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Prepared by:
Southern California-RAND Evidenced-Based Practice Center, Santa Monica, CA

Director
Paul G. Shekelle, MD, PhD
Senior Statistician/Co-Director
Sally C. Morton, PhD
Project Manager/Policy Analyst
Margaret Maglione, MPP
Statisticians
Marika Suttorp, MS
Wenli Tu, MS
Reviewers
Zhaoping Li, MD, PhD
Melinda Maggard, MD
Walter A. Mojica, MD, MPH
Lisa Shugarman, PhD
Vanessa Solomon, MA
Programmer/Analyst
Lara Jungvig, BA
Medical Editor
Sydne J. Newberry, PhD
Staff Assistants
Donna Mead, BA
Shannon Rhodes, MFA

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on *Pharmacological and Surgical Treatment of Obesity* was requested and funded by the U.S. Food and Drug Administration's Office of Women's Health. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Acting Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Susan F. Wood, Ph.D.
Director
Office of Women's Health
U.S. Food and Drug Administration

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Structured Abstract

Context: Pharmacological and surgical treatments for weight loss have become both more numerous and more commonly used. This report was commissioned to review the evidence on such treatments in adults, adolescents, and children.

Objectives: To assess the efficacy and safety of the weight loss medications sibutramine, orlistat, fluoxetine, phentermine, and diethylpropion; to assess the evidence for other medications that have been used for weight loss including bupropion, zonisamide, topiramate, and sertraline; and to assess the efficacy and safety of various types of bariatric surgery.

Data Sources: We searched numerous electronic databases electronically, including MEDLINE® and EMBASE, for potentially relevant studies. We scanned the reference lists of recent extensive reviews on sibutramine, orlistat, and bariatric surgery. We also contacted experts in the field.

Study Selection: We screened 1,063 articles. We quality-reviewed 78 medication studies that reported on sertraline (1 article), zonisamide (1 article), orlistat (49), buproprion (5), topirmate (9), and fluoxetine (13). Meta-analysis was performed for all medications except sertraline and zonisamide which are summarized in the text. We quality-reviewed 159 surgery studies reporting on weight loss and considered an additional 8 surgery studies reporting only on complications, for a total of 167 surgery studies. Of these 167 studies, 20 were duplicate publication of an already included study. Of the remaining 147 studies, 89 contributed to the weight loss analysis, 134 contributed to the mortality analysis, and 128 contributed to the complications analysis. Studies could contribute to one or more surgery analyses.

Data Extraction: We abstracted information about study design, intervention, co-interventions (diet, exercise), population, and outcomes. We also collected data on randomization, dropouts, blinding, and allocation, to assess methodological quality. We abstracted weight loss, control of comorbidities, and adverse events from controlled trials of medication, controlled trials of surgery, and surgery case series.

Data Synthesis: A recent meta-analysis of sibutramine efficacy reported a mean difference in weight loss (compared to placebo) of 3.43 kg at 6 months. At 12 months, the difference was 4.45 kg. Treatment with sibutramine was associated with modest increases in heart rate and blood pressure, very small improvements in glycemic control among diabetics, and (based on the longest-duration and best-quality studies) small improvements in HDL cholesterol and triglycerides.

In our own meta-analysis on orlistat, the pooled random-effects estimate of the mean weight loss for orlistat-treated patients, compared to placebo-treated patients, was 2.51 kg at 6 months; at 12 months, it was 2.75 kg. We found an increase in diarrhea, flatulence, and bloating/ abdominal pain/dyspepsia in orlistat-treated patients compared to placebo, with relative risks (RR) of 3.4, 3.1, and 1.5, respectively.

We identified a published review on phentermine and diethylpropion for weight loss. Our literature review identified no new RCTs of these drugs since publication. Compared to placebo, subjects treated with phentermine lost on average 3.6 additional kg of weight at 6 months**,** while subjects treated with diethylpropion lost on average 3.0 additional kg of weight (but this

difference had only borderline statistical significance). This review did not report side effects or adverse-event data.

Our meta-analysis of fluoxetine studies showed a mean weight loss, compared to placebo-treated patients, of 4.74 kg at 6 months and 3.05 kg at 12 months. There was an increase in nervousness/sweating/tremors, nausea/vomiting, fatigue/asthenia/ hypersomnia/somnolence, insomnia, and diarrhea in fluoxetine-treated patients compared to placebo, with RR of 6.4, 2.7, 2.4, 2.0, and 1.7, respectively.

