Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis

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Objective: The purpose of this study was to estimate and compare the effects of antipsychotics—both the newer ones and the conventional ones—on body weight. **Method:** A comprehensive literature search identified 81 English- and non-English-language articles that included data on weight change in antipsychotic-treated patients. For each agent, a meta-analysis and random effects metaregression estimated the weight change after 10 weeks of treatment at a standard dose. A comprehensive narrative review was also conducted on all articles that did not yield quantitative information but did yield important qualitative information. **Results:** Placebo was associated with a mean weight reduction of 0.74 kg. Among conventional agents, mean weight change ranged from a reduction of 0.39 kg with molindone to an increase of 3.19 kg with thioridazine. Among newer antipsychotic agents, mean increases were as follows: clozapine, 4.45 kg; olanzapine, 4.15 kg; sertindole, 2.92 kg; risperidone, 2.10 kg; and ziprasidone, 0.04 kg. Insufficient data were available to evaluate quetiapine at 10 weeks. **Conclusions:** Both conventional and newer antipsychotics are associated with weight gain. Among the newer agents, clozapine appears to have the greatest potential to induce weight gain, and ziprasidone the least. The differences among newer agents may affect compliance with medication and health risk.

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Antipsychotic (neuroleptic) medications are an important therapeutic option for many individuals with schizophrenia and other psychoses. For these medications to be maximally beneficial, they must have an acceptable side effect profile and be taken as prescribed. One untoward effect of many antipsychotic drugs is weight gain (1). The extent of weight gain apparently varies by drug, which may be because of the drugs' differing degrees of action on the serotonergic (2), dopaminergic (3), cholinergic (2), histaminergic (4), and other neurotransmitter systems.

Obesity is a threat to health and longevity (5). Given that over one-third of the adults in the United States are obese (6), practices causing major weight gain deserve careful consideration. Obesity and weight gain have been associated with hypertension, type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some types of cancer (endometrial, breast, prostate, and colon) (7). Moreover, obesity is a common concomitant of schizophrenia (8), and schizophrenic individuals appear to be at increased risk for certain obesity-related conditions such as type II diabetes and cardiovascular disease (9–12).

Weight gain may also cause patients taking antipsychotic medications to discontinue their medications, which may predispose them to relapse (1). Historically, the extrapyramidal side effects of antipsychotics outweighed any nonextrapyramidal side effects. With the

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TABLE 1. List of Drugs Evaluated in 81 Studies

Drug	Class	Brand Name(s)	Manufacturer
Chlorpromazine	Phenothiazine	Thorazine	SmithKline Beecham
Thioridazine/mesoridazine	Phenothiazine	Mellaril, Serentil	Novartis (Sandoz), Boehringer Ingelheim
Fluphenazine	Phenothiazine	Prolixin	Apothecon
Perphenazine	Phenothiazine	Trilafon, Triavil	Schering, Merck
Trifluoperazine	Phenothiazine	Stelazine	SmithKline Beecham
Thiothixene	Thioxanthene	Navane	Pfizer
Loxapine	Dibenzodiazepine	Loxitane	Lederle
Clozapine	Dibenzodiazepine	Clozaril	Novartis (Sandoz)
Risperidone	Benzisoxazole	Risperdal	Janssen
Haloperidol	Butyrophenone	Haldol	McNeil
Molindone	Dihydroindolone	Moban	Gate
Pimozide	Diphenylbutylpiperidine	Orap	Gate
Chlorprothixene	Thioxanthene	Taractan	Roche
Prochlorperazine	Piperazine phenothiazine	Compazine	SmithKline Beecham
Olanzapine	Thienobenzodiazepine	Zyprexa	Eli Lilly
Quetiapine[a]	Dibenzothiazepine	Seroquel	Zeneca
Sertindole[a]	Phenylindole derivative	Serlect	Abbott
Ziprasidone[a]	Benzisothiazolylpiperazine	Zeldox	Pfizer

[a] Not approved by the Food and Drug Administration at the time this research was conducted.

advent of newer "atypical" antipsychotics, extrapyramidal side effects are becoming less of a problem. These recent developments in antipsychotics have made it imperative to revisit the topic of antipsychotic-induced weight gain. Therefore, we conducted a comprehensive, quantitative review of the research literature regarding the amount of weight gain associated with each antipsychotic drug available or undergoing clinical trials in the United States.

