

# Pharmacotherapy of Childhood Obesity

## An evidence-based, conceptual approach

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**T**his review provides a comparative analysis of the benefits of lifestyle intervention and pharmacotherapy in adults and children using previously published meta-analyses, as well as new data published within the past 2 years. The manuscript critically summarizes the potential risks of various established (orlistat, sibutramine, and metformin) and new (rimonabant) pharmacologic agents and presents a conceptual approach to selection of patients for pharmacotherapy, tailored drug selection, and timing of intervention.

### Perils and promise of pharmacotherapy

Forty-five years after an amphetamine was approved for the treatment of obesity in adults, an expert in the field characterized a new therapeutic formulation as being effective and long-lasting, posing "little risk" (1). Four years later, others (2) "confirmed the weight-reducing efficacy and good tolerability" of the drug and noted that adverse effects were "generally mild and transient." The drug in question was dexfenfluramine, which was removed from the commercial market 18 months after its subsequent U.S. Food and Drug Administration approval owing to the development of valvular heart disease and primary pulmonary hypertension in a subset of patients (3,4).

This experience and many others (5) have forced us to think long and hard before making sweeping recommendations about the use of behavior-modifying drugs for the treatment of obesity.

Yet, the pediatric community confronts a serious problem: the surge of metabolic complications in obese adolescents, includ-

ing impaired glucose tolerance (IGT) and type 2 diabetes, hypertension, dyslipidemia, ovarian hyperandrogenism, hepatic steatosis, and sleep apnea (6). Two recent studies highlight the concern. First (7), despite regular lifestyle counseling in a university-based clinic, one-third of obese teenagers with profound insulin resistance and IGT developed type 2 diabetes during a follow-up period of 21 months. Second (8), among Pima-Indian children and adolescents with type 2 diabetes, the rate of development of end-stage renal disease was proportional to the duration of diabetes, but not to the age of onset of glucose intolerance. It is clear that we must effectively intervene to prevent long-term complications in obese insulin-resistant children, and, given the progressive nature of these conditions, we cannot dally.

Lifestyle intervention can reduce rates of weight gain and fat deposition in children (9 and refs. cited below) and delay or prevent the development of type 2 diabetes in obese adults during trial periods lasting as long as 4 years (see below). However, lifestyle intervention is effective only if applied intensively and continuously in highly motivated subjects. Figure 1 summarizes data from seven major randomized multicenter studies that assessed the effects of lifestyle intervention in obese adults (10–16). The data are representative, but comparisons among the groups must be interpreted with caution because of variations in patient populations and study design. In general, "intensive" lifestyle intervention, with obligatory caloric restriction, multiple individual and/or group counseling sessions, daily exercise, and numerous clinic visits, reduces body weight by an average

of 6 kg (~5.5–6.5% of body weight in most studies) during the 1st year. "Moderate" intervention, with specified caloric guidelines and exercise counseling, is less effective, while the standard lifestyle approaches delivered to nearly all obese people, namely dietary recommendations and regular clinic visits, have little or no effect. Also of note is the rebound weight gain in both the intensive and moderate groups, though some weight loss can be maintained for ≥4 years if the patient remains vigilant (10,11,13).

The story in children is similar, at least in the short run (Fig. 1). Intensive lifestyle intervention can reduce body weight by 4.3–7 kg (~4.5–6.5% of body weight) during the 1st year, while standard lifestyle intervention has little benefit for the majority of kids (17–22). Most studies demonstrating clinical benefit of lifestyle intervention in children have been short-term (6 months to 2 years) investigations, and rebound weight gain has in some cases obliterated prior weight loss (9). Nevertheless, several controlled trials provide evidence for long-term (5–10 years) weight maintenance in children who received intensive intervention, including dietary, exercise, and family counseling (9).

Why do obese people have difficulty losing weight or sustaining weight loss? Time commitments and costs of lifestyle changes may play important roles (23), and some people may simply tire of living with, or may rebel against, dietary restrictions. However, there are also important biological considerations (Fig. 2): weight loss is accompanied by reductions in plasma leptin, insulin, and tri-iodo thyronine and increases in insulin sensitivity and plasma ghrelin (6). These changes stimulate appetite, reduce sympathetic tone and energy expenditure, and promote lipogenesis, thereby facilitating rebound weight gain (6). Consequently, short-term weight loss cannot be sustained without considerable effort. Many will fail.