We identified three studies of bupropion for weight loss that were suitable for meta-analysis. The pooled result at 6 to12 months, compared to placebo treated patients, was 2.8 kg. Bupropion causes dry mouth (RR = 2.99) and insomnia.

We identified six studies (all available only as abstracts) of topiramate for weight loss that were suitable for meta-analysis. The pooled result at 6 months, compared to placebo-treated patients, was an additional 6.5 percent of pretreatment weight lost. Parasthesias (RR = 4.9) and taste perversion (RR = 9.2) are the most commonly reported side effects attributable to topiramate.

We found single studies for each of the following: zonisamide and sertraline.

We identified one large matched cohort analysis that established that surgery results in greater weight loss than does medical treatment in obese individuals with a BMI of 40 kg/m^2 or greater. Surgery resulted in a 20 to 30 kg weight loss, maintained up to 8 years and accompanied by significant improvements in several comorbidities. For patients with a BMI between 35 and 40 kg/m^2, the data strongly support the superiority of surgical therapy but cannot yet be considered conclusive. Bariatric surgical procedures in current use have been performed with an overall postoperative mortality rate of less than 1 percent. The average postoperative mortality rate is probably twice this number. Laparoscopic procedures result in fewer wound complications or incisional hernias than open procedures.

Conclusions: Sibutramine, orlistat, phentermine, diethylpropion (probably), bupropion, fluoxetine, and topiramate all promote weight loss when given along with recommendations for diet. Sibutramine and orlistat are the two most-studied drugs. The amount of extra weight loss attributable to these medications is modest (less than 5 kg at one year), but this amount still may be clinically significant. No evidence indicates that any particular drug promotes more weight loss than another drug. All of these drugs have side effects. The choice of drug may be made on an individual basis, based on tolerance to the expected side effects.

Surgical treatment is more effective than nonsurgical treatment for weight loss and the control of some comorbidities in patients with a body mass index of 40 kg/m^2 or greater. More data are needed to confirm or refute the relative efficacy of surgery for less severely obese persons. Perioperative mortality rates of less than 1 percent have been achieved by some surgeons and surgical centers. The perioperative mortality rates in other settings may be higher. Surgical treatment is associated with a substantial number of complications and adverse events, although most of these are minor.

The existing literature is almost bereft of data regarding either pharmaceutical or surgical treatment of adolescent and pediatric patients. To the extent that existing data on adults are judged to be inapplicable to adolescents or children, new studies will need to be performed.

Contents

Evidence Report 1

Chapter 1. Introduction 3
Prescription Weight Loss Medications 3
Appetite Suppressants 4
Lipase Inhibitors 4
Bariatric Surgical Procedures 5
Restrictive Procedures 5
Bypass Procedures 5
Combination Procedures 6

Chapter 2. Methods 7
Original Proposed Key Questions 7
Technical Expert Panel 7
Literature Search 8
Additional Sources of Evidence 8
Article Review 9
Extraction of Study-Level Variables and Results 10
Choice of Outcomes 10
Meta-Analyses of Weight Loss Medications 11
Selection of Trials for Meta-Analysis 11
Mean Difference 12
Sensitivity Analyses 12
Performance of Meta-Analysis 13
Publication Bias 13
Medication Adverse-Events Meta-Analysis 13
Extraction of Adverse-Event Data 13
Meta-Analysis 14
Power Calculation 15
Surgery Analyses 15
Analysis of the Efficacy of Surgical Weight Loss 15
Analysis of Surgery Mortality 16
Analysis of Surgery Comorbidity 16
Analysis of Surgery Adverse Events 17
Rating the Body of Evidence 17
Peer Review 18

Chapter 3. Results 19
Results of the Literature Search 19
Efficacy of Medications 19
Sibutramine 19
Orlistat 21
Phentermine 22
Diethylpropion 23

Fluoxetine 23
Sertraline 24
Bupropion 25
Topiramate 25
Zonisamide 26
Summary of Medication Studies 27
Efficacy of Surgery for Weight Loss 27
Benefits 28
Summary of Benefit Data 30
Risks 31
Use of Obesity Medication and Bariatric Surgery in the Adolescent and Pediatric Population 33
Efficacy and Safety of Weight Loss Medication 33
Efficacy of Bariatric Surgery 34

Chapter 4. Discussion 37
Limitations 37
Publication Bias 37
Study Quality 37
Heterogeneity 37
Followup Times 38
Applicability of Findings 38
Conclusions 38
Future Research 39
Medications 39
Surgery 40

Reference List 43

Summary Tables 57

Summary Figures 83

Note: Appendixes and Evidence Tables are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm