DEXFENFLURAMINE, FENFLURAMINE AND PHENTERMINE FOR THE TREATMENT OF MORBID OBESITY

By

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To the Faculty of Washington State University:

The members of the committee appointed to examine the ICNE Research requirements and manuscript of Linda K. Torretta find it satisfactory and recommend that it be accepted.

Chair

[Signatures]
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ABSTRACT

In the U.S., obesity is the second leading cause of preventable death. This paper examined research regarding weight reduction efficacy, side-effects and cost/benefit analysis of dexfenfluramine (Redux), fenfluramine (Pondimin) and phentermine (Ionamin, Fastin). All are schedule IV drugs. Several studies concluded these medications decreased cardiovascular risk factors. Increased risk of PPH is linked to use >3 months. 10%-15% weight loss occurs in first six months of therapy. Common side effects are dry mouth, insomnia, diarrhea and lethargy. Careful patient screening is required before prescribing. The main goal of treatment is to promote weight loss and prevent weight regain. An informed consent form may be of value. Further study of the long-term efficacy and safety of these medications seems warranted.
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DEDICATION

This manuscript is dedicated to my father, William Fisher, July 16, 1928 - July 19, 1997. You are missed.
Abstract

In the U.S, obesity is the second leading cause of preventable death. This paper examined research regarding weight reduction efficacy, side-effects and cost/benefit analysis of dexfenfluramine (Redux), fenfluramine (Pondimin) and phentermine (Ionamin, Fastin). All are schedule IV drugs. Several studies concluded these medications decreased cardiovascular risk factors. Increased risk of PPH is linked to use >3 months. 10%-15% weight loss occurs in first six months of therapy. Common side effects are dry mouth, insomnia, diarrhea and lethargy. Careful patient screening is required before prescribing. The main goal of treatment is to promote weight loss and prevent weight regain. An informed consent form may be of value. Further study of the long-term efficacy and safety of these medications seems warranted.
Introduction

Between 10% and 50% of the adult population in industrialized countries are obese (McTavish & Heel, 1992). In the United States obesity is the second leading cause of preventable death with an estimated 300,000 deaths annually (Manson & Faich, 1996). Obesity has been indicated as a major risk factor in diabetes, coronary artery disease, hypertension and some cancers (Holdaway, Wallace & Gamble, 1995; Pfohl, Luft, Blomberg, & Schumulling, 1993; Van der Merwe, Wing, Gray, Lonn. Jeff & Lanroth, 1996). Excess weight is also a source of considerable psychological distress for the obese individual (Recasens, Barenys, Blanch, Masans & Salas-Salvado, 1995).

Medical practitioners know that weight is gained when there is energy input in excess of energy output over a sustained period of time, but we don't understand the actual cause of obesity (Drent, Zelissen, Koppeschaar, Nieuwenhuzen, Lutterman & Van der Veen, 1995). Why do some gain weight easily while others with the same eating and behavior patterns don't gain weight?

Like other chronic debilitating diseases, obesity is believed to be a metabolic dysfunction expressed in genetically predisposed individuals (Breum, Kronsted, Pedersen, Ahlstrom, & Frimodt-Moller, 1994). However, there is still a significant number of medical professionals who consider obesity a character defect and, therefore, consider the use of anorexic medication an inappropriate medical intervention (Weintraub, 1992).

Until recently, the treatment of obesity centered on diet restriction, support programs, and exercise. While these interventions have a proven place in weight reduction they do not have much of an impact on the morbidly obese. The introduction of a new family of anorexic agents has been heralded as the missing piece in the quest for long-term weight management, and the prevention of the myriad of obesity-related diseases. This paper examines research
regarding weight reduction efficacy, side effects and cost/benefit analysis of three of these drugs: dexfenfluramine, phentermine, and fenfluramine.

Pharmacokinetics

Fenfluramine (Pondimin), a racemic mixture of D and L stereoisomers has an effect on the serotonergic and dopaminergic systems (Anderson, Astrup, & Quaade, 1992). Fenfluramine slows eating and increases the sense of being full after meals and snacks (Weintraub, Sundaresan, Madan, Schuster, Balder, Lasagna, & Cox, 1992).

