Impact of anorectic drugs fenfluramine, dexfenfluramine, lorcaserin, and rimonabant on obesity

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Abstract

Anorectic drugs are used to suppress appetite and increase satiety, thereby encouraging weight loss. Among the anorectic drugs that have been most commonly used are fenfluramine, dexfenfluramine, lorcaserin, and rimonabant, which promote weight loss in different ways and to different degrees. By reviewing recent literature, this paper comparatively assesses the benefits and risks of these anorectic drugs. Fenfluramine and dexfenfluramine, while highly effective in promoting weight loss, were associated with the highest risk of potentially fatal cardiac valve damage. Lorcaserin has proven to be significantly safer than fenfluramine and dexfenfluramine, but its impacts on weight loss were generally modest and it was less successful in promoting long-term weight loss. Rimonabant resulted in a more significant decrease in weight than did lorcaserin, but was associated with unpredictable psychological side effects. This review identifies lorcaserin as the safest of the anorectic drugs discussed, even if it is not the most effective in promoting and sustaining weight loss. While anorectic drugs may help to treat obesity, they are not without potentially harmful side effects and are best used in conjunction with dietary and lifestyle modifications. Future research should seek to improve the specificity of anorectic drugs and thereby reduce potential side effects.

Keywords: anorectic drugs; weight loss; obesity; fenfluramine; dexfenfluramine; lorcaserin; rimonabant.

Introduction

Obesity results from a sustained energy input-output imbalance in which caloric intake exceeds energy output. This imbalance results in the deposition of adipose tissue throughout the body (Halford et al. 2011). The current bipartite method for reducing excess adipose tissue involves decreasing caloric input while simultaneously increasing energy output for a sustained period. The reduction in caloric intake required to achieve weight loss is often extremely difficult to sustain for extended periods of time, as the human satiety control system activates intense appetite-stimulating signals when deprived of food (Halford et al. 2011). In the obesogenic environment in which we live, those who struggle to lose weight seek a solution which induces weight loss with minimal discomfort. Moreover, such a solution would be of benefit to healthcare professionals, whose options are either to recommend stringent diets or invasive surgical procedures (Padwal and Majumdar 2007). A class of drugs known as anorectics may offer a partial solution by effectively promoting weight loss.

The amount of literature concerning anorectic drugs is considerable, and researchers have studied the drugs and their effects in various ways. This paper surveys the research

literature on anorectic drugs fenfluramine, dexfenfluramine, lorcaserin, and rimonabant; assesses and summarizes their risks and benefits; and highlights avenues for further research.

Anorectic Drugs: Mechanisms of Action

The neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT) plays an important role in appetite control, operating through a signaling pathway which involves 5-HT receptors located in the hypothalamus. Most anorectic drugs function by modifying this signaling pathway (Fletcher et al. 2010; Halford et al. 2011). Lorcaserin mimics the effects of serotonin as a 5-HT receptor agonist and stimulates serotonin release. Fenfluramine and dexfenfluramine reduce serotonin reuptake in the synaptic cleft (Levin et al. 2011). Stimulation of 5-HT receptors, either by an agonist or through an increase of endogenous serotonin, can induce hypophagia by inhibiting the release of appetite stimulating hormones (Halford et al. 2011).

Recent research has focused on the effects of cannabinoid signaling pathways on satiety, specifically investigating how these pathways can be used to enhance weight loss (Tudge et al. 2015). The effects of cannabinoids on satiety are well documented. Cannabinoid signaling pathways are in part responsible for the pleasure associated with eating, and are responsible for the strong feeling of hunger often associated with the consumption of cannabis and related products. Medicinal marijuana, for example, can be prescribed legally in Canada as a treatment for the extreme weight loss associated with HIV infections (Padwal and Majumdar 2007). Drugs which inhibit the activation of cannabinoid type 1 (CB1) receptors may increase satiety and promote weight loss (Tudge et al. 2015). Rimonabant acts on CB1 receptors as a reverse agonist, producing an effect opposite that of endogenous cannabinoids, which induce hunger (Fong and Heymsfield 2009).

Anorectic drugs, however, can cause side effects. Some of these side effects have been so severe that certain drugs—despite their effectiveness—have been removed from the market (Heisler et al. 2002). Due to the unique ways in which individuals' bodies respond to a given drug, some research on the side effects of anorectic drugs is not entirely conclusive. In selecting and administering an anorectic drug, it is important that the drug's mechanism of action, its effectiveness, and its potential risks are well understood. This review aims to outline the benefits and risks of some of the anorectic drugs that have been most commonly used to treat obesity, namely fenfluramine, dexfenfluramine, lorcaserin, and rimonabant.

