

A New Breed of Fat-Loss Drugs

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Drugs Approved for Diabetes, Depression and Epilepsy

Grow Popular for their Weight-Loss Side Effects

By Dan Gwartney, MD

Weight-loss drugs are a continuous source of frustration and confusion for the public. The few alternatives that have been marketed failed to provide universally effective treatment or long-term control, are rarely covered by insurance and are very expensive. Additionally, most drugs require frequent visits to the doctor's office, incurring further expense and the inconvenience of lost time. Worst of all, several of these drugs have been pulled from the market due to serious, even fatal, side effects.^{1,2}

A National Priority

The currently available drug options for combating weight gain or treating obesity are mildly effective at best. Meridia is effective for people who respond to the drug in the first four weeks, but if weight loss isn't experienced early, it likely won't be experienced long term.³

Phentermine is only approved for short-term use, despite the common practice by physicians to prescribe it for months to years.⁴ Xenical is effective for some people; many others find no benefit or discontinue the drug due to embarrassing and uncomfortable side effects (abdominal bloating, anal leakage, etc).⁵

The last innovation in weight loss in the United States that was broadly effective came in 1997 when the combination of phentermine and fenfluramine (phen-fen) offered a remedy to millions. Unfortunately, fenfluramine and the related drug dexfenfluramine (Redux) were associated with serious side effects and subsequently withdrawn from the market. Since

that time, the popular, over-the-counter products phenylpropanolamine (e.g., Dexatrim) and ephedrine have also been pulled from the market, leaving many Americans with no practical option to aid in weight loss. Given the growing epidemic of overweight and obesity plaguing the nation and the health implications for individuals facing the challenge of excess weight, this is an issue that deserves to become a national priority.⁶

The Current State of Affairs

It's well accepted that the foundation for any long-term weight management program must be based on diet and exercise. Unfortunately, millions of Americans have had little to no success following the contradictory and changing advice relating to diet and exercise. Even more discouraging is the fact that millions more refuse to put forth the effort to engage in exercise or control their eating habits. A recently published study conducted at Washington University suggests that certain personality traits influence a person's odds of weight-loss success or failure, reinforcing the need for effective and potent drugs.⁷

American culture grooms its members to seek out health solutions through medications. It's no wonder pharmaceutical companies are scrambling to develop potent weight-loss drugs while stock analysts bite their lips.

French pharmaceutical giant Sanofi-Aventis has already received approval for its innovative drug Acomplia in the European Union, though distribution is currently limited to the United Kingdom due to the different approval processes each country employs. Acomplia is the brand name for rimonabant, a drug that suppresses the appetite, inhibits fat storage and improves insulin sensitivity.⁸ In addition to promoting long-term weight loss, rimonabant may also aid in smoking cessation and improve cardiovascular health. The FDA for non-specified reasons has stalled Acomplia's progress through the U.S. approval process, though approval is expected in the first half of 2007.

While the government drags its feet evaluating new solutions to the weight problem, some physicians are responding to the clamoring demand of overweight patients by experimenting with accessible drugs that have known weight-loss side effects.

Off-label Use

FDA (Food and Drug Administration) drug approval is restricted to defined dose ranges for treating specific diseases or conditions. When a drug is used for other purposes, it's called off-label use. Off-label use is usually legal and considered medically valid when reasonably practiced. The government has banned certain off-label uses, such as prescribing testosterone to healthy men for the purposes of increasing strength or muscularity.

An important distinction to be made clear is that until a drug receives its first approval from the FDA, it can only be used in research. However, once it has cleared FDA approval for any indication, physicians have greater flexibility in exploring other uses. Many physicians avoid off-label use as insurance carriers don't often cover it. Further, if a patient experiences a serious, negative side effect related to off-label use, the physician is exposed to a much greater risk of

being found guilty of medical malpractice as off-label use often falls outside the established standard of care (a term used to describe how other physicians would treat a similar patient).

Despite all these caveats and words of caution, it's interesting to note that many physicians are now prescribing drugs traditionally used to treat other medical conditions for weight loss. Somewhat alarming is the observation that many people are obtaining some of these drugs from the black market or online pharmacies- using them for weight loss without the guidance or supervision of a physician.

