Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis

David B. Allison, Ph.D., Janet L. Mentore, M.S.Ed., Moonseong Heo, Ph.D., Linda P. Chandler, Ph.D., Joseph C. Cappelleri, Ph.D., M.P.H., Ming C. Infante, M.S., and Peter J. Weiden, M.D.

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.

(Am J Psychiatry 1999; 156:1686–1696)

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

Presented in part at the 151st annual meeting of the American Psychiatric Association, Toronto, May 30–June 4, 1998, and the 1998 meetings of the New Clinical Drug Evaluation Unit, the Association of European Psychiatrists, and the Collegium Internationale Neuro-Psychopharmacologicum. Received Aug. 4, 1998; revision received March 8, 1999; accepted March 17, 1999. From the Obesity Research Center, St. Luke's-Roosevelt Hospital, Columbia University College of Physicians and Surgeons; the Graduate School of Education, Fordham University, New York; and Pfizer Central Research, Groton, Conn. Address reprint requests to Dr. Allison, Obesity Research Center, 1090 Amsterdam Ave., Suite 14B, New York, NY 10025; dba8@columbia.edu (e-mail).

Supported by a grant from Pfizer Central Research and grants DK-26687, DK-51716, and DK-47526 from the National Institute of Diabetes and Digestive and Kidney Diseases.

The authors thank the following for their help: Charles M. Beasley, Jr., Alan Breier, Ann Marie K. Crawford, Martin Brecher, Rolando Gutierrez, Andrew Chanlam, Rakhee Vasant, Mani Lakshminarayanan, Robert Monty, Muriel Young, Sandra Wiejowski, Christine A. Ney, Jaime Mullen, Albert S. Stunkard, Petra Platte, Christine Peterson, Donna Wirshing, Danielle Goldstein, and Michael C. Neale.

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

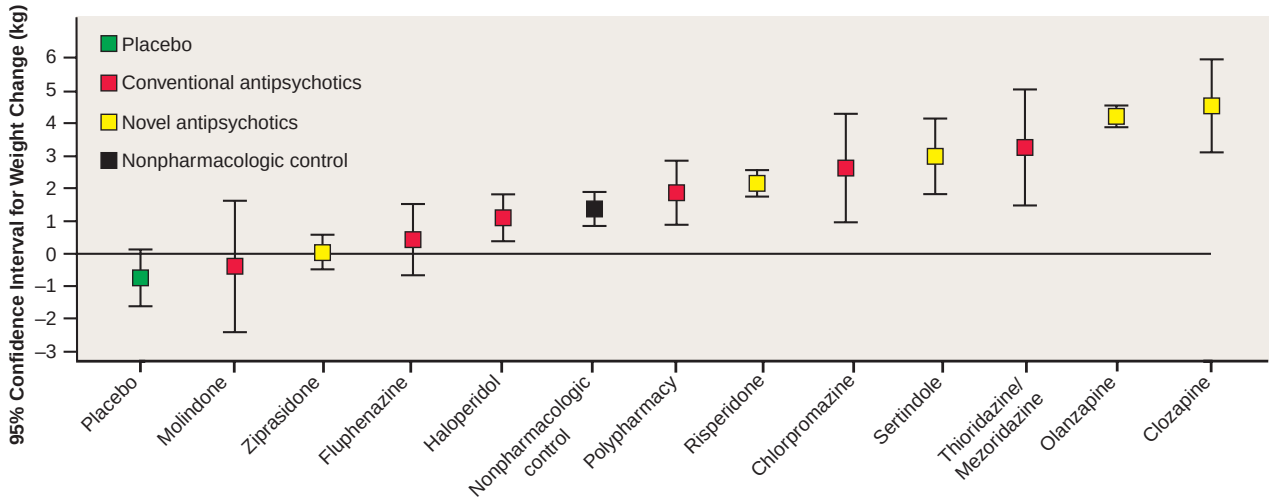
Table 3 displays the results from the verbal overview. The statements regarding specific drugs may be useful to clinicians and patients considering use of these drugs. On a very general level, two conclusions can be drawn from this tabulation. First, many drugs do seem

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.

