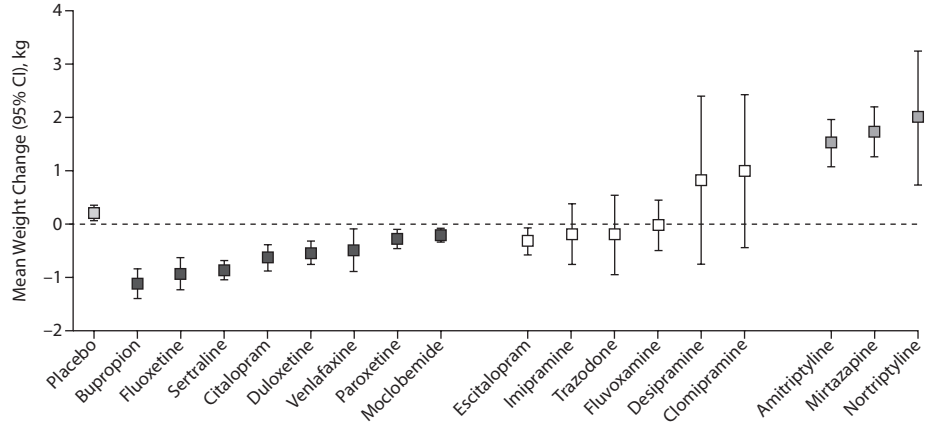
Body Weight Changes Associated to Treatment With Different Antidepressants Over Acute and Maintenance Periods

In Tables 3 and 4, the numbers of cases and controls entered to analyze the effect of each drug on body weight and results of the analyses are reported for short- and long-term treatment, respectively, including mean body weight change and 95% confidence intervals (CIs), heterogeneity among studies, and significance of publication bias test (if Egger test result is significant, the analysis may be biased). Results are also graphically reported in Figures 2 and 3.

The tricyclic antidepressant (TCA) amitriptyline was significantly associated with weight gain over both acute (though with high heterogeneity among studies and possible publication bias) and maintenance periods. Further, mirtazapine (a noradrenergic and specific serotonergic antidepressant) and the TCA nortriptyline were significantly associated with weight gain during acute treatment. Mirtazapine maintained a similar trend during the maintenance period, while nortriptyline did not differ from placebo. Although no additional effect of time on weight was seen in the medium-long term, when studies were analyzed separately over 4–7 months and over longer periods (≥8 months), mirtazapine maintained significant associations with weight gain (Figure 4J). On the other hand, paroxetine, which was associated with a marginal weight loss during acute treatment, was associated with weight gain over the medium-long period. In particular, a significant weight gain was observed after 8 months of treatment (Figure 4G).

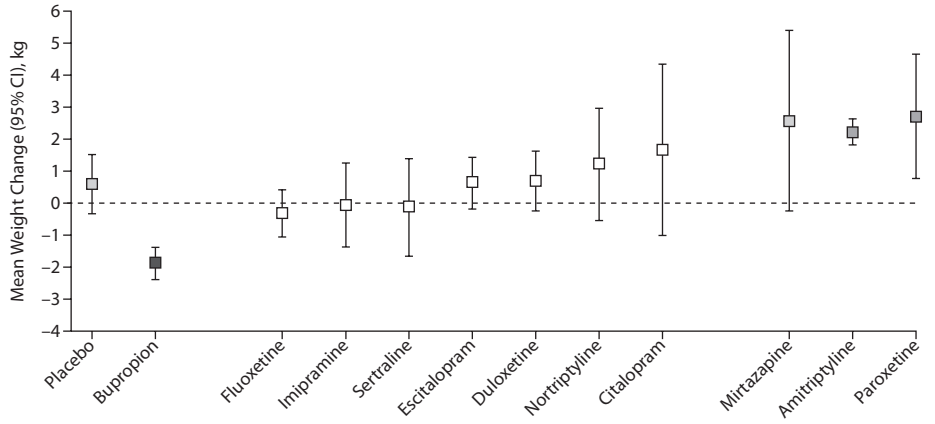
During acute treatment, a number of selective serotonin reuptake inhibitors (SSRIs; citalopram, fluoxetine, sertraline) and serotonin and norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine), together with bupropion (a norepinephrine and dopamine reuptake inhibitor and nicotinic antagonist) and moclobemide (a reversible inhibitor of monoamine oxidase A), were associated with weight loss to various extents. Nevertheless, over the longer period of treatment, only bupropion maintained a significant effect on weight, and no effect could be observed for the other antidepressants (Figure 4, parts D, F, H, I, K). However, data

Figure 2. Weight Change During Acute Treatment With Different Antidepressants[a]



[a]Filled squares indicate a significant effect.