METHOD

Antipsychotics eligible for inclusion were those that are approved for use as antipsychotic agents in the United States or that were not currently approved but were under investigation in humans for use as antipsychotics. A list (table 1) was compiled from Hyman et al. (13), the 1997 edition of the *Physicians' Desk Reference,* and expert colleagues.

To avoid publication bias (14, 15) we retrieved both published and unpublished studies and conducted the most comprehensive search possible according to White's guidelines (16). The search consisted of the following. 1) References were searched for with the use of the computerized databases MEDLINE (1966 to November 1996), PsychINFO (1967 to October 1996), CINAHL (1982 to September 1996), HealthSTAR (1975 to October 1996), and Dissertation Abstracts International (1861 to January 1997). (Contact the first author for the search terms used.) 2) In an "ancestry analysis" (17), references were obtained from bibliographies of articles retrieved through computerized literature searches. 3) Several types of consultation were used to retrieve further information: informal consultation with expert colleagues in the field; contacts with authors of primary studies obtained through other search procedures, requesting more information and asking whether they knew of additional data of which we should be aware; and registered letters sent to the manufacturer of each compound under study, requesting a list of published and unpublished studies with respect to that compound and weight gain. To companies that provided data and/or expressed an interest (Janssen, Eli Lilly, Pfizer, Zeneca), we offered the opportunity to check our raw data files on their compounds for accuracy.

The literature search yielded over 350 reports, which were then screened for eligibility. To be eligible for this review, a study had to include human subjects, have a sample size greater than one, not be a review article, investigate at least one compound listed in table 1, and measure weight change after initiating use of the drug.

English- and non-English-language articles were considered. Four non-English articles were located and read by individuals fluent in the articles' languages. Only an article by Aberg (18) contained sufficient information and met the eligibility criteria. Six studies met the criteria but were rejected because they investigated prenatal exposure to neuroleptic drugs (one study) or studied patients suffering from anorexia nervosa or Huntington's chorea (five studies). In one case, only part of a study was used; specifically, from a study by Heimberg et al. (19) that compared individuals who were on a weight-reducing diet and taking clozapine with those who were not on such a diet but taking clozapine, only the data on the group not in the diet condition were used, because the diet condition did not represent usual conditions of use.

Coding and Data Extraction

Studies were coded by one investigator (J.L.M.) and spot-checked by one of two other investigators (M.H. or D.B.A). When a discrepancy was found (a fairly rare event), the coders met to discuss and resolve the discrepancy.

The mean and standard deviation of weight change and the size of each group were the three essential pieces of information needed from the studies. In many cases, these data were reported directly in the article and simply recorded. However, in other cases, they were not. In this latter situation, one of several approaches was taken in the following order of preference.

1. Missing means, standard deviations, or sample sizes were directly calculated by using other information available in the article (for example, t, F, or p values) and standard statistical formulas (20).

2. If the article was published in 1990 or later, we attempted to contact the authors for more information.

3. Two other procedures were used to estimate (rather than directly calculate) the necessary statistics. One method was used when data were presented in "binned" categories (e.g., "Ten percent of the patients gained no weight, 30% gained 0–5 pounds, 40% gained 5–15 pounds, and 20% gained more than 15 pounds"). In these situations, by using the categories and the proportions of subjects in each category, the missing mean and/or standard deviation was estimated by maximum likelihood methods; that is, we simply found the estimates of the means and the standard deviations that maximized the likelihood of the observed data by using the normal distribution likelihood function (21). The second method was used when the standard deviation was not reported but the range was (e.g., "Weight change ranged from –4 kg to +15 kg"). In this case we adapted the approach of Tippett (22), who published tables that, given the sample size, provide the expected ratio between the sample range and the standard deviation. Using Tippett's method, we estimated the standard deviation.