### Mechanisms of action of pharmacologic agents and metabolic benefits

Can pharmacologic agents complement the effects of lifestyle intervention and re-

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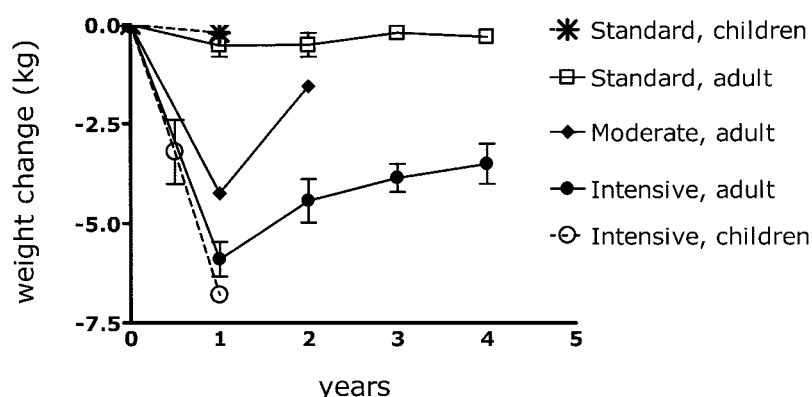
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**Abbreviations:** AMPK, AMP-activated protein kinase; DPP, Diabetes Prevention Program; IGT, impaired glucose tolerance; PCOS, polycystic ovary syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Figure 1**—Effects of lifestyle intervention on body weight in obese adults and children. Data represent placebo-subtracted mean (and when data were available,  $\pm$ SE) values compiled from seven major randomized studies in adults (10–16) and five randomized studies in children (17–21).

duce the risks of complications in those who fail to respond adequately to lifestyle change? This review focuses on four major classes of medications used to treat obesity and/or its complications. The drugs have differential mechanisms of action (Fig. 3) and, as will be seen, differential benefits and adverse effects.

Sibutramine acts centrally to inhibit reuptake of serotonin, norepinephrine, and, to a lesser extent, dopamine. It reduces hunger and increases satiety, and in brown adipose tissue, promotes thermogenesis, which increases energy expenditure (24). Rimonabant is a specific inhibitor of cannabinoid receptor 1. It reduces food intake through actions on the hypothalamus, mesolimbic system, and vagus nerve and directly stimulates the expression of adiponectin in white adipose tissue (25). Orlistat inhibits intestinal

lipases and reduces the gastrointestinal absorption of fat by 30% (24). Finally, through activation of AMP-activated protein kinase (AMPK), metformin reduces hepatic glucose production and plasma insulin concentrations and inhibits fat cell lipogenesis. It can increase peripheral insulin sensitivity and may reduce food intake by raising levels of glucagon-like peptide 1 (26,27).

#### How effective are these agents in promoting weight loss and reversing comorbidities?

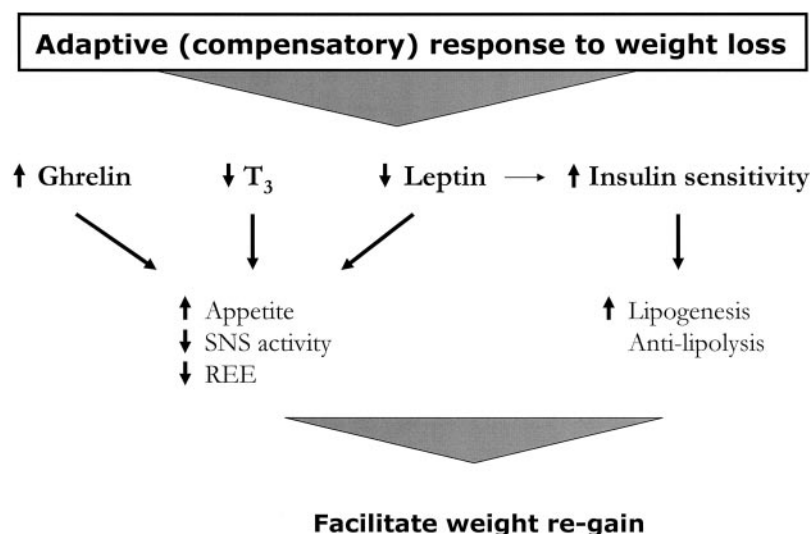
Figure 4 summarizes the findings of placebo-controlled studies performed in several thousand obese adults (11,13–16,24,28–30). The figure compares mean values calculated from data obtained in three studies of rimonabant (14–16), with the results of published

meta-analyses of the effects of sibutramine (24,28–30) and orlistat (24,28–30). Only the effects of the highest dose of rimonabant (20 mg/day) are depicted, since lower doses of the medication (5 mg/day) were far less effective. The results of the XENDOS Study (orlistat) (13) and the Diabetes Prevention Program (DPP) (metformin) (11), each of which involved >1,000 subjects, are illustrated separately. Figure 4 shows the benefits of each drug in excess of that achieved by lifestyle intervention alone. Comprising the findings of a multitude of investigators, the data do not account for differences in study design such as the nature of dietary restriction or the sex or ethnicity of the patients. Thus, group comparisons must be interpreted with caution. Moreover, the data assess only the benefits achieved during the period in which subjects actually took the drugs. In other words, Fig. 4 (and the majority of published studies) show optimal benefits for those who tolerate and accept the medications.

