An Overview of the Efficacy and Safety of Fenfluramine and Mazindol in the Treatment of Obesity

Keith A. Stahl, MD, Thomas F. Imperiale, MD

Objective: To assess the validity of the perceptions that appetite-suppressant drugs are ineffective, potentially addictive, and fraught with side effects, we reviewed the effectiveness and safety of two such drugs with purported low abuse potential in the treatment of obesity: mazindol and fenfluramine hydrochloride.

Data Sources: Relevant studies in English published before September 1991 were identified using MEDLINE, accompanied by a cross-referenced manual search.

Study Selection: All randomized clinical trials conducted with adults for at least 6 weeks' duration with weight change as an outcome.

Data Extraction: Data extracted from each report included key study characteristics, clinical information, co-interventions, and outcomes, including dropouts due to either adverse drug effects or perceived lack of effect.

Data Synthesis: Of 36 acceptable trials, 35 were double-blinded, 32 were placebo-controlled, and 13 were crossover. Median duration of drug therapy was 12 weeks. In studies reporting such data, mean patient age was 41 years, and mean baseline weight was 84 kg (143% of ideal body weight). Among 1163 patients receiving drug therapy and 866 patients receiving placebo, mean weight loss across all trials was 5.2 and 1.9 kg, respectively ($P<.001$). Among 32 direct comparisons between drug and placebo, the mean weight loss by sample size was 3.0 kg greater in the treatment group ($P<.001$), and did not vary in subgroup analyses of trial type, drug, or dose. Similar proportions of treatment and placebo groups dropped out (20% vs 22%; $P=.34$); however, overall dropout rates were higher in parallel trials (25% vs 9% for crossover trials). Dropouts due to adverse drug effects were more common in the treatment group (7% vs 2%; $P<.001$), while those due to perceived lack of effect were more common in the placebo group (6% vs 2%; $P<.001$). Mazindol resulted in fewer dropouts due to adverse drug effects (4% vs 9%; $P<.001$) and a perceived lack of effect (1% v 3%; $P=.04$). No drug addiction or adverse drug effects requiring medical intervention were reported.

Conclusion: The apparent short-term efficacy of these appetite-suppressant drugs and the lack of severe adverse drug effects or addiction suggest that they may be useful in the treatment of obesity. Further study of these agents with attention to long-term efficacy, safety, and health consequences is warranted.

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Approximately 12% of American adults are obese, defined as weighing greater than 120% of ideal body weight or having a body mass index (weight divided by height squared) of greater than 30 kg/m². Obese persons are at increased risk for several diseases including non-insulin-dependent diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, gout, and gallbladder disease. While the total health care burden of obesity is unknown, the risks of morbidity and mortality are proportional to the degree of obesity as defined by the body mass index. In addition to physical illness, there is unmeasured socioeconomic and psychosocial impairment.

Methods for voluntary weight loss include dietary change, exercise, and be-
MATERIALS AND METHODS

STUDY IDENTIFICATION AND SELECTION

All English-language literature in the MEDLINE bibliographic database from 1965 to September 1991 was identified using the following key words: obesity (drug therapy of), mazindol, fenfluramine, clinical trials, and human. In addition, a manual search was conducted using the references from each retrieved report, review articles, and chapters from textbooks. The following criteria were used in selecting studies for inclusion: study design, clinical trial; study population, overweight adults; intervention, mazindol or fenfluramine for at least 6 weeks; and outcome, weight change. Reports were excluded if the population was selected (for example, subjects with secondary causes of obesity, such as steroid-induced), or if there were insufficient data with which to ascertain outcome.

QUALITATIVE ANALYSIS

Two critical appraisers independently evaluated the quality of each trial, with attention to the following selected standards and principles for clinical trials (Table 1): explicit patient inclusion and exclusion criteria; blinding (single, double, or nonblinded); baseline similarity of treatment and control groups; equivalent and comparable use of ancillary treatments (diet and behavioral modification); an assessment of compliance; and statistical presentation of the results. A trial was given 1 point for each satisfied standard, 0.5 point for a partially satisfied standard, and no points if satisfaction was indeterminate from the data presented in the trial. A quality score was generated by summing the standards. For parallel trials, scores ranged potentially from 0 (no standards satisfied) to 8 (all standards satisfied), and for crossover trials, from 0 to 9. Trials with a quality score of 6 or greater were considered to be of high quality.

