Chapter 4. Discussion

In this chapter, we describe the limitations of our review and meta-analysis and then present our conclusions. We also discuss the implications of our findings for future research.

Limitations

Publication Bias

Our literature search procedures were extensive and included canvassing experts regarding studies we may have missed. However, we tested for evidence of publication bias only in the medication meta-analysis and found such evidence in one case (orlistat at 12-month followup). We made explicit assumptions about the lack of reporting of mortality and other adverse events and discussed the possible bias that might result. We acknowledge that publication bias may still exist despite our best efforts to conduct a comprehensive search and the lack of statistical evidence for the existence of bias. Publication bias may occur for a variety of reasons, including investigators' loss of interest in the study if "negative" results are obtained or if results are contrary to the interest of the sponsor or investigator.

Study Quality

An important limitation common to systematic reviews is the quality of the original studies. Recent efforts to identify elements of study design and execution that may be associated with bias have, in many cases, been unable to distinguish biased studies or provided results that were not reproducible. Therefore, the current state of the science is to avoid rejecting studies or using quality criteria to adjust the results of meta-analysis. Thus, we made no attempt to assign greater importance to some studies based on "quality." Because empirical evidence is lacking regarding the relationship of other study characteristics to bias, we did not attempt to use other criteria. Most of the studies of orlistat and fluoxetine had Jadad scores of 3 or greater, a threshold that in other settings has been shown to be associated with less bias. Our sensitivity analyses on these higher-quality RCTs upheld our main result. Also, to be as inclusive as possible for purposes of assessing safety, we did consider nonrandomized and noncontrolled studies in our surgery analysis while noting the limited inferences that can be drawn from such designs.

Heterogeneity

Evidence of heterogeneity was observed for all the medication meta-analyses. We used a pooled random-effects approach to attempt to incorporate any heterogeneity and assessed the results of sensitivity analyses using variables that might account for heterogeneity (quality, completeness of followup, dose, year of publication). However, we were unable to explain most of the heterogeneity. Our pooled results should be interpreted in light of the observed heterogeneity.

Followup Times

For medication studies, we were able to perform meta-analysis only on 6-month and 12-month followup results for medication studies. For the surgical studies, the wide variation in followup times should be kept in mind when considering our pooled results.

Applicability of Findings

The results of the studies we synthesized are directly applicable only to the persons included in those studies. In some cases, enrollment was highly selective to avoid certain comorbidities. Whether the results are applicable to more representative populations is unknown.

Conclusions

With the above limitations in mind, we reached the following conclusions:

- RCT data are sufficient to allow us to conclude that sibutramine, orlistat, phentermine, diethylpropion (probably), fluoxetine, bupropion, and topiramate all promote weight loss for at least six months when given along with recommendations for diet (and possibly other behavioral and exercise interventions). The amount of extra weight loss attributable to these medications is modest (less than 5 kg at one year) but still may be clinically significant. The most well-studied medications are sibutramine and orlistat; thus, our conclusions for these medications are stronger than for the others.

- One RCT supports the efficacy of zonisamide for weight loss. Stronger conclusions cannot be drawn without additional studies.

- All these drugs have side effects. The side-effect profile varies by drug. Sibutramine causes modest increases in heart rate and blood pressure; gastrointestinal symptoms predominate in the use of orlistat; phentermine causes cardiovascular and gastrointestinal side effects; fluoxetine causes agitation and nervousness in addition to gastrointestinal side effects; bupropion causes paresthesia, insomnia, and central nervous system effects; topiramate causes paresthesia, and changes in taste. The choice of medications for weight loss probably rests on individual tolerance to the side effect profile.

- In general, these drugs have not been studied sufficiently to evaluate the risk of rare (less than one per 1,000) side effects.

- No data exist to allow the relative efficacy of these drugs to be compared. Based on placebo-controlled studies, no drug appears to be substantially more effective than any other. The lack of published, pharmaceutical company-sponsored head-to-head trials of weight loss medications is itself illuminating.

- No experimental data address the optimal duration of treatment with medication or how the optimal duration may vary by age, gender, or race.

- Bariatric surgical treatment results in greater sustained weight loss than nonsurgical treatments in very obese individuals (BMI ≥ 40), resulting in improved health outcomes (reduction in diabetes and sleep apnea, improved quality of life). While not conclusive, the data suggest greater sustained weight loss for bariatric surgical treatment than for nonsurgical treatment in patients with BMI between 35 and 40.

- RYGB, VBG, and adjustable banding procedures all result in substantial weight loss.

- RYGB results in greater weight loss than VBG in severely obese individuals.

- Postoperative mortality rates of less than 1 percent have been achieved by a number of surgeons and bariatric surgical centers. The postoperative mortality rate in other settings may be higher.