Test for Random Effects Variance or 10-Week Estimate			Estimated Weight Change (kg) at 10 Weeks: Random Effects Model[c]	
χ^2	df	p	Mean	95% CI
68.4	20	<0.0005	2.58	0.91 to 4.25
38.3	9	<0.0005	4.45	3.02 to 5.88
6.9	6	0.23	0.43	–0.65 to 1.51
63.3	20	<0.0005	1.08	0.35 to 1.81
			—	—
49.5	12	<0.0005	–0.39	–2.43 to 1.65
1.5	2	0.69	1.33	0.84 to 1.82
709.5	152	<0.0005	4.15	3.82 to 4.48
			—	—
			—	—
237.1	20	<0.0005	–0.74	–1.60 to 0.12
75.3	21	<0.0005	1.82	0.84 to 2.80
			—	—
161.9	33	<0.0005	2.10	1.69 to 2.51
0.2	2	0.88	2.92	1.76 to 4.08
32.9	11	0.0003	3.19	1.39 to 4.99
			—	—
			—	—
21.2	20	0.39	0.04	–0.49 to 0.57

[c] Estimated with the same predictors as in the fixed effects model. However, the estimates and their standard errors were derived iteratively through maximum likelihood, as described by Raudenbush (30).

[d] Because the maximum duration for this drug was 6 weeks, estimates at 10 weeks are not reported so as to avoid extrapolations. When the effects were evaluated at 6 weeks, the estimates were 2.18 kg (95% CI=1.53–2.83) for both fixed and random effects models. For random effects variance for the 6-week estimate, χ^2= 1.55, df=3, p=0.67.

This heterogeneity among studies is indicated by the chi-square test for heterogeneity in the third column. In almost all cases, the values are highly significant, indicating that different studies with different durations and different dosages gave different answers. Therefore, we used a random effects estimate in the fourth column. This takes between-study variation into account but does not specifically attribute this variation to sources such as study duration and dosage. In the fifth column there is an estimate of the 10-week weight change based on a fixed effects regression (29) as described earlier. The chi-square values to the right of this column are calculated according to Raudenbush (30). As can be seen, for many drugs the heterogeneity tests were no longer significant, indicating that accounting for dosage and duration adequately explained the variation among studies. However, in some cases, the chi-square statistics were still significant, suggesting the importance of using a random effects model. The final column contains the point estimates for each drug for patients on standard doses for 10 weeks. These were calculated by means of the regression described earlier. We believe that these estimates in the final column of table 4 are the most reasonable estimates. Figure 1 summarizes these results graphically. Several points are noteworthy.

First, subjects in placebo conditions typically lost about 0.74 kg. This may be because in many of the placebo-controlled studies, subjects were taking some other neuroleptic drug before the trial. Therefore, when this drug was removed, some of the weight gain it previously induced may have been lost. Another possibility is that studies including placebo usually have acutely psychotic subjects, and food intake may be lower in individuals whose acute psychotic symptoms are not improved.

Two drugs, molindone and pimozide, were also associated with weight loss. In the case of molindone, this has been reported previously in the literature (50–52). Although the estimated weight loss with molindone (–1.06 kg) was significant overall, the estimated loss at 10 weeks (–0.39 kg) was not significant. For pimozide, the estimated weight loss was 2.69 kg (in the random effects model), but the standard error was quite large and the estimate was not significantly different from zero.

For other drugs, the degree of weight gain, estimated by the random effects regression at 10 weeks, ranged from 0.04 kg for ziprasidone (not significantly different from zero) to 4.45 kg for clozapine. Among the five new atypical antipsychotics in the study (ziprasidone, risperidone, sertindole, olanzapine, and clozapine), ziprasidone had the lowest weight gain (0.04 kg) and clozapine had the highest (4.45 kg). Table 5 contains z statistics and p values for pairwise significance tests comparing the estimated 10-week weight changes for patients taking the specific compounds. Although reported data were somewhat limited, there was little apparent difference across drugs in the average age of subjects in the studies and in the percentage of male subjects.

Finally, table 6 shows results of a sensitivity analysis of estimated 10-week weight gains (random effects model) based on different definitions of standard dose. The results are quite robust to the choice of standard dose except for clozapine, which does not show sizably different weight gains (between 2.96 and 4.45 kg) across the different standard doses.

DISCUSSION

Most neuroleptic drugs were associated with weight gain. It does not appear as though any of this weight gain can be attributed to a placebo effect, since patients on placebo appear to have lost weight. The degree of weight gain clearly increased with time for the drugs considered. Weight gain was estimated at 10 weeks because there were many data for this time interval. However, estimated weight gain while patients are taking a drug for longer periods would be expected to be substantially higher. This expectation is based on both the physics and the physiology of weight gain (59) and empirical observations from studies of selected compounds for which longer-term data were available (60).