Four general conclusions appear warranted. First, few studies have lasted >1 year. Second, all of the agents promote weight loss, although the magnitude of the effect varies considerably among individuals. Third, the short-term benefits of sibutramine and rimonabant (20 mg/day) exceed those of orlistat and metformin. Finally, some weight regain occurs after 1 year, and the final absolute weight loss is modest. Nevertheless, the combination of lifestyle intervention plus medication can promote as much as 10–12 kg of weight loss, amounting to 7.5–10% of overall body weight (13,31).

It is interesting that striking reductions in body weight are not always associated with reductions in blood pressure or improvements in glucose tolerance (11,13–16,24,26–30) (Table 1). For example, sibutramine appears to have little or no effect on fasting glucose or insulin levels in adults, and the effects of metformin on glucose and insulin greatly exceed those of either rimonabant or orlistat. On the other hand, rimonabant may increase plasma adiponectin (15), a marker of insulin sensitivity, while metformin (in contrast to the thiazolidinediones) may have little or no effect (32). Metformin and orlistat cause variable and small reductions in blood pressure, while rimonabant has no effect. Sibutramine causes 1- to 3-mm increases in mean systolic and diastolic pressure.

A major goal of pharmacotherapy is reduction in long-term cardiovascular



**Figure 2**—The adaptive response to short-term weight loss (6). REE, resting energy expenditure; SNS, sympathetic nervous system;  $T_3$ , tri-iodo thyronine.

**Table 1—Effects of pharmacologic agents on blood pressure and fasting glucose and insulin levels in obese adults**

Treatment	Blood pressure (SBP/DBP) (mmHg)	Glucose (mg/dl)	Insulin ( $\mu$ U/ml)
Orlistat	−1.8/−1.2	−1.8	−1.8
Sibutramine	+0.8/1–2	None	None
Rimonabant	None	−0.7	−2.2
Metformin	Variable, small decrease	−6.2	−3.6

Data represent placebo-subtracted mean values compiled from meta-analyses of studies of sibutramine (24,28–30) and orlistat (24,28–30) and from the results of the DPP (metformin) (11) and three multicenter studies of rimonabant (14–16). Only the effects of the higher dose of rimonabant (20 mg/day) are shown; a lower dose (5 mg/day) had no consistent effect on fasting glucose or insulin. None, no significant effect detected. SEs of the means are ~10–25% of the mean values. Rimonabant also increased (+1.6  $\mu$ g/ml) serum adiponectin, a marker of increased insulin sensitivity. DBP, diastolic blood pressure; SBP, systolic blood pressure.

risk. In adults, orlistat is most effective in reducing serum cholesterol and LDL levels and slightly lowers the LDL-to-HDL ratio (11,13–16,24,16–30) (Table 2). Sibutramine has variable and small effects on HDL and triglycerides, while rimonabant at 20 mg/day robustly increases HDL and reduces serum triglycerides. Lower doses of rimonabant cause small and variable increases in plasma HDL and have no consistent effects on plasma triglycerides. The effects of metformin on plasma lipids are variable. The drug reduced LDL in women with polycystic ovary syndrome (PCOS) (37) and increased HDL in insulin-resistant adults in the DPP (12).

### How do the effects of the medications in obese children compare with those in adults?

The literature comprises eight randomized placebo-controlled studies in obese adolescents: one major study with orlistat (21), four with sibutramine (17,19,22,33), three with metformin (34–36), and none with rimonabant (Table 3). Certain outcomes in obese adolescents appear similar to those in adults: for example, weight loss with sibutramine exceeds that with orlistat or metformin, and metformin reduces plasma insulin levels (mean decrease 8  $\mu$ U/ml) and, to a lesser extent, plasma glucose concentrations in glucose-tolerant subjects. In contrast to its effects in adults with IGT, orlistat had no significant effects on glucose or insulin levels in glucose-tolerant children (21). The effects of sibutramine on glucose metabolism were highly variable. A major multicenter study (33) demonstrated that weight loss with sibutramine is accompanied by reductions in plasma insulin (7  $\mu$ U/ml) but not glucose. In contrast, three smaller studies of sib-

utramine (17,19,22) demonstrated no effects of the drug on plasma glucose or insulin levels.