- Few clinical trials have compared outcomes among different bariatric surgical procedures. The existing data suggest the possibility of clinically important differences in the proportion of patients reporting various complications and adverse events among those treated with RYGB, VBG, and adjustable banding procedures.

- Laparoscopic procedures result in fewer wound complications or incisional hernias than open procedures.

- The actual proportions of patients who experience some complications of bariatric surgery may be quite substantial, greater than 20 percent (although most are minor in severity).

- 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.

Future Research

Medications

A number of RCTs of weight loss medications have been conducted; nevertheless, significant unanswered questions remain regarding the medications assessed in this report. One of our key questions concerned relative efficacy, a question that cannot be conclusively answered without head-to-head RCTs that compare the different agents. However, the placebo-controlled trial data we reviewed suggest that if any statistically significant differences are seen, they are likely to be clinically small (a difference of a few kilograms at 12 months). Whether it is worth trying to detect such differences is a matter for policymakers. A more relevant question regarding efficacy may be whether combinations of agents promote greater weight loss than individual agents. One study that combined orlistat and sibutramine reported no increase in weight loss over sibutramine alone. Another relevant question is whether use of any of those drugs combined with more aggressive behavioral interventions and diet therapies would be more

effective than the results seen in the RCTs to date, where many of the dietary interventions were modest.

Another of our key questions concerned the optimal duration of treatment and whether it varies by age, gender, or race. We found no RCT data to answer this question; therefore, new clinical trials would need to be performed. Some physicians have expressed the opinion that they expect their overweight patients will always need to take diet medications, in essence treating overweight as a chronic disease like hypertension. Given that possibility, information about long-term (i.e., much longer than 12 months) effectiveness and safety is needed.

The question of side effects, particularly the possibility of rare adverse events, remains unanswered for most of these drugs.

Surgery

For patients with BMI ≥ 40, we regard the data as conclusive concerning the superiority of surgical therapy compared to existing pharmaceutical and diet therapy. Significant advances will need to occur in the medical control of obesity or its complications for new comparative studies to be warranted. For patients with a BMI between 35 and 40, we do not regard the existing published data as conclusive, because the data are derived from case series without a concurrent comparison group. Although randomized clinical trials would be welcome, given the widespread adoption of bariatric surgery in adults, it might be difficult to mount a trial comparing surgical and nonsurgical weight loss methods. If RCTs cannot be performed, conclusive data could be obtained from well-conducted observational studies, such as a population-based matched cohort study similar to the SOS study, that would assess the effectiveness of bariatric surgery compared to nonsurgical therapy. Nonsurgical therapies to be evaluated should include high-intensity behavioral interventions in addition to pharmacotherapy. Such a study should address the balance between benefits (in terms of weight loss and comorbidities) and risks in relevant patient subgroups and should consider costs. The criteria used to identify subgroups should be those clinical factors that may be related to increased or decreased benefits or risks of surgery. For example, patient age, weight, and severity of comorbidity all may influence the net benefit of surgery compared to nonsurgical therapy. In this example, patient subgroups might be identified based on BMI; age might be stratified as below or above 55 years old; and comorbidities such as diabetes could be stratified by measures such as hemoglobin A1c or the presence of end organ damage. Only by conducting such a study can it be determined whether the net benefits of surgical therapy compared to nonsurgical therapy apply equally to all patient subgroups. Surprisingly few patients would need to be studied to assess whether or not bariatric surgery provides greatly superior outcomes compared to nonsurgical therapy. We calculate that as few as 215 patients would need to be included in each group to provide 80 percent power to detect an effect of bariatric surgery on reducing diabetes equal to only half that reported in the SOS trial. Given that more than 100,000 bariatric operations are performed yearly, attempting to enroll 0.2 percent of these patients in a clinical study seems feasible.

If the eligibility criteria for bariatric surgery were relaxed (such as allowing inclusion of people with a BMI of 30 to 32), then it becomes more justifiable to require an RCT to assess the relative health benefits and risks of surgical versus nonsurgical treatment prior to widespread

adoption of surgery in this patient population. Precedent exists for mounting such studies, even when the surgical therapy is already disseminated in the community. The studies comparing medical and surgical therapy for carotid artery stenosis are good examples.

RCTs would also be useful to compare the effectiveness and safety of various surgical procedures (e.g. adjustable band procedures versus RYGB).

Last, given the increasing rate of obesity in adolescent and pediatric populations, the need is urgent for more data about the relative efficacy of treatments. In our opinion, conducting a randomized trial of bariatric surgery in the adolescent population is still feasible. Such a study would go a long way toward establishing the role of surgery in this patient population.