Figure 3. Weight Change During Maintenance Treatment With Different Antidepressants[a]



[a]Filled squares indicate a significant effect.

were not available for venlafaxine and moclobemide over the maintenance period.

Finally, imipramine (Figure 4B) and, in acute treatment only, fluvoxamine, desipramine, clomipramine, and the atypical trazodone (which presumably exerts antagonistic effects at the level of 5-HT_2 receptors) showed no significant effect on body weight.

Quality of studies and sample diagnoses did not impact the analyses. Further, although significant changes were observed over time, duration of treatment did not actually influence the effect of each antidepressant on body weight by meta-regression analysis. However, the larger number of studies of acute treatment could have masked the impact of time exerted by the fewer studies of the maintenance period that was clear from the average values.

DISCUSSION

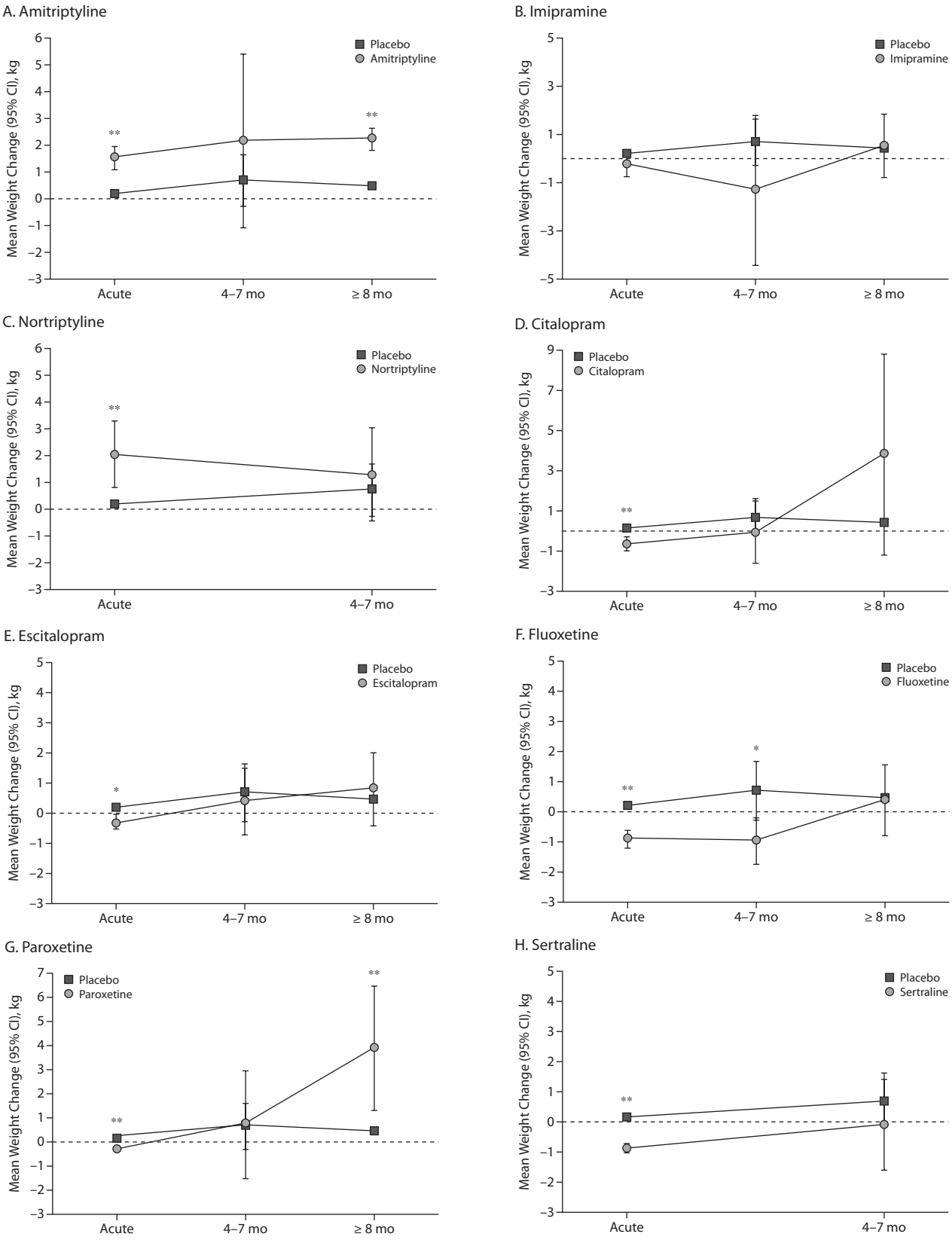
To our knowledge, this is the first meta-analysis focusing on antidepressant-induced weight change covering almost all antidepressant drugs available in the main markets and thus making possible a comparison among them. Further, data on both acute and maintenance periods were analyzed separately in order to investigate the effect of time of treatment. Despite some limitations, mainly due to the fact that many trials did not account for weight gain among side effects and heterogeneity in the report of weight, we obtained interesting results, often confirming the existing sparse clinical observations but adding useful quantitative data.