TABLE 5. Results of Pairwise Tests of Differences Between Drugs' Estimated Effects on Weight at 10 Weeks (z statistics above diagonal

Drug or Study Condition	Chlorpromazine	Clozapine	Fluphenazine	Haloperidol	Molindone	Nonpharmacologic Control	Olanzapine	Placebo
Chlorpromazine		1.67	–2.12	–1.62	–2.21	–1.41	1.81	–3.47
Clozapine	0.09		–4.40	–4.12	–3.81	–4.04	–0.40	–6.09
Fluphenazine	0.03	<0.0001		0.98	–0.70	1.49	6.46	–1.66
Haloperidol	0.11	<0.0001	0.33		–1.33	0.56	7.54	–3.17
Molindone	0.03	0.0001	0.48	0.18		1.61	4.31	–0.31
Nonpharmacologic control	0.16	0.0001	0.14	0.58	0.11		9.33	–4.09
Olanzapine	0.07	0.69	<0.0001	<0.0001	<0.0001	<0.0001		–10.37
Placebo	0.0005	<0.0001	0.10	0.002	0.76	<0.0001	<0.0001	
Polypharmacy	0.44	0.003	0.06	0.23	0.05	0.38	<0.0001	0.0001
Risperidone	0.58	0.002	0.005	0.02	0.02	0.02	<0.0001	<0.0001
Sertindole	0.74	0.10	0.002	0.008	0.006	0.01	0.05	<0.0001
Thioridazine	0.62	0.28	0.01	0.03	0.01	0.05	0.30	0.0001
Ziprasidone	0.004	<0.0001	0.52	0.02	0.69	0.0004	<0.0001	0.13

[a] Absolute z values greater than 3.31 are significant even after accounting for the multiple comparisons conducted. Only drugs for which a 10-week estimate was available are included in this table. The random effects estimates were used.

TABLE 6. Analysis of Sensitivity of Estimated Weight Gain at 10 Weeks, From Random Effects Models, According to Three Alternative Definitions of Standard Drug Dose

	Standardized Dose[a]		Chlorpromazine Equivalents[b]		Average Dose[c]		
Drug	Dose (mg/day)	Weight Gain (kg)	Dose	Weight Gain (kg)	Dose (mg/day)	Weight Gain (kg)	Source of Information on Average Dose
Clozapine	500	4.45	250	2.96	468	4.28	Conley et al. (53)
Haloperidol	11	1.08	10	1.09	9	1.09	Muller-Siecheneder et al. (54)
Olanzapine	12.5	4.15	12.5	4.15	13.2	4.15	Nemeroff (55)
Risperdone	10	2.10	7.5	2.06	5.9	2.00	Jeste et al. (56)
					9.4	2.09	Lindstrom et al. (57)
Thioridazine/mesoridazine	375	3.19	500	2.45	378	3.17	Keks et al. (58)

[a] Actual doses used in studies, divided by the midpoint of the recommended dose range and with the natural log of the resulting ratio taken.
[b] Dose equivalent to 500 mg of chlorpromazine according to APA's *Practice Guideline for the Treatment of Patients With Schizophrenia* (27).
[c] Average dose used in clinical settings as reported in the peer-reviewed literature.

Limitations of the Study

This study has several limitations. First, standard errors were calculated under the assumption that all observations were independent, which was not true in every case because some studies assessed subjects at repeated time points. When such data were available, we included all data points in the interest of using all available information. Our estimates of weight change with use of the weighted least squares method remain accurate (i.e., unbiased), but their standard errors may be too small. Ordinarily, one would take this dependency into account through the use of generalized least squares estimation (26). Unfortunately, generalized least squares implementation requires knowledge of the covariance structure among the observations, and this information was not available. Therefore, the standard errors presented here and the significance levels based on them may, in some cases, be biased. To estimate the plausible degree of this bias, we assumed that all dependent observations had a correlation as high as 0.90 and conducted the fixed effects regression analyses through generalized least squares. The largest putative change in standard error for any drug occurred with chlorpromazine and was 59%. For no other drug did the increase in estimated standard error exceed 4%. Thus, this sensitivity analysis suggests that our standard errors are unlikely to have been underestimated to any substantial degree.

A second limitation concerns our inability to examine the extent to which weight change with antipsychotic drugs varied as a function of patients' characteristics, such as age, sex, and initial body mass index. Unfortunately, the limited information presented in each study on the distributions of age, sex, and starting body mass index and the limited number of studies available for each drug precluded inclusion of terms for such patient characteristics in the metaregressions.

A third limitation is that for most drugs, insufficient information was available to provide precise estimates of weight change when patients were on the drug for extended periods of time, such as 6 months or more. Although we initially attempted to calculate such estimates, this frequently required extrapolations outside the observed range of data, and the resulting estimates were often extremely imprecise (i.e., had very large standard errors).