The effects of the medications on plasma lipids in adolescents appear to be highly variable. Sibutramine reduced plasma triglycerides (17–25 mg/dl) in two studies (19,33) and increased plasma HDL (3.1 mg/dl) in one study (33) but had no effect on plasma lipids in two other studies (17,22). Metformin reduced serum cholesterol (−14 mg/dl), triglycerides (−47 mg/dl), and free fatty acids (−0.07 mmol/l) in one investigation (36) but had no significant effect on plasma lipids in the remaining two studies (34,35). In contrast to its effects on plasma lipids in adults, orlistat had no ef-

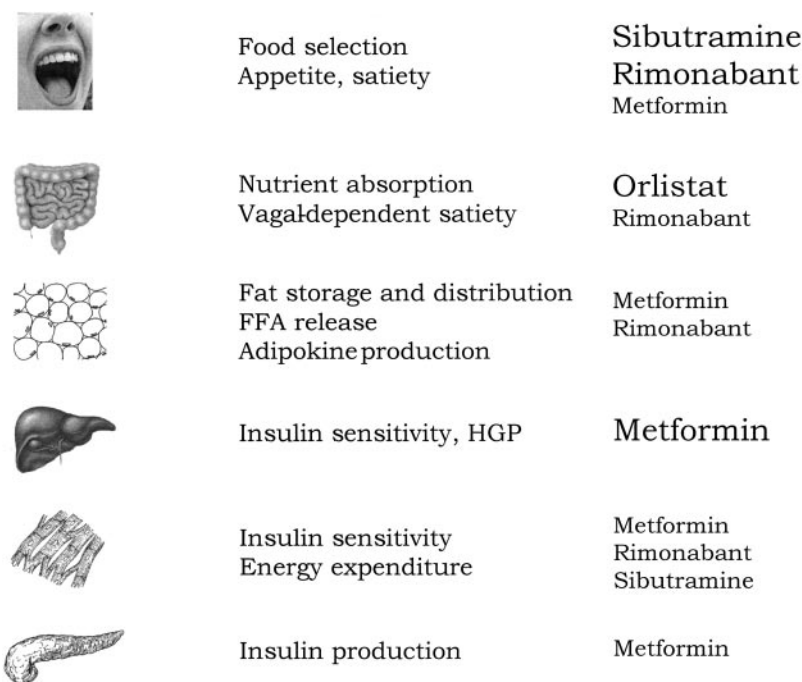
fect on plasma lipids in a multicenter study of obese adolescents (21).

### Do medications act in concert with lifestyle change to facilitate weight loss?

The demonstration that medications in combination with lifestyle change reduce weight more than lifestyle intervention alone is indirect evidence for synergism or additivity of the effects. A 12-month randomized study in obese adults (31) showed that sibutramine alone was as effective as intensive lifestyle intervention in reducing weight (mean  $\pm$  SD weight loss for sibutramine alone  $5.0 \pm 7.4$  kg, amounting to 4.6% of body weight; intensive lifestyle  $6.7 \pm 7.9$  kg, 6.4% of body weight); the addition of so-called brief lifestyle intervention to sibutramine therapy provided no additional benefit, while the effects of sibutramine plus intensive lifestyle intervention ( $12.1 \pm 9.8$  kg, 11.4% of body weight) exceeded the benefits of either intervention alone. These findings suggest that lifestyle change plus pharmacotherapy may act in concert when lifestyle intervention is pursued with resolve.

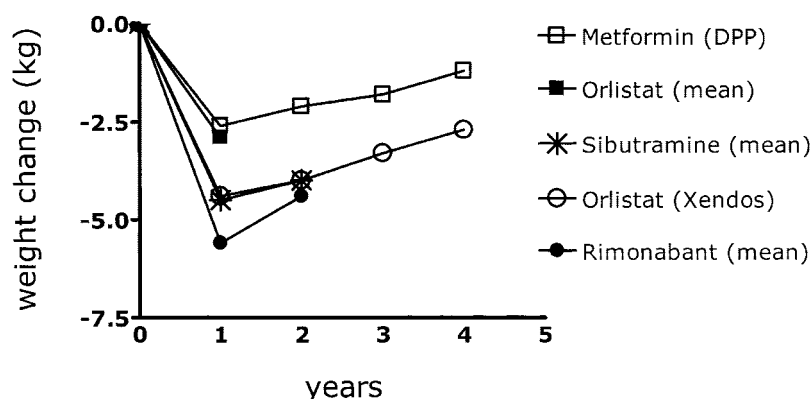
### Do pharmacologic agents prevent the development of long-term complications?

In theory, this is the most important question regarding any intervention for obe-



**Figure 3—**The major sites of action of various pharmacologic agents and potential mechanisms by which they limit weight gain. FFA, free fatty acid; HGP, hepatic glucose production.





**Figure 4**—Effects of pharmacologic agents on body weight in obese adults. Data represent placebo-subtracted mean values compiled from meta-analyses of studies of sibutramine (24,28–30) and orlistat (24,28–30) and from the results of the DPP (metformin) (11), the XENDOS Study (orlistat) (13), and three multicenter studies of rimobabant (14–16). The effects of only the higher dose of rimobabant (20 mg/day) are depicted. A lower dose (5 mg/day) caused mean weight loss of 1.5 kg at 1 year and 0.6 kg at 2 years. SEs of the means were ~10–15% of the mean values.

sity. Four types of studies have explored this issue.