QUANTITATIVE ANALYSIS

Quantitative data were independently abstracted from each trial, including demographic and clinical characteristics of the trial populations; the numbers of patients randomized and completing each trial; mean weight change; the numbers of dropouts and reasons, limited to adverse drug effects (ADEs) or perceived lack of drug effect (PLE); and reported cases of drug abuse or drug dependence.

Summary-point estimations of effect (mean weight change) were computed using weighted means of individual study weight changes. Due to a lack of uniform reporting of measures of variance (SDs and SEMs), the weights could not be derived from the reciprocals of the variance, as is customarily done. Since sample size is inversely proportional to variance, it was used as a proxy for variance, with weights proportional to sample size. For each trial, weight change (Δ) was multiplied by the number of subjects who completed the study (N). The product (NΔ) was summed and divided by the total sample size of all trials, resulting in a weighted mean weight change (ΔW). Weighted mean weight changes were calculated for subgroups of trials, and stratified by trial type (parallel vs crossover), drug (mazindol vs fenfluramine), dose (low vs high), and quality score (low vs high). The cutoff points for dose and quality score were determined prior to analysis. Paired t tests were used to test for differences in weight change from zero. Unpaired t tests were performed on the subgroups from each stratified analysis to test for differences in weight change. χ² and Fisher's Exact tests were used to test for differences between proportions. For a subgroup of 10 trials that reported means and SDs for weight change, we conducted a traditional meta-analysis. For this analysis, the effect size, defined as the difference between the mean weight change in the treatment and control groups divided by the pooled SD, was computed for each trial. Effect sizes from the 10 individual trials were analyzed with a test for homogeneity. This test addresses the statistical validity of aggregating the trials and assumes that all trial results are homogeneous. Following the conclusion that the effect sizes were homogeneous and could be aggregated, we calculated a pooled estimate of the treatment effect size from a weighted combination of individual effect sizes, with the weights derived from the reciprocals of the variances of individual trials. All analyses and calculations were performed on SuperCalc spreadsheets (version 5.0, Computer Associates International Inc, San Jose, Calif.).

Behavior modification, often used in combination; gastrointestinal surgery for carefully selected patients with severe obesity; and drug treatment, in the form of appetite-suppressant drugs (ASDs). A recent National Institutes of Health Consensus Development Conference Panel concluded that none of the available therapies for severe obesity had been evaluated adequately; that consideration should be given to combined approaches including drug therapy; and that long-term drug therapy needed further evaluation. Of all treatments for obesity, the use of ASDs is perhaps the most controversial. A number of barriers to the use of ASDs in the treatment of obesity have been described and include hindrance by state licensing agencies; regulatory rigidity; legislative grandstanding; and an expectation that ASDs should "cure" obesity. In addition to these barriers are perceptions that ASDs are ineffective and fraught with side effects. Concerned with the validity of these perceptions, we conducted a qualitative and quantitative overview of the effectiveness and safety of two ASDs in the treatment of obesity. The agents fenfluramine hydrochloride and mazindol were selected because of their purported low abuse potential.
RESULTS

Forty-three trials from 40 reports met the inclusion criteria.34-67 Seven trials were excluded, three51-53 because of selected study populations and four54-57 because of inadequate information from which to ascertain weight change. Three reports each presented the results of two separate trials. Of 36 trials analyzed, 23 were parallel and 13 were crossover; 20 trials used fenfluramine and 16 used mazindol; 35 were double-blinded and 32 were placebo-controlled. Twenty-five (78%) of the placebo-controlled trials reported significantly greater weight loss in the drug-treated group.

The numbers of subjects who completed the study ranged from 21 to 292. Mean age of the study populations was 41 years; only 8% were male. Baseline weight in the drug group was 84.3 kg, representing 143% of ideal body weight, while the placebo group weighed 84.0 kg, representing 145% of ideal body weight. The median duration of drug treatment was 12 weeks (range 6 to 36 weeks). Twenty-four trials included a low-energy diet as a cointervention and one used behavior modification.

While all included trials reported mean weight change, nearly half assessed the impact of ASDs on at least one other physiologic parameter (heart rate, blood pressure, glucose, and lipids) with results that were variable and of uncertain clinical importance. Furthermore, because of the aggregate level of reporting of the data, it is unclear whether the effect of the ASDs on these parameters resulted from a direct or an indirect effect through weight change.