Strengths of the Study

To our knowledge, this is the most comprehensive literature synthesis on antipsychotic-induced weight gain to date. Although it is plausible that some studies assessing the effect of antipsychotic medications on

and two-tailed per-comparison p values below diagonal)[a]

Poly-pharmacy	Risperdone	Sertindole	Thioridazine[b]	Ziprasidone
–0.77	–0.55	0.33	0.49	–2.85
–2.97	–3.09	–1.63	–1.07	–5.67
1.87	2.84	3.09	2.57	–0.64
1.19	2.40	2.64	2.13	–2.27
1.92	2.35	2.77	2.58	0.40
0.88	2.36	2.48	1.95	–3.51
–4.41	–7.59	–2.00	–1.03	–12.88
3.84	5.83	4.97	3.85	1.51
	0.52	1.42	1.31	–3.13
0.60		1.31	1.16	–6.02
0.16	0.19		0.25	–4.44
0.19	0.25	0.80		–3.29
0.002	<0.0001	<0.0001	0.001	

[b] Includes both thioridazine and mesoridazine.

body weight were not discovered by our literature search, our procedures kept this to a minimum. We conducted a thorough search of the electronic literature and made efforts to access undetected literature through the "Invisible College" and formal contacts with pharmaceutical companies. Moreover, we conducted electronic searches of databases that also include unpublished literature, such as Dissertation Abstracts International and PsychINFO.

A common problem in meta-analysis is inadequate and incomplete reporting of key information in the primary articles. We attempted to minimize the impact of such incomplete reporting by contacting authors when feasible. Moreover, for studies that did not yield sufficient information to be included in the formal quantitative synthesis, we still attempted to extract whatever information was available in these reports and provide that in a structured verbal overview (table 2).

Our literature retrieval procedures also maximized the chances of obtaining relevant unpublished data. Publication bias is a commonly acknowledged problem in applied research. This problem confronts all literature reviewers, whether they conduct formal meta-analyses or not. We believe our efforts were quite strong in this regard and therefore should serve to minimize publication bias.

Clinical Implications

In the early days of chlorpromazine pharmacotherapy, Planansky and Heilizer (61) reported that weight gain was associated with symptom improvement, and weight loss was associated with symptom deterioration. The subsequent availability of multiple antipsychotic medications has led to the observation that weight gain is a common side effect of antipsychotic treatment. There is some conjecture that the drugs which cause the most weight gain are the most effective. However, results are inconsistent and equivocal (58, 62–65), and further research is needed on this question.

How clinically meaningful are these degrees of weight gain? Some compounds were estimated to produce close to a 5-kg weight gain at 10 weeks. Furthermore, the shorter-term controlled studies usually included data on all subjects, whereas long-term use was usually restricted to individuals showing a positive therapeutic response to the drug. If therapeutic response and weight gain are correlated (which may or may not be true), then this would imply that the 10-week weight gain may be higher than we have estimated. On the basis of the compounds for which longer-term data were available (chlorpromazine, clozapine, and olanzapine), it seems clear that although weight gain might reach a plateau after a certain period (e.g., for olanzapine, after 4–5 months), total weight gain will still be much larger after periods longer than 10 weeks. Thus, weight gains far in excess of 5 kg may be seen in patients on long-term therapy. However, even a weight gain of 5 kg will represent a weight gain of more than 5% of initial body weight for the majority of individuals. To place this in perspective, it is useful to consider that a number of authoritative bodies, such as the Institute of Medicine (66), have suggested that weight losses of as little as 5% in obese individuals can result in clinically meaningful reductions in morbidity and risk of early mortality. It might be plausible, then, to expect that increases in body weight of as much as 5% would result in corresponding increases in morbidity and risk of early mortality.

Although the literature assessing the effects of weight gain on "hard" end points reveals a complex set of relations and modifiers, certain general conclusions can be drawn. For end points such as mortality (67, 68), incidence of cancer (69, 70), cardiovascular disease (71, 72), and diabetes (73), when factors such as smoking are accounted for, it appears that weight gains of 5% or greater during the adult lifespan are associated with important increases in risks. This is especially true for individuals who are overweight to begin with. Finally, although results are clearly preliminary, emerging data suggest that the drugs causing weight gain (i.e., clozapine and olanzapine) may, perhaps as a result, also be causing type II diabetes (74–77). Clearly, then, antipsychotics can induce medically meaningful degrees of weight gain.

Weight gain induced by antipsychotic drugs may also discourage patients from reliably taking their medication. This would, in turn, increase the likelihood of relapse. Although we are aware of no data that would allow precise quantification of the impact of weight gain on compliance with medication, we have observed that a number of patients complain of weight gain and occasionally report it as a reason for noncompliance. On the other hand, in studies conducted with olanzapine, Tollefson et al. (78) and Beasley et al. (60) found that for acute trials and studies lasting a year, drug discontinuation attributed to weight gain was quite rare. For example, in a 6-week study, Tollefson et al. (78) found that "none of 1,336

olanzapine-treated patients discontinued early because of weight gain."