Fenfluramine and Dexfenfluramine

Introduced in 1973, fenfluramine and its active enantiomer dexfenfluramine (or d-fenfluramine) were used to promote weight loss (Heisler et al. 2002). Fenfluramine and dexfenfluramine stimulate the release of endogenous serotonin by modifying serotonin transport proteins, in turn activating serotonin 5-HT receptors throughout the body and thereby enhancing overall satiety (Halford et al. 2011). Additionally, fenfluramine and dexfenfluramine can act as serotonin 5-HT reuptake inhibitors by restricting the rate at which the neurotransmitter is reabsorbed (Heisler et al. 2002). When fenfluramine or dexfenfluramine are combined with a sympathomimetic drug, satiety is increased synergistically. As a result, pharmaceutical companies have combined fenfluramine with phentermine (a combination known as “fen-phen”) or related drugs (Heisler et al. 2002).

Fenfluramine and dexfenfluramine have proven to be highly effective in promoting weight loss. One study in which dexfenfluramine was administered to overweight individuals resulted in a significant average weekly weight loss of 0.22 kg in 86% of individuals who completed the study (Halford et al. 2011). Most participants neither gained nor lost additional weight after the treatment ended. Moreover, Pratt and Ford (2010) found that fenfluramine and

dexfenfluramine had sustained inhibitory effects on cue-induced eating patterns in rodents, and suggested that it may have similar effects on humans.

Despite the marked success of fenfluramines in promoting weight loss, the United States Food and Drug Administration removed the drugs from the American market in 1997 due to multiple incidences of valvular heart disease in patients to whom they were prescribed. The drugs' lack of specificity resulted in the activation not only of 5-HT receptors in the central nervous system, but also those located in other regions of the body, including heart valves. Rothman and Baumann (2009) suggested that the increased activation of 5-HT receptors in heart valves may induce mitogenesis, adversely affecting valve function. A study by Dahl et al. (2008) supported these findings, also noting that women were at higher risk than men for valve damage due to fenfluramines. Moreover, the risk of valve damage increased with duration of fenfluramine use. The highest risk rates were observed after 30 months of treatment, and as many as 35% of enrolled individuals showed signs of damage (Rothman and Baumann 2009). Although fenfluramine and dexfenfluramine have been removed from the market, future research could seek to improve their specificity to target only the 5-HT receptors in the central nervous system.

Lorcaserin

Developed in 2009, anorectic drug lorcaserin has thus far demonstrated its potential as a safe and modestly effective means of promoting weight loss. At present, lorcaserin is available in the United States but has yet to be approved in Canada. Much like fenfluramine and dexfenfluramine, lorcaserin activates serotonin 5-HT receptor pathways, but it does so by way of a different mechanism of action (Smith et al. 2010). Namely, lorcaserin functions as a selective serotonin 5-HT_{2C} receptor agonist (Thomsen et al. 2008), with its selectivity being the key to its potential success. By activating serotonin 5-HT_{2C} receptors mainly within the central nervous system, lorcaserin may significantly increase satiety and promote weight loss in overweight individuals (Smith et al. 2010). Levin et al. (2011) demonstrated in a murine study that lorcaserin reduces other reward-driven addictive behaviors (namely nicotine self-administration), which supports its identified mechanism of action and suggests potential future uses (such as aiding in smoking cessation).

Preliminary conclusions about the effectiveness of lorcaserin in promoting weight loss can be drawn from several high-quality human studies. Chan et al. (2013) observed that individuals who were administered lorcaserin saw an average additional weight loss of 3.23 kg in the first year of treatment compared to a placebo group. Decreases in blood pressure, waist circumference, and low-density lipoprotein concentration were also noted in the lorcaserin group (Chan et al. 2013). Additionally, Smith et al. (2010) observed an increase in effectiveness when lorcaserin was

combined with lifestyle changes. Of the patients enrolled in their study, those who were administered lorcaserin and received dietary and exercise counselling experienced an average weight loss of 5.8 kg, a 79% greater loss than those who were administered lorcaserin but did not receive additional counselling (Smith et al. 2013). Other studies have suggested, however, that lorcaserin may be moderately effective at preventing obesity, but has little effect on satiety, as only a marginal decrease in energy intake was observed (Halford et al. 2011).

As lorcaserin is a serotonergic drug, the most concerning possible side effect is the increased risk of valvular heart disease, as was documented in studies of fenfluramine and dexfenfluramine (Rothman and Baumann 2009). Nevertheless, several studies have suggested that this risk is negligible. Smith et al. (2010) maintained that the increased specificity of lorcaserin eliminates the risk of such adverse side effects. Since lorcaserin only targets serotonin 5-HT_{2C} receptors, which are generally confined to the central nervous system and not found in abundance in cardiac valve tissue, the drug has remarkably low potential to cause heart valve damage (Halford et al. 2011). Moreover, Smith et al. (2010) found that patients who were given lorcaserin for 2 years showed no increase in cardiac valvulopathy rate compared to individuals in the placebo group. Chan et al. (2013) noted that more common side effects of lorcaserin were headache, reported in 26.7% of patients, and nausea or dizziness, reported in 11.2% of patients.