TABLE 2. Authors' Descriptions of Weight Change Due to Antipsychotic Drugs

Study	Year	Drug	Dose (mg/day)	Number of Subjects	Duration of Study	Mean Age (years)	% Male
Bechelli et al. (32)	1985	Haloperidol	—[a]	41	6 months	33	100
Darling (33)	1971	Haloperidol	1.5–20	30	5 months	18–56	—
Falloon et al. (34)	1978	Fluphenazine	25	19	1 month to 1 year	39 (range=17–60)	45
		Pimozide	8	24 (1 month); 19 (1 year)	1 month to 1 year	39 (range=17–60)	45
Frazier et al. (35)	1994	Clozapine	370.5	11	6 weeks	14	73
Hanlon et al. (36)	1970	Fluphenazine (and/or chlordiazepoxide, imipramine)	6.6	211	32 days	36	27
Hemphill et al. (37)	1975	Clozapine	100–600	52	6–12 months	—	42
Huttunen et al. (38)	1995	Risperidone	4–20	48	6 weeks	Median=34.0	50
Lindstrom (39)	1989	Clozapine	—	96	12 years	36.1	67
Naber et al. (40)	1992	Clozapine	191	480	49 days	34	42
Nair et al. (41)	1977	Clozapine	75–800	19	12 weeks	39.3	84
Norris and Israelstam (42)	1975	Clozapine	—	13	—	Adolescents	—
Povlsen et al. (43)	1985	Clozapine	317	85	Mean=2.75 years (men) and 3 years (women)	37	85
		Other neuroleptics	—	131	Mean=2.75 years (men) and 3 years (women)	37	85
Rada and Donlon (44)	1972	Thioridazine	800 max.	13	8 weeks	40	30
Sletten and Gershon (45)	1966	Chlorpromazine	—	18	18 days	—	—
Small et al. (46)	1997	Quetiapine	≤250; ≤750	159	6 weeks	22	76
Winkelman (47)	1964	Chlorpromazine	205	200	6 months to 10 years	—	—
Wistedt et al. (48)	1984	Haloperidol	122	25	20 weeks	39.1	68
		Fluphenazine	84	26	20 weeks	35.6	62
Young (49)	1970	Fluphenazine	6.25–250	103	—	—	—

[a] 100 mg/month.

TABLE 3. Duration of Treatment at the Time Weight Change Was Measured[a]

Drug or Study Condition	Duration of Treatment (weeks)		
	Mean	Minimum	Maximum
Chlorpromazine	8.8	1	36
Clozapine	20.7	4	84
Nonpharmacologic control	7.5	2	16
Fluphenazine	37.6	3	84
Haloperidol	12.3	2	56
Loxapine	43.2	12	104
Molindone	7.4	1	13
Olanzapine	21.7	1	52
Perphenazine	2.0	2	2
Pimozide	40.0	40	40
Placebo	10.9	4	52
Risperidone	13.0	1	30
Sertindole	8.7	7	14
Thioridazine/mesoridazine	10.1	4	36
Thiothixene	16.8	3	36
Trifluoperazine	5.0	2	8
Ziprasidone	14.3	6	52
Quetiapine	5.4	3	6
Polypharmacy	23.0	2	100
Total	17.3	1	100

[a] One poorly controlled study with follow-ups as long as 11 years was excluded as an outlier.

4. If only the standard deviation was missing, it was estimated as the square root of the weighted average variance across all other studies where the weights used were the sample sizes in each study. It was necessary for a standard deviation to be available in order to estimate the variance of the mean for each study, so that the inverse of this variance could be used as a weighting factor in subsequent analyses.

Finally, if none of these methods could be used to estimate the mean, standard deviation, and size of a study sample or a subgroup within a study, that study or subgroup was excluded from further consideration in the formal statistical meta-analysis. The total number of studies yielding usable data was 81. These studies yielded a total of 418 estimates of weight change in some antipsychotic drug condition or nondrug control condition. Of these 418 data points, 96.7% of the means, 69.6% of the standard deviations, and 100% of the numbers of study subjects were obtained by transcription or calculation, and the remainder by some form of estimation or imputation. Table 2 shows the mean and range of time on medication (in weeks) for the observed data points on each drug.

Analysis of the Data

Before the statistical meta-analysis was conducted, a verbal overview was done, because several articles provided descriptive data on weight change that could not be included in the quantitative analysis but nevertheless offered some information. Key quotations that characterized the effect of the drugs in question were extracted from such articles.

Statistical analyses were conducted with SPSS, version 7.5 (23). The effects of antipsychotic drugs were analyzed separately for each drug, since preliminary analyses indicated marked differences among the specific compounds in terms of their effects. Because most studies did not include a placebo comparison group, the effect size we used was the raw weight change from baseline to posttreatment. Only 18 studies included placebo comparisons. By using the pretreatment-to-posttreatment weight change in all studies, we were able to make full use of all of the available data.