Dexfenfluramine (Redux) is the dextro-rotatory (d)-isomer of fenfluramine and has a more specific effect on the serotonergic system than fenfluramine (Breum, Moller, Anderson, & Astrup, 1996; Cheymol, Weissenburger, Poirier, & Gellee, 1996; Lafreniere, Lambert, Rasio, & Serri, 1993). Dexfenfluramine is an indirect serotonin agonist with stimulatory effect on serotonin release and inhibitory effect on reuptake of serotonin (Drent, 1995). Besides having a more specific effect on the central serotonin system, dexfenfluramine also acts peripherally on lipogenesis, thermogenesis and gastric emptying (Cheymol, 1995). Dexfenfluramine is associated with fewer side effects because of its pure serotonergic effects (Horowitz, Maddox, Wishart, Vernon-Roberts, Chatterton & Sherman, 1990). According to the package inserts, both drugs are highly lipophilic, cross the blood brain barrier, and are widely distributed to the tissues. Dexfenfluramine is equipotent at half the dose of fenfluramine (Bremer, Scott, & Lintott, 1994).

Phentermine (Ionamin, Fastin) is a sympathomimetic with similar pharmacologic activity as its prototype, the amphetamines, and functions as an appetite suppressor (Weintraub, Sundaresan, Madan et al., 1992). Phentermine and fenfluramine are usually prescribed together and are commonly referred to as Fen-Phen. Dexfenfluramine is prescribed as a solo drug. At this time only
phentermine is available as a generic drug. All three are schedule IV medications.

**Effect on Cardiovascular Risk Factors**

Obesity is associated with an increased risk of cardiovascular disease. Low density lipids (LDL) and triglycerides are linked to coronary artery disease. High density lipids (HDL) are considered to be the positive lipoproteins in the lipid equation. The goal of practitioners is to increase the "good" HDL and to decrease the "bad" LDL and triglycerides in patients at risk for cardiovascular disease. For those patients who also have obesity as part of their disease profile this goal has been difficult if not impossible to reach.

Several studies used Fen-Phen or dexfenfluramine as a means to decrease very serious risk factors (Brenner, Scott & Lintott, 1984; Kolanaski, Younis, Van butsele & Detry, 1992; Pfohl, Luft, Blomberg & Schmulling, 1994; Swinburn, Carmichael & Wilson, 1996). The Long Term Weight Control Multimodal Intervention Study was funded by the National Heart, Lung and Blood Institute. The study (N=121) showed significant decrease in the total cholesterol and a statistically significant increase in HDL (15% above baseline; p<0.01) and decrease in triglycerides (16% below baseline; p<0.01) in the participants using phentermine and fenfluramine at the end of the four year study (Weintraub, Sundaresan, & Schuster, 1992). To date, this has been the only long-term study of this magnitude. A 12-week long study (n=29) using dexfenfluramine showed similar results: a 13% reduction in total cholesterol (p<0.001), a 15% reduction in LDL (p<0.001), a 22% reduction in triglycerides (p<0.05) and an increase of 11% in HDL (p<0.01) (Bremer, Scott, & Lintott, 1994). Another study (n=29) of one year's duration using dexfenfluramine, the results showed no significant changes in cardiovascular risk factors. In fact three years after the end of the treatment the participants were shown to have
significantly increased serum cholesterol (p=0.01) and triglycerides (p=0.002) over their baseline levels (Pfohl, Luft, Blomberg, & Schmuuling, 1994).

**Weight Loss**

The literature supports the finding that both the combination drugs phentermine and fenfluramine or dexfenfluramine aids in weight loss. The amount of weight loss depends on the particular research being considered. The Long Term Weight Control Multimodal Intervention Study showed the greatest initial weight loss. The participants of this four year research project lost an average of 14.2 kg (phentermine and fenfluramine) vs 4.6 kg (placebo) at week 34 (Weintraub, Sundaresan, Madan et al., 1992). At week 104 the participants, had an overall weight loss of 10.8 kg (Weintraub, Sundaresan, Schuster, Ginsberg, Madea, Stein & Byrne, 1992). Using a dosing algorithm during the next phase of the study revealed a weight gain with participants still below their baseline weights by an average of 9.4 kg at week 156 (Weintraub, Sundaresan, Schuster, Moscucci, & Stein, 1992). The second double blind phase ended at week 190 with the phentermine/fenfluramine group 5.0 kg below baseline and the placebo group 2.1 kg below baseline (Weintraub, Sundaresan, Schuster, Averbauch, Stein, Cos & Byrne, 1992). From weeks 190 to 210, participants remaining in the study stopped all medication. At the 210th week, the remaining participants were on average 1.4 kg below their baseline weight of four years earlier at the start of the research project (Weintraub, Sundaresan, Schuster, Averbuch, Stein & Bryne, 1992).