A Rundown of Drugs

Several drugs are being touted by physicians or the newly skinny as off-label miracles in the battle of the bulge. As reported in a recent article published in The Wall Street Journal, within this list are drugs traditionally prescribed to treat diabetes, depression, attention-deficit disorder and epilepsy.⁹ Many of these drugs would be expected to reduce fat as they affect the body in ways that improve fat burning, reduce appetite, decrease fat storage or improve insulin sensitivity. Others don't have a clearly defined role in the physiology of fat loss, but have been noted to have the side effect of appetite suppression in patients using the drug for "normal" reasons. Though the list is by no means exclusive, off-label drugs used for lose weight include: Adderall (amphetamine), Ritalin (methylphenidate), Wellbutrin/Zyban (bupropion), Topamax (topiramate), Zonigran (zonisamide), Glucophage (metformin), Byetta (exenatide) and Provigil (modafinil).

Adderall & Ritalin

Adderall and Ritalin are drugs used to treat adults and children with attention-deficit disorder. These drugs work by increasing the levels of the excitatory neurotransmitter norepinephrine in the brain. Basically, they're stimulants. When norepinephrine levels are increased in the brain, a person's appetite is suppressed because the chemical signals the brain is responding to are telling the body that something exciting or frightening is happening. To your brain, it would make no more sense to be thinking about eating than it would have for Jamie Lee Curtis to stop and have some Haagen-Dazs while being chased by an ax murderer in the movie "Halloween."

In addition to not feeling hungry, many people experience a tremendous increase in energy while taking these two drugs. Both of these effects can be major positives, as users will eat less and be more active (hopefully exercising).^{10,11} However, there are some major concerns with using potent stimulants for weight loss. The most serious is the risk of sudden death.¹² A rash of sudden, unexplained deaths occurred in children taking Adderall, causing the Canadian health authority (Health Canada) to remove the drug from the market for several months in 2005. The risk appears to be much higher in people with certain heart abnormalities, but deaths occurred in otherwise healthy people (including adults) without heart abnormalities taking the recommended dose. Another frightening feature involving stimulant use is the risk of addiction, which lead to the withdrawal of Obetrol (containing the exact same formulation as Adderall) for treating obesity in the 1970s.¹³ Amphetamine addiction (Bennies, speed, Dex, etc.) is very similar to cocaine (rock, flake, crack, etc.) and methamphetamine addiction (crank).

Approximate monthly cost (generic): \$50 to \$75.

Wellbutrin & Zyban

Wellbutrin and Zyban are the brand names of the drug bupropion; one is used to treat depression, the other to aid in efforts to stop smoking. Bupropion also works by affecting neurotransmitter levels in the brain- specifically dopamine, serotonin and norepinephrine. It's interesting that bupropion hasn't been approved for weight loss as yet, since several published studies have appeared in medical journals documenting its potent weight-loss effect.^{14,15}

It's possible that this is due to the relatively high risk of brain seizure experienced by those taking bupropion (approximately four out of 1,000 people taking the recommended dose).¹⁶ The risk of seizure limits the utility of bupropion and is the reason that Zyban therapy is generally restricted to seven to 12 weeks, though some physicians will extend Zyban therapy longer for those who have successfully quit to prevent a smoker's relapse.

Bupropion may also worsen depression, ironic since it's an antidepressant. In fact, some patients being treated with Wellbutrin have been reported to experience a worsening of their depression, to the point of suicide.^{17,18} Some individuals with a history of substance abuse have reacted to bupropion as though it were a stimulant, so it's not recommended in such cases. The primary weight loss mechanism of bupropion appears to be appetite suppression. Though much of the effect is likely due to alterations in the brain's hunger mechanisms due to bupropion's effect on neurotransmitter levels, some of the effect may be due to the associated nausea and constipation reported as common side effects.¹⁸

Approximate monthly cost (generic): \$75.

Topamax & Zonigran

Topamax (topiramate) and Zonigran (zonisamide) are used to treat epilepsy. As opposed to most other off-label drugs used to treat obesity, the exact mechanism responsible for the weight loss seen in those being treated with these drugs is unknown.^{19,20} The weight loss is directly related to appetite suppression, and it's assumed that the drugs reduce the nerve pathways involved with appetite in the same manner as they reduce the abnormal brain activity seen in epilepsy (by blocking sodium and calcium channels). Though no one is exactly certain how these drugs work, it's been proven that they do aid in weight loss in published studies.^{21,22} Other side effects noted with these drugs, aside from weight loss, include: glaucoma, kidney stones, confusion, nausea and diarrhea.

Approximate cost (including generic): \$75 to \$150.