Given this background, it is important to consider methods for minimizing the impact of weight gain induced by antipsychotic drugs. One approach might be to implement weight control procedures with schizophrenic individuals who are taking antipsychotic medications. Several such efforts have been made in the past, including pharmacologic (79, 80) and nonpharmacologic (81–85) approaches. In some cases, particularly with subjects in inpatient settings, results have been good. However, results with outpatients are less clear, and more research on this topic is needed. Some investigators have even begun to explore the potential of amantadine in pharmacologic treatment specifically for neuroleptic-induced weight gain (86–88), but this is not a generally accepted treatment at this time.

The use of pharmacologic treatments of obesity with this population may present challenges. With one exception (89), all pharmacologic agents for the treatment of obesity that are currently available or likely to be released in the very near future achieve their effects by increasing noradrenergic, dopaminergic, and/or serotonergic activity (90). In contrast, antipsychotic medications typically achieve much of their effect by decreasing dopaminergic and serotonergic activity. Therefore, the use of pharmacologic agents to treat obesity in individuals with schizophrenia may exacerbate their psychotic symptoms (91–95). Indeed, weight loss itself has even been reported to provoke psychotic symptoms in rare cases (96). Therefore, any use of centrally acting pharmacologic agents to treat obesity in this population should be undertaken with the utmost caution and, in our opinion, be preceded by well-controlled clinical trials to establish efficacy and safety.

Finally, the selection of the right compound for the right patient might minimize the impact of weight gain with antipsychotic medications. There are schizophrenic individuals who are sufficiently thin that weight gain would likely be harmless and perhaps even beneficial (8). In such cases, not all weight gain will necessarily represent fat. Studies also indicate that weight gain is highest in individuals with a low baseline body mass index (60). Although these patients are rare, for such patients there would be little reason to avoid the use of drugs that produce greater degrees of weight gain. However, for patients with an average body mass index or higher or patients with a history of obesity, clinicians may wish to consider using compounds associated with less weight gain. The estimates provided in table 4 may help clinicians make such choices. The preceding notwithstanding, we wish to emphasize that weight gain should never be a sole reason for choosing one antipsychotic drug over another. Both therapeutic efficiency and other factors such as dose-related extrapyramidal syndromes should also be considered in drug selection. For many individuals the degree of risk imposed by the weight gain from a drug will not outweigh the degree of benefit achieved by alleviation of schizophrenic symptoms. In the end, clinical choices must be made on a case-by-case basis, with careful consideration of issues of weight, therapeutic efficacy, and other relevant factors.

REFERENCES

1. Bernstein JG: Induction of obesity by psychotropic drugs. Ann NY Acad Sci 1987; 499:203–215
2. Schotte A, Janssen PF, Megens AA, Leysen JE: Occupancy of central neurotransmitter receptors by risperidone, clozapine and haloperidol, measured ex vivo by quantitative autoradiography. Brain Res 1993; 63:191–202
3. Brief DJ: Chronic treatment with neuroleptic drugs and weight gain. Dissertation Abstracts International 1985; 45(11B):3653
4. Salomon MS: Histamine: a new factor in the control of feeding behavior. Dissertation Abstracts International 1992; 53(2B): 1102
5. Allison DB, Pi-Sunyer FX: Obesity treatment: examining the premises. Endocrine Practice 1995; 1:353–364
6. Centers for Disease Control: Update: prevalence of overweight among children, adolescents, and adults—United States, 1988–1994. MMWR Morb Mortal Wkly Rep 1997; 46: 198–202
7. National Institute of Health: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. Obes Res 1998; 6(suppl 2):51S–209S
8. Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, Weiden PJ, Cheskin LJ: The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999; 60:215–220
9. Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL: Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996; 37:68–73
10. McKee HA, D'Arcy PF, Wilson PJ: Diabetes and schizophrenia—a preliminary study. J Clin Hosp Pharm 1986; 11:297–299
11. Tsuang MT, Perkins K, Simpson JC: Physical diseases in schizophrenia and affective disorder. J Clin Psychiatry 1983; 44:42–46
12. Brambilla F, Guastalla A, Guerrini A, Riggi F, Rovere C, Zanoboni A, Zanoboni-Muciaccia W: Glucose-insulin metabolism in chronic schizophrenia. Dis Nerv Syst 1976; 37:98–103
13. Hyman SE, Arana GW, Rosenbaum JF: Handbook of Psychiatric Drug Therapy, 3rd ed. New York, Little, Brown, 1995
14. Allison DB, Faith MS, Gorman BS: Publication bias in obesity treatment trials. Int J Obes 1996; 20:931–937
15. Begg CB, Berlin JA: Publication bias and the dissemination of clinical research. J Natl Cancer Inst 1989; 81:107–115
16. White HD: Scientific communication and literature retrieval, in The Handbook of Research Synthesis. Edited by Cooper H, Hedges LV. New York, Russell Sage Foundation, 1994, pp 41–55
17. Cooper H, Hedges LV (eds): The Handbook of Research Synthesis. New York, Russell Sage Foundation, 1994
18. Aberg A: Viktforandring i samband med psykofarmakabehandling. Opusc Med 1964; 20:13–19
19. Heimberg C, Gallacher F, Gur RC, Gur RE: Diet and gender moderate clozapine-related weight gain. Human Psychopharmacology 1995; 10:367–371
20. Rosenthal R: Meta-Analytic Procedures for Social Research. Newbury Park, Calif, Sage Publications, 1991
21. Hogg RV, Craig AT: Introduction to Mathematical Statistics, 4th ed. New York, Macmillan, 1978
22. Tippett LHC: The Methods of Statistics. London, Williams & Norgate, 1931
23. Norusis MJ: SPSS for Windows: Base System User's Guide, Release 7.5. Chicago, SPSS, 1997
24. Shadish WR, Haddock CK: Combining estimates of effect size, in The Handbook of Research Synthesis. Edited by Cooper H, Hedges LV. New York, Russell Sage Foundation, 1994, pp 261–281