The most weight loss was shown in a six-month study (N=45) where the participants were placed on a very low calorie diet for eight weeks, then started on dexfenfluramine along with the diet therapy. The weight loss for this group of participants (BMI >35) was on average 14.9 kg after 8 weeks on the diet alone, and an additional weight loss of 5.8 kg when dexfenfluramine was also added to the regimen (Finer, Finer, & Naoumova, 1992).
A year long study (n=60) conducted in Australia revealed that at the six-month period the participants (BMI=30-40) of dexfenfluramine had lost an average of 9.7 kg vs the placebo group’s average loss of 4.9 kg (O’Connor, Richman, Steinbeck, & Caterson, 1995). However, five months after discontinuing the medication the dexfenfluramine group had an average loss of 6.0 kg and the placebo group had an average loss of 6.2 kg (1995).

Researchers in Denmark conducted a year long study (N=42, BMI=28-54) in which they demonstrated that while weight was lost during the first six months, the participants began to regain weight during the next six months even though diet and drug dosage did not change (Anderson, Astrup, & Quaade, 1992). A flattening of the weight loss curve after six months was also noted by E.M.H. Mathus-Vliegen in his year-long double-blind study in the Netherlands (1993). The reason(s) for the gaining of weight or the significant slow down in weight loss after six months may be the development of a partial tolerance to the dexfenfluramine, unchanged emotional eating or a metabolic adaptation to a lower weight (Mathus-Vliegan, Voorde, Kok, & Res, 1992). The research supports the average loss of 10% to 15% of an obese person’s baseline weight (Weintraub, 1992; package insert, 1996).

Risk of Primary Pulmonary Hypertension

Fenfluramine and dexfenfluramine have been associated with an increased risk of rare but life threatening primary pulmonary hypertension (PPH). Dexfenfluramine is considered to be the primary at risk agent with an increased risk after three months of treatment. Even then the risk is low with 28 cases per million persons exposed per year (Abenhaim, Moride, Brenot, Rich, Benichou, Kurz et al., 1996). It has been postulated that the magnitude of the risk of death from PPH is similar to that of penicillin-induced anaphylaxis or venous thromboemboli from the use of birth control pills (Manson & Faich, 1996). While the statistical odds are low, for the
unfortunate person who develops PPH, the results are often either a need for a heart-lung transplant or death. Therefore, as practitioners it is important to educate patients in the signs and symptoms of PPH. The primary symptoms are dyspnea, syncope, angina pectoris, and lower extremity edema (McTavish & Heel, 1992). If any of these symptoms develop it is imperative to discontinue the medication immediately and to monitor the patient closely for worsening conditions. Currently, there are no long-term studies addressing the issue of possible lower risk by a rotating cycle of 3 months on and 2-3 months off the medication.

Adverse Reactions

Primary Pulmonary Hypertension, which was discussed earlier, is the most worrisome adverse reaction that could occur using the anorexic drugs being discussed. Other common reactions are dry mouth, insomnia, diarrhea, and lethargy (Table 1) (Swinburn, Carmichael, & Wilson, 1996). The researchers for the Long Term Weight Control Multimodal Study noted that after four years of therapy, a partial tolerance to these mild adverse reactions developed, although dry mouth and sleep disruptions still occurred (Weintraub, 1992). The adverse reactions were most notable in the first month of treatment, although those patients on intermittent therapy experienced an increase in the above mentioned reactions each time they were put back on the drug(s) (Weintraub, Sundaresan, Schuster et al., 1992).

Cost

Treatment for obesity using phentermine/fenfluramine or dexfenfluramine can be expensive (Table 2). Very few, if any, insurance companies pay for weight reduction medications and this can quickly become expensive for the patient. Depending on the particular clinic's protocol, patients return for follow-up every two to three weeks for the first month or so and then every month for a blood pressure and weight check. Appointments can cost between
$35-$55 depending on the clinic's fee structure. The cost of the drugs themselves vary. Dexfenfluramine is prescribed as 15 mg bid with meals, and costs approximately $60.00 for a one month supply. Fenfluramine has a dosing range from 20-40 mg tid with meals. Depending on dosage the average cost is $38.00-$75.00. Phentermine, which is prescribed with fenfluramine, is available as a generic equivalent. The dosing range of this drug is also 15-30 mg and is taken in the morning before breakfast. The cost of the generic version of the drug is approximately $10.00-$15.00 per month. These are the expenses for a basic program. For those clinics that provide extra services like support groups and exercise programs, the costs increase with the added services.