Since there were 19 different drugs/conditions (including placebo; nonpharmacologic, nonplacebo control; and polypharmacy), 19 separate analyses were conducted (one for each condition). For each condition we attempted to calculate the weighted mean weight change and standard error based on both a fixed effects model (24) and a random effects model (24). Although both the fixed and ran-

Findings
"The number of patients who gained 5 kg or more was 3/19 (16%) in the HD [haloperidol decanoate] group" (p. 669).
"There was no edema, oversedation or increased weight" (p. 33).
Five experienced weight gain after one month; 10 experienced weight gain after 1 year/relapse.
Eight experienced weight gain after 1 month; 10 experienced weight gain after 1 year/relapse.
"The most prominent side effects were hypersalivation (eight cases), sedation (seven), and weight gain (seven)" (p. 660).
"Overall mean weight gain was only 1–2/3 lbs" (p. 175).
"Weight gain: most cases gained about 1 kg/week for 6 weeks and weight remained stable thereafter" (p. 2122).
"No relevant changes occurred in clinical laboratory parameters or body weight" (p. 275).
"Common but usually mild side effects were sedation, hypersalivation, weight gain, and obstipation" (p. S85).
Thirteen percent experienced weight gain (7.1% experienced slight weight gain; 4.1% experienced moderate weight gain; 1.8% experienced severe weight gain).
"Weight gain occurred in seven patients; the pre-drug versus post-drug change for the group being significant at the p<.01 level. One patient gained 27 pounds" (p. 289).
"Four patients have gained between 10 and 20 kg within a period of 2 months" (p. 385).
Eleven people (12.9%) gained weight.
Fourteen people (10.7%) gained weight.
"Eight [patients] on thioridazine showed weight gain" (p. 375).
"Weight increased abruptly with onset of chlorpromazine administration and decreased rapidly after cessation of medication" (p. 30).
"Treatment with quetiapine was associated with clinically significant weight gain (an increase of ≥7% from baseline weight) in 25% of the patients in the high-dose group compared with 16% in the low-dose group and 5% in the placebo group" (p. 556).
Eighteen people gained weight; three experienced excessive weight gain.
"A trend in weight increases for both men and women which favoured haloperidol compared to fluphenazine after 20 weeks of treatment was found. In the haloperidol group 12 had lower weight and 10 higher after 20 weeks of treatment" (p. 810).
"For fluphenazine 7 had lower and 18 higher weight" (p. 810).
"93% of the patients lost weight and 5% gained weight" (p. 708).

dom effects estimates are presented in the tables, only the random effects estimates are discussed in the text, given the significant heterogeneity present for most compounds (see the Results section).

For each drug, when sufficient data (i.e., six or more data points) were available, we regressed mean weight change on standardized drug dosage and length of treatment. One older, poorly controlled study (25) was eliminated because it was an outlier, and its exceptionally long follow-up of 11 years caused it to act as a leverage point (26); all of the other follow-ups were less than 200 weeks long. These regressions were conducted as weighted least squares multiple regressions, where the weights were equal to the inverse of the variances of the dependent observations. To more reasonably compare drugs by controlling for different dosage levels, we calculated standardized doses by dividing the actual doses used in the studies by the midpoint of the recommended dose range and taking the natural log of the resulting ratio. (Although we adhered to this procedure for all drugs in the interest of consistency, it is possible that in some cases, the midpoint of the recommended dose range may not have been the best estimate of the standard dose. Therefore, for the atypical antipsychotics, haloperidol, and thioridazine [the most commonly used drugs], we conducted a sensitivity analysis by recomputing the results. We replaced the standardized dose first with the typical dose in chlorpromazine equivalents according to APA's *Practice Guideline for the Treatment of Patients With Schizophrenia* [27] and second with the average dose used in clinical settings as reported in the peer-reviewed literature.) Recommended dose ranges were obtained from the appendix of a consensus report (28), the *Physicians' Desk Reference,* or the drug manufacturer. The regression equation we used was $\Delta_{kg}=\beta_0 + \beta_1(\text{weeks} - 10) + \beta_2(\text{weeks} - 10)^2 + \beta_3(D) + \beta_4(D)^2 + e$, where Δ_{kg} is weight change in kilograms, the βs are parameters to be estimated, weeks is number of weeks of treatment, D is the standardized dose calculated as described above, and e is an error term. In this equation, β_0 is a direct estimator of weight change at 10 weeks at the standard dose. For placebo, nonpharmacologic control, and polypharmacy, dosage information was not included in the regression.