First, the effects of orlistat and metformin on development of type 2 diabetes have been examined in obese adults with IGT. Comparative 3-year study data are shown in Fig. 5. The XENDOS Study (13) showed that orlistat reduced by 32% the cumulative incidence of type 2 diabetes in Swedish adults, whose rates of diabetes were relatively low (cumulative 3-year incidence: placebo control subjects 23.5%, metformin-treated patients 16%). The DPP (11) and the Indian DPP (37) found that metformin reduced the incidence of diabetes in adults at higher risk by 25–31% (estimated 3-year cumulative incidence: DPP placebo control subjects 28.9%, metformin-treated patients 21.7%; Indian DPP placebo control subjects 55%, metformin-treated patients 40.5%). The findings of the DPP and the Indian DPP suggest that metformin can curb the development of diabetes in high-risk adults.

Second, a number of studies (38–40) show that metformin reduces free testosterone levels and hirsutism scores and increases ovulation rates in adolescents and

adults with PCOS, most of whom are obese. Metformin also decreases blood pressure and LDL levels in adults with PCOS (38) and decreased BMI and insulin resistance in hyperandrogenic girls (39,40).

Third, preliminary and thus far inconclusive studies suggest that metformin or orlistat may reduce liver fat content and hepatic enzyme levels in adults and adolescents with nonalcoholic steatohepatitis (41–43).

Finally, two studies suggest that metformin may reduce the rates of cardiovascular disease in high-risk adults. In the UK Prospective Diabetes Study of adults with new-onset type 2 diabetes, metformin reduced the incidence of various diabetes-related end points, including death, by 32–42% (44). The PRESTO Study of adults with type 2 diabetes and coronary artery disease showed that metformin reduced the rates of myocardial infarction and deaths by 28% compared with patients treated with sulfonylureas or insulin (45). No comparable long-term studies of cardiovascular risk with sibutramine, orlistat, or rimobabant currently exist.

### Study attrition rates and adverse effects of pharmacologic agents

It is notable that the magnitude of weight loss achieved with these various medications appears to positively correlate with the rate of attrition or drop out from experimental studies (11,13–16,24,26–30,33) (Table 4). This finding suggests that the more potent weight-reducing agents may also be the least well tolerated. This raises an important question: are the drugs safe (Table 5)?

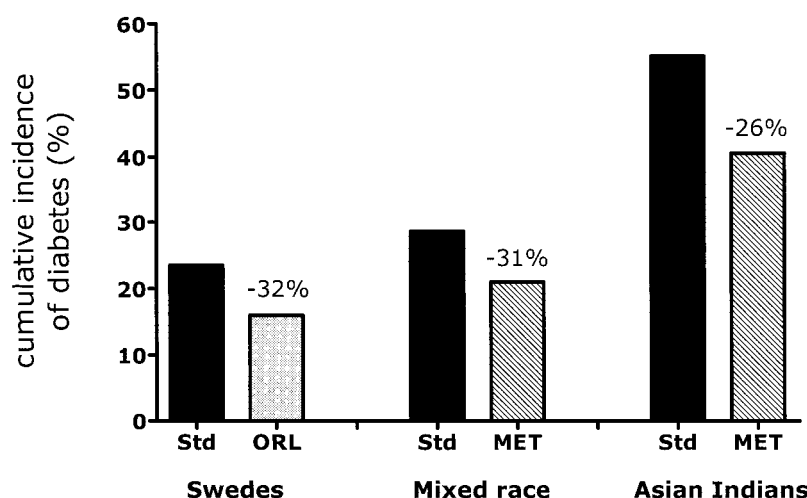
Orlistat is considered safe because it is minimally absorbed. It can, however, cause flatulence, diarrhea, and malabsorptive stools and may reduce vitamin D levels and increase bone turnover in some patients (24,45); a multivitamin may help to prevent osteopenia. Of possible concern was the development of seven new cases of gall bladder disease among the 357 children who took orlistat for a single year (21). One of these children required cholecystectomy. Among the placebo-treated patients, only 1 of 182 developed new gall bladder disease. Since cholecystitis occurs more commonly even in untreated obese individuals (6), it is unclear whether orlistat increases the risk of gall bladder disease or whether long-term use of the drug should be discouraged for patients with preexisting gall stones.