QUALITY SCORE AND STUDY CHARACTERISTICS

The mean quality score for parallel trials was 5.7 (range, 4 to 8) of a possible 8, while for crossover trials, the mean score was 5.0 (range, 3.5 to 6.5) of a possible 9. Twenty-five trials (70%) provided a definition of obesity (usually a percent overweight derived from life tables). Only nine trials (25%) assessed patient compliance with treatment group assignment, usually by pill count. A measure of statistical variance for changes in weight was presented in 10 (27%) trials. Three parallel trials satisfied all quality criteria.

QUANTITATIVE ASSESSMENT

Unweighted overall mean weight loss was derived from 36 drug-treatment groups and 32 placebo groups. Of 1454 recipients of ASDs, 1163 (80%) completed the trial, and of 1104 subjects treated with placebo, 866 (78%) completed the study. Mean weight loss was 5.15 kg in the treatment groups and 1.91 kg in the placebo groups. Among the 32 direct comparisons between drug and placebo, the unweighted mean difference in weight loss was 3.2 kg greater (median, 2.9 kg; range, 0.6 to 7.3 kg) in the drug-treated groups (P<.001). When the differences in weight loss were weighted by study sample size, mean weight loss was similar—3.02 kg more for the treatment groups (P<.001).

Table 2 displays both the weighted and unweighted differences in weight loss in subgroup analyses of trial type (parallel vs crossover), drug (mazindol vs fenfluramine), dose (high vs low), and quality score (high vs low). Weight loss was consistently greater in the drug treatment groups. While all differences between drug and placebo were statistically different from zero, these differences did not differ by trial type, drug, dose, or quality score.

Among the 10 trials included in the traditional meta-analysis, individual effect sizes were homogeneous (P=.65), indicating that the trials could be combined statistically.
The pooled effect size of 1.23 (95% confidence interval, 
−0.4 to 2.87) indicates that the average effect of drug therapy is approximately 1.23 SDs greater than that of placebo. Conversion of these results to percentile rank-ings (assuming normality) makes these results more mean-
ingful clinically and indicates that weight loss of the av-
erage person in the treatment group exceeds that of 89% of the control group (95% confidence interval, 35% to 98%).

DO Dropout Rates

Overall dropout rates were similar between drug and place-
ob groups (Table 3)—291 (20%) of 1454 drug-
treated patients vs 238 (22%) of 1104 placebo-treated patients. However, overall dropout rates were greater in parallel trials than in crossover trials (25% vs 9%; P<.001) and were somewhat higher with fenfluramine than with mazindol (22% vs 18%; P=.06) (Table 3). Not surprisingly, dropouts due to ADEs were more common in the drug-treatment group (7% vs 2%; P<.001), while dropouts due to PLE were more common in the placebo group (6% vs 2%; P<.001). Drop-
outs due to ADEs and PLE were more common in par-
allel trials (5% vs 3%; P=.04). No ADEs requiring medical intervention were described nor were cases of drug dependence.

This overview was conducted because of the widespread perceptions that ASDs are ineffective and unsafe for the treatment of obesity. We chose to examine the efficacy and safety of mazindol and fenfluramine because of their reputed low potential for abuse. With a median duration of 12 weeks, these ASDs resulted in a mean weight loss of 3 kg greater than placebo. This difference did not vary in subgroup analyses of trial type, drug, dose, and quality score. Predictably, subjects who dropped out of these trials did so more frequently because of ADEs in the drug-
treated group (7% vs 2%) and more frequently because of a PLE in the placebo group (6% vs 2%). A greater pro-
portion of subjects in parallel trials dropped out of the study (25% vs 9%). Dropouts due to ADEs and PLE were more frequent among subjects receiving fenfluramine. Fi-
ally, there were no reported cases of either ADEs re-
quiring medical intervention or drug abuse or depen-
dency.

There are several limitations to this overview. First, a more formal quantitative analysis (meta-
analysis) could not be conducted on all trials because several did not report a measure of statistical variance for the mean change in weight. We attempted to com-
pensate for this by using sample size as a proxy mea-
sure for the inverse of the variance. The fact that weighted and unweighted differences in weight change were essentially the same suggests that either sample size was a poor proxy or, more likely, a formal quan-
titative analysis with all trials would not have substan-
tially altered the results. Among the 10 trials reporting appropriate variance data, a traditional meta-analysis sup-
ported the overall results but was not statistically significant most likely because of both the small num-
ber of trials and the variation about the mean weight change in treatment and control groups.