Rimonabant

Anorectic drug rimonabant was used in Europe between 2006 and 2008 as an effective treatment for excess adiposity. The United States Food and Drug Administration, however, refused to approve the drug due to concerns about its safety. Rimonabant was removed from most international markets in 2008, and is no longer under development. Unlike fenfluramines or lorcaserin, rimonabant does not operate by way of serotonin receptors, but through CB1 receptors located in the central and peripheral nervous system (Fong and Heymsfield 2009). Rimonabant acts on CB1 receptors through a reverse agonistic signaling pathway. Its effect is not an inhibitory one, but an opposite effect to the feeling of hunger produced by endogenous cannabinoids binding to the same receptors (Fong and Heymsfield 2009). Through this reverse agonist pathway, rimonabant decreases energy intake and increases energy output (Fong and Heymsfield 2009).

There is a general consensus in the literature that rimonabant promotes weight loss. The observed magnitude of weight reduction, however, and the overall effectiveness of rimonabant, varies across studies. In a study conducted by Padwal and Majumdar (2007), overweight and obese individuals (as well as those with diabetes and dyslipidemia) in Europe and North America were administered rimonabant. In all treatment groups, a significant weight loss of 4 to 6 kg was observed after 1 year of treatment. Padwal and

Majumdar (2007) also observed that individuals from North America regained weight when switched to the placebo group after 1 year, whereas those who remained on rimonabant did not.

Further research is needed to determine whether rebound weight gain in individuals who stop taking rimonabant can be controlled through lifestyle changes, which would attest to rimonabant's viability as treatment option for obesity. A murine trial conducted by Karlsson et al. (2014) found that the level of weight loss in response to rimonabant appeared to be proportional to the initial weight of the individual mouse. Karlsson et al. (2014) also found that the effectiveness of rimonabant was proportional to the level of endogenous cannabinoid agonists present in the mouse, suggesting that endogenous cannabinoid agonist levels could be used as biomarkers to estimate rimonabant's effectiveness. Future studies should investigate whether these can serve reliably as biomarkers in humans, and thereby aid in evaluating further the effectiveness of CB1 receptor reverse agonists in promoting weight loss in humans.

Nevertheless, negative psychiatric side effects have led to questions about rimonabant's safety, resulting in the prohibition of its sale and use in Canada and the United States, and its eventual removal from European markets. Padwal and Majumdar (2007) observed a study withdrawal rate of 6 to 7% due to rimonabant's psychiatric side effects, the most common of which was depression, a side effect which may increase suicide risk (Padwal and Majumdar 2007). Fong and Heymsfield (2009) have suggested, however, that these negative psychiatric side effects could possibly be reduced or eliminated if rimonabant could be restricted to target only those CB1 receptors located in the peripheral nervous system, and this is an avenue which merits further research.

Discussion and Conclusion

From this review of recent literature, several conclusions (some more preliminary than others) can be drawn about the overall effectiveness and safety of fenfluramine, dexfenfluramine, lorcaserin, and rimonabant. Of the anorectic drugs discussed, fenfluramine and dexfenfluramine resulted in the greatest weight loss, which was achieved without additional behavioural or dietary modifications by the patient (Halford et al. 2011). Moreover, fenfluramine and dexfenfluramine were also the only drugs shown to have a sustained effect on caloric intake (Pratt and Ford 2013). Despite having the most significant results, fenfluramine and dexfenfluramine also had the most serious and most frequently experienced side effects, most notably cardiac valve damage (Rothman and Baumann 2009). For this reason, fenfluramines, in their current state, are not viable treatment options for obesity. Future research is encouraged to explore whether the side effects of fenfluramine and dexfenfluramine could be reduced or eliminated by increasing the drugs' specificity.

Lorcaserin's selectivity—the drug targets only serotonin 5-HT_{2C} receptors located in the central nervous system—dramatically reduces risk of cardiac valve damage compared to fenfluramine and dexfenfluramine (Smith et al. 2010). Although lorcaserin has a similar method of action to fenfluramine and dexfenfluramine, studies of lorcaserin reported a significantly lower reduction in weight than did studies of fenfluramine and dexfenfluramine (Chan et al. 2014). The effectiveness of lorcaserin could potentially be augmented through lifestyle and dietary changes, though patients have typically found this option undesirable (Smith et al. 2013). Additionally, the possibility of significant weight gain after treatment reduces lorcaserin's overall viability as a primary treatment option (Halford et al. 2011). Nevertheless, lorcaserin is considered to be a relatively safe anorectic drug, and promotes, if not sustains, weight loss.

Studies of rimonabant reported more significant weight loss than those of lorcaserin, but fell short of the weight loss reported in fenfluramine and dexfenfluramine studies (Padwal and Majumdar 2007). Rimonabant also eliminated the risk of cardiac damage, but significantly increased the risk of depression (Padwal and Majumdar 2007). As rimonabant has been removed from the market due to its psychiatric side effects, it is currently not a viable treatment for obesity.

This survey of the literature highlights lorcaserin as an anorectic drug considered to be a safe treatment option for obesity. Due to the drug's limited success in promoting long-term weight reduction, it is best used alongside individuals' efforts to modify their caloric intake. It can be said that the safest way to manage obesity is through dietary and behavioural modification. If a patient is unable to lose weight in this manner, anorectic drugs may be considered as a treatment option. Further research and development are needed, however, before an anorectic drug can make significant headway in curbing the obesity epidemic.

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