Meta-analyses show that sibutramine increases pulse rate by 4–8 bpm and increases blood pressure 1–3 mmHg in adult subjects (24,28–30). In a major placebo-controlled study of sibutramine in obese adolescents (19), hypertension forced 19 of 43 subjects to reduce the dose of the drug and 5 of 43 (11.6%) to discontinue the medication altogether. The follow-up multicenter study (33) excluded subjects with baseline systolic and/or diastolic blood pressures exceeding 130 and 85 mmHg, respectively. Nevertheless, sibutramine increased mean systolic and diastolic blood pressure by 1 mm and 1.7 mmHg, respectively, and 2.1% of patients developed hypertension

**Table 2**—Effects of pharmacologic agents on plasma lipids in obese adults

Treatment	Cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	Cholesterol/HDL	LDL/HDL	Triglyceride (mg/dl)
Orlistat	–12.7	–10.4	–0.8	–0.15	–0.2	–2.2
Sibutramine	None	None	Variable increase	None	None	Variable decrease
Rimobabant	None	None	+1.5	–0.28	–0.26	–13.7
Metformin	Variable	–0.44	Variable increase	Variable	Variable decrease	None

Data represent placebo-subtracted mean values compiled from meta-analyses of studies of sibutramine (24,28–30) and orlistat (24,28–30) and from the results of the DPP (metformin) (11) and three multicenter studies of rimobabant (14–16). Only the effects of the higher dose (20 mg/day) of rimobabant are shown. A lower dose (5 mg/day) had no consistent effect on plasma cholesterol, LDL, or triglycerides and caused small and variable increases (~0.5 mg/dl) in plasma HDL at 1 year, with no change at 2 years. SEs of the means are ~10–20% of the mean values. None, no significant effect detected.



**Figure 5**—Effects of pharmacologic agents on rates of development of type 2 diabetes in adults with IGT. Shown here are comparative 3-year data from the XENDOS Study in Swedes (orlistat,  $n = 1,640$ ) (13), the DPP in a mixed racial group (metformin,  $n = 1,073$ ) (11), and the Indian DPP (metformin,  $n = 133$ ) (36). Values represent the means of control (standard treatment, Std) and medication-treated groups. MET, metformin; ORL, orlistat.

during treatment. A total of 6.3% of patients became tachycardic, and mean pulse rate increased by 2.5 bpm. No patients developed arrhythmias, but there are reports of ventricular ectopy and prolonged QT syndrome in a few patients treated with sibutramine (47). Sibutramine can also cause insomnia (3.2% of adolescents), dizziness (4%), dry mouth, and constipation and must not be used with monoamine oxidase inhibitors or a variety of other medications that can cause the serotonin syndrome (24).

In the three major studies of rimonabant in adults (14–16), the drug (at the most effective dose of 20 mg/day) caused an excess (5.6%) of “psychiatric and nervous system disorders” including anxiety, depression, and insomnia. At the less-effective dose of 5 mg/day, there were lesser increases in the incidence of anxiety, insomnia, and dizziness. Whether such problems would occur in young pa-

tients is unclear; however, we must be vigilant given the prevalence of eating and mood disorders in severely obese children (48).

Finally, both rimonabant and metformin can cause abdominal discomfort, nausea, and even vomiting. The great majority of adolescents tolerate metformin, and gastrointestinal problems are often transient and dose related. No cases of lactic acidosis have been described in children; indeed, lactic acidosis appears to be extremely rare even in adults in the absence of chronic cardiopulmonary, renal, or hepatic disease. Long-term studies demonstrate the overall tolerability and relative safety of the drug (49).

### Summary of the benefits and risks of pharmacologic agents

In summary, pharmacologic agents provide modest to moderate, short-term reduction in body weight and (in some

cases) cardiovascular risk factors. The effects of the drugs appear to be facilitated by lifestyle change. Their efficacy appears highly variable among individuals, which may reflect genetic influences, perinatal programming, parental motivation, and past and current behavior. The medications have differential effects on weight and metabolic function. Adverse effects are concerning in a subset of patients, and attrition rates from experimental studies are high. The length of time required for treatment is unclear, and the long-term risks of anorectic agents are unknown. Importantly, certain agents (metformin and orlistat) delay the development of type 2 diabetes in high-risk adults, but the long-term benefits for cardiovascular disease or malignancy are unclear.

### Approach to pharmacotherapy in pediatric patients

**Can we identify pediatric candidates for pharmacological therapy?** The major goals of any intervention or treatment for childhood obesity are: 1) to prevent or reverse metabolic comorbidities, 2) to reduce the risk of long-term complications including cardiovascular disease and malignancy, and 3) to improve psychosocial function and quality of life. The risk of metabolic complications correlates with the severity of obesity and insulin resistance (6,50) and with the presence of abdominal adiposity and/or ovarian hyperandrogenism/PCOS, which predispose to glucose intolerance. A family history of maternal gestational diabetes or of early-onset glucose intolerance or cardiovascular disease also bodes poorly (50). Consequently, the author believes that peripubertal children and adolescents with severe insulin resistance, IGT,

**Table 4**—Drug efficacy and rates of attrition from experimental studies of pharmacologic agents in adolescents and adults

	Weight loss at year 1 (kg)	Attrition rate (%)
Orlistat	2.5–2.9	33–35
Sibutramine	4.5–7.7	24–43
Rimonabant	5.6	40
Metformin	2.6	6–7

Data represent the mean 1-year values compiled from 1) meta-analyses of studies of sibutramine (24,28–30) and orlistat (24,28–30) in adults, 2) the results of the DPP (metformin) (11), 3) three multicenter studies of rimonabant (14–16) in adults, and 4) eight randomized controlled studies of sibutramine, orlistat, and metformin in adolescents (17,19,21,22,33–36).