According to previous observations,[19] we found amitriptyline to be the most potently weight gain–inducing compound among the TCAs. Amitriptyline indeed has a high affinity for α-adrenergic, histaminergic, and cholinergic receptors.[20] The effect of imipramine is less clear, although it is usually associated with weight gain.[19] Our meta-analysis showed no effect on body weight during acute or maintenance periods. Imipramine has anticholinergic and antimuscarinic effects, but it is also a strong reuptake inhibitor of norepinephrine and has some affinity with D_1 and D_2 receptors that could counterbalance the effect.

According to previous evidence,[21] mirtazapine is a definite weight-gain promoter. Mirtazapine enhances noradrenergic and serotonergic neurotransmission by acting as an antagonist at the central α_2-adrenergic autoreceptors and heteroreceptors as well as by postsynaptic blockade of 5-HT_2 and 5-HT_3 receptors. Blockade of α_2-adrenoceptor, together with affinity for histamine H_1 receptors and low affinity for dopaminergic D_1 and D_2 receptors,[22] may explain the induced weight gain associated to treatment with mirtazapine.

Drugs that selectively act to enhance serotonin function (SSRIs) were expected to have a weight-reducing effect; in fact, strong evidence indicates that serotonin controls the ratio of carbohydrate versus protein ingestion.[23] Our meta-analysis confirmed fluoxetine as a potent anorexigenic drug[6,24]; however, the effect may be transient, and some restoration of weight may occur during the maintenance period. This finding is in agreement with a previous similar observation by Michelson et al,[25] who reported an initial weight loss in patients treated with fluoxetine, while after 50 weeks of treatment the mean absolute weight increase during

Figure 4. Course of Weight Change During Acute[a] and Maintenance Treatment for Each Antidepressant Drug (when data on both acute and maintenance periods were available)



(continued)

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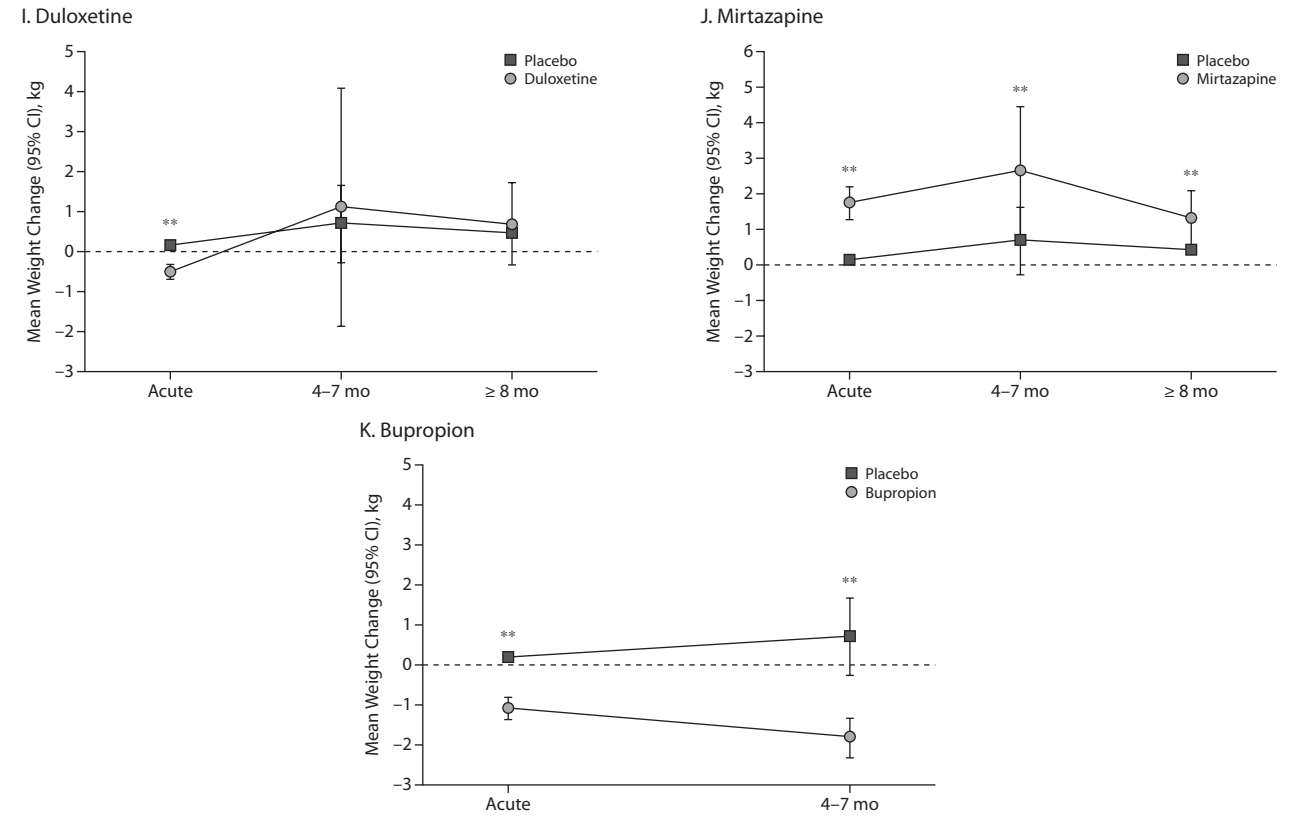
Figure 4 (continued). Course of Weight Change During Acute[a] and Maintenance Treatment for Each Antidepressant Drug (when data on both acute and maintenance periods were available)