Using the aforementioned equation, we estimated the weight-promoting effects of each drug at the midpoint of its recommended dose at 10 weeks with the use of both fixed effects (29) and random effects (30) models. Ten weeks was chosen as the time point because this value required no extrapolation beyond the observed data for any drug.

Finally, we used pairwise comparisons for the estimated weight changes at 10 weeks at the standard dose of each compound. The significance of differences was tested with a z statistic. The quantity $(\theta_i - \theta_j)/(\div SE^2[\theta_i] + SE^2[\theta_j])$ is asymptotically (in the number of subjects not the number of means) distributed as a standard normal deviate, where θ_i and θ_j are the estimates of weight change for the *i*th and *j*th compounds, respectively (29). To account for multiple comparisons, we used Monte Carlo simulation with 100,000 simulated data sets to determine the z value that, given the number of tests being conducted, would hold the overall alpha rate to the two-tailed 0.05 level. The simulated data were generated from a model with normal distribution based on the sample sizes we had. (For the concept behind this approach, see reference 31.) The critical z value obtained was 3.31. Therefore, any pairwise comparison yielding a z statistic greater in absolute value than 3.31 is statistically significant even after accounting for conducting multiple comparisons. This is slightly less conservative than the 3.41 required for the ordinary Bonferroni correction.

RESULTS

Table 3 displays the results from the verbal overview. The statements regarding specific drugs may be useful to clinicians and patients considering use of these drugs. On a very general level, two conclusions can be drawn from this tabulation. First, many drugs do seem

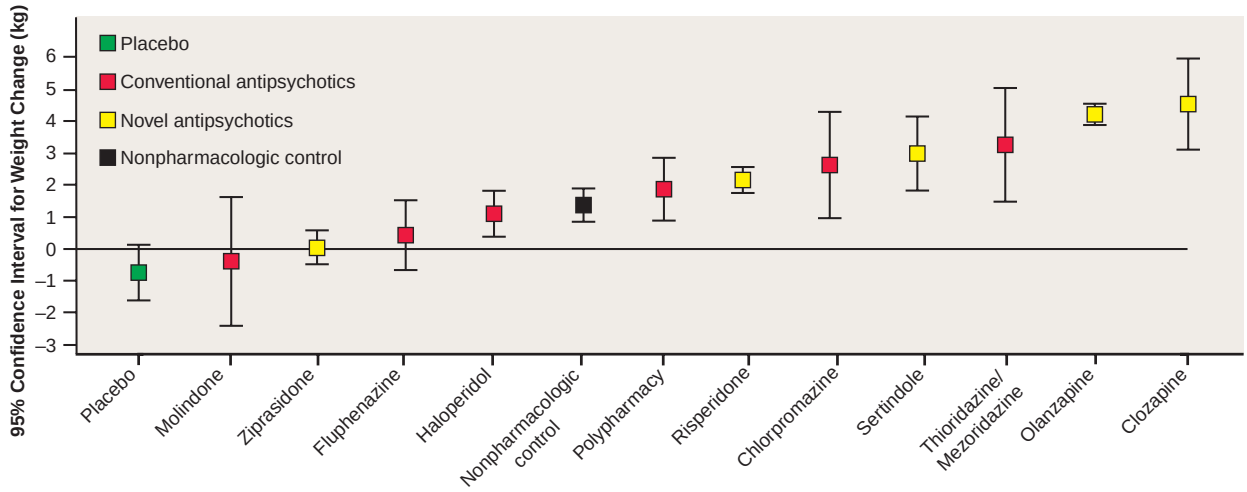
TABLE 4. Estimated Weight Change in Patients Taking Study Drugs