**Table 3**—Effects of pharmacologic agents on BMI and metabolic dysfunction in obese adolescents

	Orlistat ( $n = 357$ )	Sibutramine ( $n = 464$ )	Metformin ( $n = 54$ )
Weight (kg)	−2.5	−7.7	−3.15
BMI ( $\text{kg}/\text{m}^2$ )	−0.86	−2.8	−1.38
BMI $z$ score	Not measured	−0.20	−0.18
Glucose (mg/dl)	None	None	−3.9
Insulin ( $\mu\text{U}/\text{ml}$ )	None	0 to −7	−8.2
Lipids	None	0 to −25.2 mg/dl* 0 to +3.1 mg/dl†	Variable benefit

Data represent placebo-subtracted mean values compiled from randomized, placebo-controlled studies (orlistat [21], sibutramine [17,19,22,33], and metformin [34–36]). SEs of the means are ~15% of the mean values. None, no significant effect detected. \*Triglyceride; †HDL. BMI  $z$ , BMI SD score.

Table 5—Potential adverse effects of pharmacologic agents

	Cardiovascular	Gastrointestinal	Central nervous system
Orlistat		Malabsorption with or without ADEK deficiency; bone turnover; gall bladder disease	
Sibutramine	Increased pulse; increased blood pressure; ectopy; long QT	Dry mouth; constipation	Insomnia; dizziness; drug interactions (serotonin syndrome)
Metformin		Gastrointestinal distress with or without vitamin B deficiency with or without lactic acidosis	
Rimonabant		Gastrointestinal distress	“Psychiatric and nervous system disorders” (anxiety, depression, dizziness, insomnia)

Information compiled from studies of sibutramine, orlistat, and metformin in children and adults (11,13,17,19,24,28–30,33–36) and from the results of the three multicenter studies of rimonabant (14–16) in adults. ADEK, vitamins A, D, E, K.

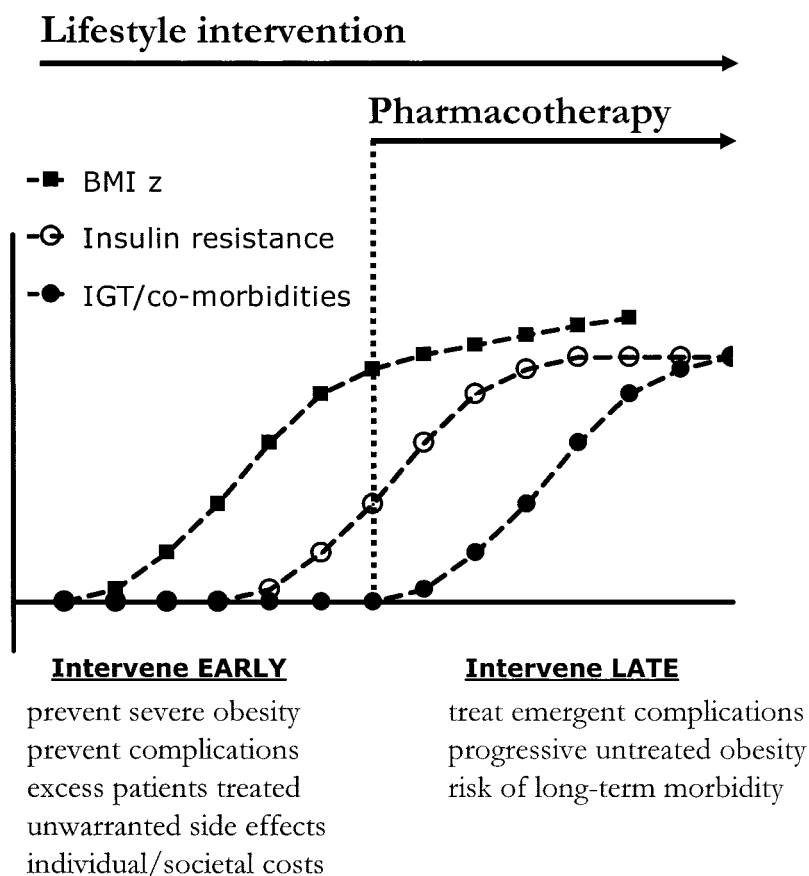
hepatic steatosis, and/or ovarian hyperandrogenism are potential candidates for pharmacotherapy, particularly if there is marked abdominal adiposity and/or a strong family history of gestational diabetes, early-onset type 2 diabetes, myocardial infarction, or stroke. No absolute guidelines can be provided for the selection of pediatric patients for pharmacologic therapy; the decision to begin medication(s) should be undertaken only after a comprehensive evaluation of the child's metabolic status and family history and after an assessment of the current and previous responses to lifestyle intervention. An open and sympathetic discussion with the parents or caretakers is obligatory.