25. Gopalaswamy AK, Morgan R: Too many chronic mentally disabled patients are too fat. Acta Psychiatr Scand 1985; 72: 254–258
26. Sen A, Srivastava M: Regression Analysis. New York, Springer-Verlag, 1990
27. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry 1997; 154(April suppl)
28. Treatment of schizophrenia: steering committee, the expert consensus. J Clin Psychiatry 1996; 57(suppl 12B):3–58
29. Hedges LV: Fixed effects models, in The Handbook of Research Synthesis. Edited by Cooper H, Hedges LV. New York, Russell Sage Foundation, 1994, pp 285–299
30. Raudenbush SW: Random effects models. Ibid, pp 301–321
31. Westfall PH, Young SS: Resampling-Based Multiple Testing: Examples and Methods for P-Value Adjustment. New York, John Wiley & Sons, 1993
32. Bechelli LPC, Iecco MC, Acioli A, Pontes MC: A double-blind trial of haloperidol decanoate and pipothiazine palmitate in the maintenance treatment of schizophrenics in a public outpatient clinic. Curr Ther Res 1985; 37:662–671
33. Darling HF: Haloperidol in 60 criminal psychotics. Dis Nerv Syst 1971; 32:31–34
34. Falloon I, Watt DC, Shepherd M: A comparative controlled trial of pimozide and fluphenazine decanoate in the continuation therapy of schizophrenia. Psychol Med 1978; 8:59–70
35. Frazier JA, Gordon CT, McKenna K, Lenane MC, Jih D, Rapoport JL: An open trial of clozapine in 11 adolescents with childhood-onset schizophrenia. J Am Acad Child Adolesc Psychiatry 1994; 33:658–663
36. Hanlon TE, Ota KY, Kurland AA: Comparative effects of fluphenazine, fluphenazine-chlordiazepoxide and fluphenazine-imipramine. Dis Nerv Syst 1970; 31:171–177
37. Hemphill RE, Pascoe FD, Zabow T: Acute and chronic schizophrenia and gross behavior disorders. S Afr Med J 1975; 49: 2121–2125
38. Huttunen MO, Piepponen T, Rantanen H, Larmo I, Nyholm R, Raitasuo V: Risperidone versus zuclopenthixol in the treatment of acute schizophrenic episodes: a double-blind parallel-group trial. Acta Psychiatr Scand 1995; 91:271–277
39. Lindstrom LH: A retrospective study on the long-term efficacy of clozapine in 96 schizophrenic and schizoaffective patients during a 13-year period. Psychopharmacology (Berl) 1989; 99:S84–S86
40. Naber D, Holzbach R, Perro C, Hippius H: Clinical management of clozapine patients in relation to efficacy and side effects. Br J Psychiatry Suppl 1992; 17:54–59
41. Nair NPV, Zicherman V, Schwartz G: Dopamine and schizophrenia. Can Psychiatr Assoc J 1977; 22:285–293
42. Norris DL, Israelstam K: Clozapine (Leponex) overdosage (letter). S Afr Med J 1975; 49:385
43. Povlsen UJ, Noring U, Fog R, Gerlach J: Tolerability and therapeutic effect of clozapine. Acta Psychiatr Scand 1985; 71: 176–185
44. Rada RT, Donlon PT: Piperacetazine vs thioridazine for the control of schizophrenia in outpatients. Psychosomatics 1972; 13:373–376
45. Sletten IW, Gershon S: The effect of chlorpromazine on water and electrolyte balance. J Nerv Ment Dis 1966; 142:25–31
46. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG: Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997; 54:549–557
47. Winkelman NW: A clinical and socio-cultural study of 100 psychiatric patients started on chlorpromazine 20 and one-half years ago. Am J Psychiatry 1964; 20:861–869
48. Wistedt B, Persson T, Hellbom E: A clinical double-blind comparison between haloperidol decanoate and fluphenazine decanoate. Clin Ther Res 1984; 35:804–814
49. Young E: Hospital experience with fluphenazine enanthate. Dis Nerv Syst 1970; 31:705–709
50. Gallant DM, Bishop MP, Steele CA, Bishop G, Guerrero-Figueroa R: Molindone: a crossover evaluation of capsule and tablet formulations in severely ill schizophrenic patients. Curr Ther Res 1973; 15:915–918