A second limitation is the potential for publication bias, by which trials showing a difference are published preferentially over trials showing no effect of treatment. Whether unpublished studies should be included in an overview is controversial and we did not search for them. Some methods attempt to quantify the effect of this bias by calculating the number of trials showing no differences that would be required to nullify the results.48 Due to the lack of data on statistical variance, however, this number cannot be determined; therefore, this theoretical limitation cannot be quantified.

The issue of combinability of the trials is more difficult to address. While subgroup analyses con-
trolled for some differences among the trials (trial type, drug used, dosage, quality), the degree of clinical simi-
arity of the trial populations is unclear. While no study population was reported to have significant co-
morbid disease, mean ages ranged from 33 to 59 years, and definitions of obesity (if reported at all) varied. Most trials enrolled subjects who had made previous attempts to lose weight; however, the different settings for the trials (office vs hospital based) could have re-
sulted in a selection bias in the degree of refractoriness to previous treatments.

Lastly, only 8% of the entire study population was male. Since we were unable to stratify weight change by gender, the results have little, if any, generalizability to adult males.
While the average weight difference in favor of these ASDs was small (3.0 to 3.2 kg [6.6 to 7.0 lb]), the median duration of drug therapy was only 12 weeks (mean, 10 weeks). Whether longer treatment durations would result in greater differences in weight loss is unclear. In one parallel, placebo-controlled trial of 16 weeks' duration, subjects who received fenfluramine had a mean weight loss of 6.0 kg more than the placebo group. In a parallel, drug-controlled trial of 36 weeks' duration, subjects who received fenfluramine had a mean weight loss of 12 kg. However, in a crossover trial of 20 weeks' duration, subjects receiving mazindol had a weight loss of only 2 kg more than the placebo group.

**ASDs . . . modest short-term effectiveness**

What happened to subjects after ASDs were discontinued? Since parallel trials usually did not follow up subjects beyond the duration of active treatment, we examined crossover trials for subjects who crossed over from active treatment to placebo. Among 11 crossover trials in which data were available, eight treatment groups showed weight gain after crossing over to placebo while two treatment groups showed a marked slowing in weight loss. Only one group continued to lose weight, which approximated that of the active treatment group. These descriptive results are likely to be a conservative estimate of what occurs following discontinuation of ASDs in the clinical setting, as placebo treatment would, if anything, slow subsequent weight gain. Regaining lost weight following discontinuation of ASDs is believed to be further proof of their efficacy.

While both ASDs appear to be modestly effective in the short term, clinicians must be mindful of the potential for ADEs. For both agents that we studied, nervousness, restlessness, constipation, and palpitations are among the most common ADEs. In addition, among thousands of patients treated with fenfluramine, at least three cases of pulmonary hypertension have been described, one of which did not resolve with cessation of treatment.

Finally, the trials do not address the issue of tolerance, in which increasing doses of drug are required to achieve the same effect. While tolerance could have existed among some subjects in these trials of relatively short duration, we believe that this issue would be addressed more effectively by trials of longer duration.

The results of this overview suggest that the ASDs mazindol and fenfluramine have modest short-term effectiveness in the treatment of obesity. Adverse effects requiring discontinuation of these drugs are uncommon. Short-term use of these agents, particularly in addition to alterations in diet and physical activity and behavior modification may be helpful in promoting weight loss. However, as obesity is a long-term human condition for which short-term interventions are not likely to alter its national history, we believe that further study of these agents, particularly with regard to long-term efficacy and safety, and to combination therapy, is warranted.

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Reprint requests to MetroHealth Medical Center, 2500 MetroHealth Dr, H-331, Cleveland, OH 44109-1998 (Dr Imperiale).

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**REFERENCES**

23. Woodhouse S, Nye ER, Anderson K, Rawlings J. A double-blind controlled trial...
44. Innes JA, Campbell IW, Millar J, Munro JF. A comparison of the efficacy and acceptability of fenfluramine tablets (BP) and prolonged-action capsules. Postgrad Med J. 1975;51(suppl):150-162.