[a]Acute treatment: 4–12 weeks.
*$P < .01$.
**$P < .005$.

continuation treatment was similar for both the placebo- and fluoxetine-treated patients.

The effect of fluvoxamine on body weight is unclear,[26] with some preliminary evidence of no effect.[19] We had poor information about its effect over acute treatment and even less during a maintenance period (2 studies including a total of 53 patients only), but the analysis of the few studies of acute treatment (165 subjects) supports this view. Paroxetine and citalopram were associated with a negligible to small weight loss during acute treatment. However, no significant effect could be observed for citalopram during maintenance treatment, while paroxetine was associated with an increase in body weight over the longer period of treatment. Accordingly, paroxetine is considered to be the SSRI producing the greatest long-term increase in body weight.[27]

The effect of sertraline is also unclear.[19] Initially, sertraline was proposed as an anorexigenic agent,[28] but a subsequent attempt at comprehensive investigation found no significant effect of sertraline on body weight.[29] Despite a slight weight loss observed during acute treatment, no effect of sertraline on body weight was observed over the maintenance period. Finally, no evidence at all exists in the literature regarding the more recently introduced SSRI escitalopram. From a preliminary analysis of few studies, we observed a trend of association with a slight loss of weight during acute treatment, but no effect over the maintenance period. Overall, SSRIs seem to have a small effect on body weight, except for fluoxetine, which has an effect only during the acute period, and paroxetine, which has its effect over longer periods of treatment. SSRIs are not the same in their selectivity and pharmacologic action, and they interact differently with pathways involved in the regulation of appetite behavior.[30] For instance, fluoxetine has a high level of noradrenergic and dopaminergic activity in contrast to citalopram and escitalopram, which are more selective. Among SSRIs, paroxetine has the greatest affinity for cholinergic receptors, a fact that could explain its effect.

SNRIs combine serotonin and norepinephrine reuptake inhibition and were thus expected to have stronger anorexigenic effects as compared to SSRIs.[30] Nonetheless, previous studies of venlafaxine or duloxetine reported only a slight reduction of body weight during short-term treatment, followed by a trend of increase over the long-term treatment.[31–34] Our meta-analysis confirms these trends for both venlafaxine and duloxetine over the course of acute treatment, and to some extent for duloxetine over the medium-long term. However, no data were available for venlafaxine over the medium-term period.

The effects of other antidepressant compounds, such as reboxetine, moclobemide, and trazodone, are less clear.

From previous evidence, moclobemide seems to have no influence on body weight,[35] while trazodone was indicated as a potential weight gain–inducing drug.[5,36] Our meta-analysis confirmed only a minor effect of moclobemide on weight (a loss of less than one-half kg), while no effect of trazodone on weight was observed, at least during acute treatment. Reboxetine could not be analyzed given the existence, to our knowledge, of only 1 study[158] reporting weight change in adults. However, according to previous evidence, reboxetine should not have a major impact on body weight.