Drug or Study Condition and Number of Studies[a]	Weight Change (kg): Fixed Effects Model		Test for Heterogeneity in Fixed Effects Model			Weight Change (kg): Random Effects Model		Estimated Weight Change (kg) at 10 Weeks: Fixed Effects Model[b]	
	Mean	95% CI	χ^2	df	p	Mean	95% CI	Mean	95% CI
Chlorpromazine (N=25; 13)	6.19	5.84 to 6.54	746.2	24	<0.0005	4.19	2.94 to 5.44	2.10	0.85 to 3.35
Clozapine (N=14; 12)	4.37	4.00 to 4.74	148.2	13	<0.0005	5.67	4.34 to 7.00	3.99	2.72 to 5.26
Fluphenazine (N=11; 10)	0.95	0.73 to 1.17	142.0	10	<0.0005	1.13	0.09 to 2.17	0.43	–0.65 to 1.51
Haloperidol (N=25; 19)	0.18	0.02 to 0.34	78.5	24	<0.0005	0.51	0.20 to 0.82	0.48	0.07 to 1.03
Loxapine (N=5; 3)	0.75	0.06 to 1.44	71.4	4	<0.0005	0.65	–2.56 to 3.86	—	—
Molindone (N=17; 10)	–1.06	–1.51 to –0.61	154.0	16	<0.0005	–0.10	–1.39 to 1.19	–0.81	–2.16 to 0.54
Nonpharmacologic control (N=7; 4)	0.79	0.46 to 1.12	21.0	6	0.002	0.82	0.08 to 1.56	1.33	0.84 to 1.82
Olanzapine (N=157; 7)	1.53	1.49 to 1.57	4009.8	156	<0.0005	4.17	3.70 to 4.64	3.51	3.29 to 3.73
Perphenazine (N=4; 4)	2.79	1.63 to 3.95	19.4	3	<0.0005	5.77	0.44 to 11.10	—	—
Pimozide (N=2; 2)	–3.53	–7.65 to 0.59	21.1	1	0.15	–2.69	–9.30 to 3.92	—	—
Placebo (N=25; 22)	–0.50	–0.70 to –0.30	238.7	24	<0.0005	–0.97	–1.79 to –0.15	–0.41	–1.29 to 0.47
Polypharmacy (N=26; 13)	0.47	0.25 to 0.69	89.9	25	<0.0005	0.46	0.24 to 0.68	1.22	0.36 to 2.08
Quetiapine (N=8; 3)[d]	2.61	2.07 to 3.14	28.8	7	<0.0005	2.49	1.51 to 3.47	—	—
Risperidone (N=38; 26)	1.38	1.28 to 1.48	289.6	37	<0.0005	1.67	1.38 to 1.96	2.00	1.61 to 2.39
Sertindole (N=7; 4)	2.94	2.70 to 3.18	6.2	6	0.39	2.94	2.70 to 3.18	2.92	1.76 to 4.08
Thioridazine/mesoridazine (N=16; 12)	1.97	1.58 to 2.36	129.1	15	<0.0005	2.81	1.59 to 4.03	3.49	1.75 to 5.23
Thiothixene (N=4; 3)	2.31	1.45 to 3.17	5.2	3	0.16	2.89	1.01 to 4.77	—	—
Trifluoperazine (N=2; 2)	0.34	–0.86 to 1.54	0.1	1	0.75	0.34	–0.86 to 1.54	—	—
Ziprasidone (N=25; 22)	0.64	0.40 to 0.88	69.2	24	<0.0005	0.28	–0.27 to 0.83	0.04	–0.49 to 0.57

[a] Some of the observations entering into the calculations are not independent (i.e., they may be from the same subjects measured at multiple points in time). This was not taken into account in calculation of the standard errors. The Ns shown are total number of means and number of independent cohorts the means came from. The number of means will always be greater than or equal to the number of independent means, because some cohorts may have been measured at multiple points in time. However, the number of independent means can exceed the number of trials, because some trials contained more than one independent cohort. For example, six trials provided data on ziprasidone, but because the data for men and women were provided separately and several different dose conditions were used with multiple groups, the six trials yield 22 independent cohorts.

[b] Estimated from the fixed effects fitted regression (see text).

FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model



to induce clinically meaningful weight gain. Second, many authors report their weight gain data in an incomplete, idiosyncratic, and poorly defined manner. This is clearly an area that would benefit from guidelines and standardization.

Table 4 displays the results from the quantitative meta-analysis in detail. (Because of space limitations, studies used in the meta-analysis but not cited are not listed in the reference list. A complete reference list can be obtained from the first author.) The second column in table 4 indicates the estimated mean weight change across all studies with the use of a fixed effects model (29) and the 95% confidence interval for that mean. These means, though interesting, are probably not maximally informative, because the studies varied greatly in terms of length of treatment and dosage.

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