51. Gardos G, Cole JO: Weight reduction in schizophrenics by molindone. Am J Psychiatry 1977; 134:302–304
52. Kellner R, Rada RT, Egelman A, Macaluso B: Long-term study of molindone hydrochloride in chronic schizophrenics. Curr Ther Res 1976; 20:686–694
53. Conley RR, Carpenter WT Jr, Tamminga CA: Time to clozapine response in a standardized trial. Am J Psychiatry 1997; 154:1243–1247
54. Muller-Siecheneder F, Muller MJ, Hillert A, Szegedi A, Wetzel H, Benkert O: Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. J Clin Psychopharmacol 1998; 18: 111–120
55. Nemeroff CB: Dosing the antipsychotic medication olanzapine. J Clin Psychiatry 1997; 58(suppl 10):45–49
56. Jeste DV, Klausner M, Brecher M, Clyde C, Jones R: A clinical evaluation of risperidone in the treatment of schizophrenia: a 10-week, open-label, multicenter trial (ARCS Study Group: Assessment of Risperidal in a clinical setting). Psychopharmacology (Berl) 1997; 131:239–247
57. Lindstrom E, Eriksson B, Hellgren A, von Knorring L, Eberhard G: Efficacy and safety of risperidone in the long-term treatment of patients with schizophrenia. Clin Ther 1995; 17: 402–412
58. Keks N, McGrath J, Lambert T, Catts S, Vaddadi K, Burrows G, Varghese F, George T, Hustig H, Burnett P, Kerr K, Zorbas A, Hill C, Stedman T, Johnson G, Leibert B, Copolov D, Mackenzie M, Dillenbeck C: The Australian multicentre double-blind comparative study of remoxipride and thioridazine in schizophrenia. Acta Psychiatr Scand 1994; 90:358–365
59. Weinsier RL, Bracco D, Schutz Y: Predicted effects of small decreases in energy expenditure on weight gain in adult women. Int J Obes Relat Metab Disord 1993; 17:693–700
60. Beasley CM Jr, Tollefson GD, Tran PV: Safety of olanzapine. J Clin Psychiatry 1997; 58(suppl 10):13–17:19–21 (figure N)
61. Planansky K, Heilizer F: Weight changes in relation to the characteristics of patients on chlorpromazine. J Clin and Experimental Psychopathology and Q Rev Psychiatry Neurol 1959; 20:53–57
62. Amdisen A: Drug-produced obesity: experiences with chlorpromazine, perphenazine, and clopenthixol. Dan Med Bull 1964; 11:182–189
63. Lawson WB, Karson CN: Clinical correlates of body weight changes in schizophrenia. J Neuropsychiatry Clin Neurosci 1994; 6:87–188
64. Bustillo JR, Buchanan RW, Irish D, Breier A: Differential effect of clozapine on weight: a controlled study. Am J Psychiatry 1996; 153:817–819
65. Umbricht DS, Pollack S, Kane JM: Clozapine and weight gain. J Clin Psychiatry 1994; 55(Sept suppl B):157–160
66. Institute of Medicine: Weighing the Options: Criteria for Evaluating Weight-Management Programs. Washington, DC, National Academy Press, 1995
67. Fulton JE, Shekelle RB: Cigarette smoking, weight gain, and coronary mortality: results from the Chicago Western Electric Study. Circulation 1997; 96:1438–1444
68. Lee IM, Paffenbarger RS Jr: Changes in body weight and longevity. JAMA 1992; 268:2045–2049
69. Barnes-Josiah D, Potter JD, Sellers TA, Himes JH: Early body size and subsequent weight gain as predictors of breast cancer incidence (Iowa, United States). Cancer Causes Control 1995; 6:112–118
70. Cerhan JR, Torner JC, Lynch CF, Rubenstein LM, Lemke JH, Cohen MB, Lubaroff DM, Wallace RB: Association of smoking, body mass, and physical activity with risk of prostate cancer in the Iowa 65+ rural health study (United States). Cancer Causes Control 1997; 8:229–238
71. Suadicani P, Hein HO, Gyntelberg F: Weight changes and risk of ischaemic heart disease for middle-aged and elderly men: an 8-year follow-up in the Copenhagen male study. J Cardiovasc Risk 1997; 4:25–32