On the contrary, much evidence does exist regarding bupropion, which is considered a weight loss–inducing drug and has been proposed as a treatment for obesity.[37] Results of our analysis support this indication. Bupropion selectively inhibits dopamine and, to a lesser extent, norepinephrine reuptake. Bupropion does not act on postsynaptic histamine, β-adrenergic, or acetylcholine receptors.[38]

To summarize, antidepressants greatly differ in their ability to affect body weight, although only slight effects were observed for the majority of antidepressants, with few exceptions (amitriptyline, mirtazapine, paroxetine, bupropion). Further, ranges of weight change for each antidepressant were quite large in many cases, probably indicating a role for individual variables such as sex, premorbid weight, and age. Moreover, among individual features, genetic liability may have a significant impact. For instance, genetic control of weight gain has been recently reported for antipsychotics.[39] Further, as previously mentioned, not all changes in weight observed in psychiatric patients are induced by drug treatment,[40] and disease-associated features significantly impact body weight independently and in concurrence with treatment. Unfortunately, we could not take into consideration such variables, because the majority of studies do not account for them (for example, rates of loss of appetite or atypical symptoms). Further, inconsistency across studies as pertaining to treatment doses, duration, and treated patients may also explain large variations observed for some antidepressants.

We excluded studies of obese individuals and those with eating disorders, since these conditions may be too closely related with weight concerns. Further, many subjects are informed about the potential effect of antidepressants on weight even if they seek treatment for other reasons (information by clinicians, drugs information sheets, hearsay, and so on) and thus may have expectations or may make plans for change their eating styles. Nevertheless, we expect less concern for body weight in depressed, anxious, and other non–weight-related disorders than in obese, bulimic, or anorexic patients.

Analyses were often characterized by heterogeneity of studies and publication biases. Nevertheless, methodological quality of studies did not impact significantly on results. For this reason, we did not exclude poor-quality studies, also because the procedure has been criticized. It has in fact been reported that quality measures often provide estimates not considerably different from overall estimates.[41] As pertains to publication bias, the Egger regression method often gives false-positive rates, especially in the case of large treatment effects and small size samples.[18] Further, a low number of studies could be included in the meta-analysis of each antidepressant drug. Meta-analyses usually require at least 5 studies, whereas some analyses here were carried out on a small number of studies, thus strongly limiting the reliability of results.

Lumping together observational studies and randomized placebo-controlled trials may be questionable. Indeed, the creation of "virtual" controls may artificially increase the number of unexposed subjects in the meta-analysis, thereby potentially increasing the amount of evidence. Further, the "virtual" control groups that we employed to contrast specific drug effects could have been different from the studied population. To reduce this problem, we tried to make placebo samples as reliable as possible by calculating weighted means and standard deviations of weight changes divided in the 2 periods of observation and balancing the number of subjects according to the compared sample of treated patients. Moreover, we performed a preliminary analysis comparing estimates derived from placebo-controlled studies and nonplacebo observational trials as compared to the virtual samples and found no significant differences. Finally, the high number of analyses performed may have produced a number of false-positive results, for which only a marginal correction was applied ($P < .01$). Nevertheless, the large convergence of our results with previous observations and reports found in the literature increases our confidence in the data presented in this article.

Similarly, pooling diagnoses other than major depression could introduce a bias, although again the sensitivity analysis did not yield any significant difference.

In conclusion, results obtained in the present meta-analysis confirmed that antidepressants markedly differ in their ability to induce changes in body weight. Overall, the impact is of mild significance, except in the cases of mirtazapine and amitriptyline, which were the most potent weight gain promoters. Some reduction of body weight can result from treatment with fluoxetine and bupropion, although for fluoxetine the effect may be only transient. To our knowledge, this is the first systematic and comprehensive review of the effect of antidepressants on body weight. However, further studies taking into account other important variables such as depressive severity, loss of appetite, atypical features, premorbid weight, and sex are warranted to better understand the impact of antidepressants on weight gain. Indeed, the topic is of great interest, since it may have important implications in the clinical practice, particularly when dealing with overweight or underweight patients or patients affected by medical conditions related to obesity. Moreover, changes in body weight may profoundly affect the psychological well-being of individuals. Quality of life, apart from patients' medical and mental state, deserves more attention in every health care setting.[42]

Drug names: bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and

others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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