**When should we intervene?** Lifestyle intervention represents the core treatment for obese and insulin-resistant children and adults (9,11,13,19,31). In the opinion of the author and many other clinicians, lifestyle changes should be undertaken before pharmacotherapy and maintained during pharmacotherapy (Fig. 6). The addition of a pharmacologic agent may be considered if diet and exercise fail to achieve the medical objectives established by the health care professional and family. The use of medication early in the course of adiposity (Fig. 6) might in theory prevent the progression to severe obesity and metabolic complications; nevertheless, such an approach would likely treat many children without due cause or benefit, raise the rate of “unwarranted” side effects, and increase the costs to individuals and to society. On the other hand, initiation of medication very late in the course of obesity may run the risk, by delaying treatment, of “runaway” or irreversible weight gain and long-term morbidity. One approach that reconciles these difficulties is to begin pharmacotherapy when the risk of comorbidities is

very high or soon after complications emerge (denoted by the dotted vertical line in Fig. 6). Such complications include IGT, hepatic steatosis, dyslipidemia, and severe menstrual dysfunction. The timing of pharmacointervention could in theory be moved to the left (in other words slightly sooner) if the family history for a major comorbidity such as type 2 diabetes is particularly strong.

**Which medication should be used?** The available evidence suggests that drug selection should be tailored to the individual patient, with strong attention paid to the family history and potential adverse effects.

The author considers metformin, which reduces the rates of type 2 diabetes in high-risk adults (11,37), a valuable adjunct to the treatment of obese patients



**Figure 6**—The author's conceptual approach to balancing lifestyle intervention and pharmacotherapy in the management of obese children.

with severe insulin resistance, IGT, or PCOS. Orlistat also reduces rates of adult-onset diabetes (13) and might prove beneficial in glucose-intolerant children. Dyslipidemic patients may benefit from orlistat or metformin, which reduce LDL levels and the LDL-to-HDL ratio in adults (12,13,38). Metformin or orlistat may also prove useful for obese patients with hepatic steatosis, although additional study is clearly required.

Of the medications tested thus far in children, sibutramine is most effective at reducing body weight, at least in the short term. However, its tendencies to raise blood pressure and pulse are concerning, given the high rates of systolic hypertension among obese adolescents (6). Sibutramine should not be used in children with poorly controlled hypertension or cardiovascular disease and is contraindicated in adolescents with preexisting psychiatric disorders. The long-term safety of anorectic agents in children has not been established, and, in the author's opinion, sibutramine remains an experimental approach for the treatment of pediatric obesity, requiring long-term study in carefully controlled clinical trials.

Whether rimonabant will prove effective and safe in children is unclear. Given its propensity for inducing behavioral problems in adults, and the relatively high prevalence of eating and mood disorders among severely obese children (48), the author believes that rimonabant should not be used in young individuals without extensive additional investigation. Rimonabant should not be administered to children with a history of psychiatric disease or severe mood disorders.

In the future, other classes of pharmacologic agents (e.g., centrally/vagally active incretin mimetics, melanocortin 4 receptor agonists, ghrelin antagonists, etc.) may be used for the treatment of obesity or maintenance of weight loss in adolescents or adults. Other medications, including the thiazolidinediones, target one or more components of the metabolic syndrome and reduce the risk of type 2 diabetes in adults with IGT (51); however, their tendency to cause weight gain, edema, and, rarely, heart failure (51,52) may be problematic in obese subjects. All of these drugs will require systematic investigation and careful consideration of their potential risks, as well as benefits, before they can be used in the general pediatric population.

**How long do we need to treat?** Obesity is a chronic, and in many cases life-long,

condition. Yet, pharmacotherapy might be discontinued or the dose of medication reduced significantly if short-term objectives of treatment are achieved, i.e., reduction in BMI z score and normalization of blood pressure, plasma lipids, and hepatic and renal function and in girls with PCOS, reduction in hirsutism scores and restoration of ovulatory menses.

Nevertheless, the Rimonabant North America Study (16) showed that discontinuation of drugs was associated with nearly complete regain of lost weight within 1 year. Thus, adults may require long-term pharmacotherapy for long-lasting benefit. We don't know if this is the case for children. Still, if an anti-obesity medication is discontinued or its dose reduced, it is essential that lifestyle intervention be maintained throughout; this may limit rebound weight gain and might prevent relapse of comorbidities.

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