Glucophage & Byetta

Glucophage (metformin) and Byetta (exenatide) are diabetes drugs that are chemically very different. However, the similarity the two drugs share- likely accounting for much of their weight loss promotion- is the ability to reduce sugar output by the liver.^{23,24} When people don't eat for extended periods of time, the body is forced to create its own sugar to feed the brain and other vital organs. It does that by using a stored form of sugar called glycogen or robbing the muscle of amino acids by breaking down protein and converting the amino acids into sugar (glucose). The liver then exports the sugar into the bloodstream, feeding hungry tissues. However, if the sugar production goes on too long or at too high a level, then the excess sugar is stored in fat cells, just like a candy bar. Metformin reduces the amount of sugar the liver produces throughout the day.

By contrast, Byetta is injected under the skin and shuts down sugar production by the liver more effectively when meals are consumed. Byetta is also reported to slow down digestion, prolonging the satiety effect of a meal. Both of these drugs have proven to be effective for many people, diabetics and non-diabetics alike, for losing significant amounts of weight.²⁵⁻²⁸

Metformin has been associated with a rare but potentially fatal side effect called lactic acidosis (though this association has been disputed following statistical review). Nausea, vomiting and diarrhea have been reported in the Byetta clinical trials. Both of these drugs have the potential to cause hypoglycemia (low blood sugar), so users should remain alert for signs, such as anxiety, shakiness, irritability and hunger. These drugs appear to induce weight loss by reducing fasting glucose levels, reducing fat storage and improving the body's response to calorie restriction.

Approximate monthly cost (including generic): \$25 to 200.

Provigil

Provigil (modafinil) is a popular drug used by the party crowd, shift workers and anyone who's forced to burn the midnight oil on a regular basis. More observant readers may recognize it as one of the drugs reported to be used by major league baseball great Barry Bonds, in the book *Game of Shadows*.²⁹

Provigil is prescribed for people who suffer from narcolepsy (a condition that causes people to suddenly fall asleep at inappropriate times). However, the black-market crowd has discovered that not only does Provigil allow one to party late into the night and function perfectly normal the next day, it also promotes steady weight loss.³⁰ Provigil acts in the brain similar to amphetamines, but it has a much lower potential for abuse and is generally milder, as it doesn't tend to cause anxiety or have a rebound effect (the "crash" experienced by amphetamine users).

Provigil shares the common side effects of nausea and diarrhea reported with other drugs in the off-label list. Importantly, it has been noted to interfere with birth control pills, so women may wish to consider other means of

contraception.

Approximate monthly cost: \$175.

No One Magic Pill for All

The popular press is quick to report on the miraculous results achieved by people using off-label drugs for weight loss. As easy as it is to empathize with every single person out there struggling to lose weight, either for health or beauty reasons, it's difficult to make a general recommendation to seek out these alternative solutions to obesity or unwanted pounds. While it's true that the existing options for weight loss are modest, expensive and limited, off-label substitutions may be no better.

Certainly, there are individuals who have dropped well over 50 or even 100 pounds using Byetta or a combination of antidepressants and a drug used to treat seizures. However, this is a small sample, and until the off-label drug regimens are better studied, it's difficult to recommend their use in otherwise healthy people, particularly when used in combination. Adverse effects and drug interactions are difficult to predict and many of these drugs have a short history of use outside of clinical trials.

A possible recommendation that can be made is to evaluate medications currently being prescribed (antidepressants, hypoglycemic or diabetes drugs, etc.) and ask your physician if you might be switched from a drug promoting weight gain to one promoting weight loss. If you're fortunate enough to be healthy and aren't being treated for an approved condition relating to these or similar drugs and your personal physician is willing to consider off-label use to aid in weight loss, follow his/her directions closely and be certain to report any side effects.

Of the drugs listed, several are associated with serious side effects, such as addiction, depression, suicide and sudden death; others may show up on a drug screen, causing problems at work or in an athletic organization. Though there are risks with any drug, of the ones mentioned most prominently in off-label weight-loss therapy, metformin and modafinil appear to have the greatest margin of safety. Byetta has been amazingly effective for type 2 diabetics, but it remains to be seen if similar results are enjoyed by normal, but overweight, people.

Government Intervention?

As the practice of off-label use becomes more popular, it's likely that the government will intervene to prevent the use of many of these drugs for the purpose of weight loss. Those of you desperate for a solution to excess fat or those having a pioneering spirit may be tempted to get these drugs through the Internet or illegitimate sources. In one word: don't! Please enlist the guidance and supervision of a physician and order your drugs from legitimate sources. Black market practitioners and illegal drugs often involve health or legal consequences that could place you in dire straits.

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