72. Walker M, Wannamethee G, Whincup PH, Shaper AG: Weight change and risk of heart attack in middle-aged British men. Int J Epidemiol 1995; 24:694–703
73. Sakurai Y, Nakamura K, Sakurai M, Muto T, Tanaka H: Relationship between weight change in young adulthood and the risk of NIDDM: the Sotetsu study. Diabetes Care 1997; 20: 978–982
74. Hagg S, Joelsson L, Mjorndal T, Spigset O, Oa G, Dahlqvist R: Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. J Clin Psychiatry 1998; 59:294–299
75. Popli AP, Konicki PE, Jurjus GJ, Fuller MA, Jaskiiw GE: Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997; 58:108–111
76. Mukherjee S, Roth SD, Sandyk R, Schnur DB: Persistent tardive dyskinesia and neuroleptic effects on glucose tolerance. Psychiatry Res 1998; 29:17–27
77. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC: Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998; 44:778–783
78. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, Graffeo KA, Thieme ME: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997; 154:457–465
79. Kolakowska T, Gadhvi H, Molyneux S: An open clinical trial of fenfluramine in chronic schizophrenia: a pilot study. Int J Clin Psychopharmacol 1987; 2:83–88
80. Sletten IW, Ognjanov V, Menendez S, Sundland D, El-Toumi A: Weight reduction with chlorphentermine and phentermine in obese psychiatric patients during chlorpromazine therapy. Curr Ther Res 1967; 9:570–575
81. Bernard JL: Rapid treatment of gross obesity by operant techniques. Psychol Rep 1968; 23:663–666
82. Harmatz MG, Lapuc P: Behavior modification of overeating in a psychiatric population. J Consult Clin Psychol 1968; 32: 583–587
83. Knox JM: A study of weight reducing diets in psychiatric in-patients. Br J Psychiatry 1980; 136:287–289
84. Rotatori AF, Fox R, Wicks A: Weight loss with psychiatric residents in a behavioral self-control program. Psychol Rep 1980; 6:483–486
85. Sletten I, Mou B, Cazenave M, Gershon S: Effects of caloric restriction on behavior and body weight during chlorpromazine therapy. Dis Nerv Syst 1967; 28:519–522
86. Stanton JM: Weight gain associated with neuroleptic medication: a review. Schizophr Bull 1995; 21:463–472
87. Baptista T, Lopez ME, Teneud L, Contreras Q, Alastre T, de Quijada M, Araujo de Baptista E, Alternus M, Weiss SR, Musseo E, Paez X, Hernandez L: Amantadine in the treatment of neuroleptic-induced obesity in rats: behavioral, endocrine and neurochemical correlates. Pharmacopsychiatry 1997; 30:43–54
88. Correa N, Opler LA, Kay SR, Birmaher B: Amantadine in the treatment of neuroendocrine side-effects of neuroleptics. J Clin Psychopharmacol 1987; 7:91–95
89. Guerciolini R: Mode of action of orlistat. Int J Obes Relat Metab Disord 1997; 21(suppl 3):S12–S23
90. National Task Force on the Prevention and Treatment of Obesity: Long-term pharmacotherapy in the management of obesity. JAMA 1996; 276:1907–1915
91. Dietz AJ: Amphetamine-like reactions to phenylpropanolamine. JAMA 1981; 245:601–602
92. Khan SA, Spiegel DA, Jobe PC: Psychotomimetic effects of anorectic drugs. Am Fam Physician 1987; 36:107–112
93. Oswald I: Fenfluramine and psychosis (letter). Br Med J 1974; 4:103
94. Raison CL, Klein HM: Psychotic mania associated with fenfluramine and phentermine use (letter). Am J Psychiatry 1997; 154:711
95. Shannon PJ, Leonard D, Kidson MA: Fenfluramine and psychosis (letter). Br Med J 1974; 3:576
96. Robinson S, Winnik HZ: Severe psychotic disturbances following crash diet weight loss. Arch Gen Psychiatry 1973; 29: 559–562