Careful Patient Screening is Required

Anorectic medications should not be randomly prescribed to any patient that requests them due to the potentially serious adverse reactions. It is important to get an accurate medical history and to have the patient undergo a thorough head-to-toe physical before starting the medication regimen (Table 3). The manufacturers of these drugs recommend that a person have a body mass index (BMI) of at least 30 kg/m$^2$ or 27 kg/m$^2$ if there is the presence of other risk factors like diabetes, hypertension or hyperlipidemia. Medications that are contraindicated to be used concurrently with these anorexics are any of the Selective Serotonin Reuptake Inhibitors (SSRI) used to treat depression, MAO inhibitors, sumatriptan (Imitrex), or dihydroergotamine. These medications when used with the anorexics have been linked with a potentially fatal serotonin syndrome. Physical assessments need to rule out any underlying heart, lung or thyroid disease. Other conditions that are contraindicated for the use of the medications are pregnancy or if a woman is breast feeding. Therefore, a pregnancy test should be ordered for any woman of child-bearing age. Another area that should be assessed is the patient's
motivation to make significant dietary and behavioral changes, as well as the awareness of the basic expenditures that will be required to maintain the therapy (Table 4).

Maintenance Issues

The main goal of treatment is to promote weight loss and to prevent weight regain. Implementing extended treatment programs that include behavior modification, support groups, exercise, diet therapy, individual counseling and medication have been used with varying degrees of success (Breum, Pedersen, Ahlstrom et al., 1994; O'Connor, Richman, Steinbeck, & Caterson, 1995; Weintraub, Sundaresan, Madan et al., 1992). Weight regain after cessation of the medication has been a phenomenon that several studies have observed. This weight regain has prompted the recommendation that the medications be continued for an indefinite period of time (O'Connor, 1995). Some researchers have postulated that the continued use of these drugs could serve a useful role in the adherence of diet therapy necessary to decrease the risk factors of lifelong chronic obesity (Mathus-Vliegen, Van DeVoorde, Kok, & Res, 1992). A German study looked at the effects of giving patients a "drug break" from dexfenfluramine. The participants gained weight when off of the medication, then when restarted the weight loss was minimal (Ditschuneit, Flechtner-Mors, & Adler, 1996). The four year Multimodal Intervention study drew similar conclusions using fenfluramine/phentermine. The participants receiving continuous medication were much more successful in remaining below their baseline weights (Weintraub, Sundaresan, Schuster et al., 1992). The package inserts for these drugs currently do not support the safety of these drugs when used past one year's duration.

Informed Consent

The decision of whether or not to use fenfluramine/phentermine or dexfenfluramine for the treatment of obesity is one of complex issues. While
multiple research studies have been conducted, the long-term efficacy and safety of the treatment is still unknown at this time. Patients need to be aware that these are new medications with possible adverse reactions that have not yet been fully discovered. These drugs are designed for the morbidly obese to aid in decreasing BMI 10% to 15%, therefore, the majority of patients will not reach their ideal weight range. The use of these drugs will commit the patient to a long-term investment in significant life-style changes. Due to the complexity of the treatment protocols, an informed consent (Table 5) form may be of value to both the patient and to the practitioner.

Conclusion

Dexfenfluramine (Redux), fenfluramine (Pondimin), and phentermine (Ionamin, Fastin) are all drugs that help in the treatment of obesity. Just as we treat hypertension, hyperlipidemia and other chronic diseases with dietary and medication interventions, so we are finding that obesity may also best be treated in a similar way (Weintraub, 1992). Anorexics should be used only for the medically obese and then as adjuncts to a complete dietary program (Manson & Faich, 1996). Nurse Practitioners, are in the position to encourage patients that the key to success is to maintain a modest weight loss (Weintraub, 1992). We do not know the cause of obesity nor the complete treatment. But through the research being done with drugs like dexfenfluramine, fenfluramine and phentermine, we are closer to being able to help improve the quality of life for the medically obese. However, further study of the long-term efficacy and safety of these particular medications seems warranted.
References


Table 1

Possible adverse reactions of fenfluramine/phetaprine and dexfenfluramine

<table>
<thead>
<tr>
<th></th>
<th>% on Medication vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Pulmonary Hypertension (may be fatal)</td>
<td>28/million</td>
</tr>
<tr>
<td>Serotonin syndrome (may be fatal)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>12.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>19.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.5</td>
</tr>
<tr>
<td>Lethargy</td>
<td>7.1</td>
</tr>
<tr>
<td>Medication</td>
<td>Dosage Details</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>15 mg bid</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>20-40 mg tid with meals</td>
</tr>
<tr>
<td>Phentermine</td>
<td>15-30 mg q am</td>
</tr>
</tbody>
</table>
### Table 3

**Basic screening issues**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health History</td>
<td></td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ask if taking SSRIs, MAO inhibitors, Imitrex or dihydroergotamine</td>
</tr>
<tr>
<td>Screen for:</td>
<td></td>
</tr>
<tr>
<td>lung disease</td>
<td></td>
</tr>
<tr>
<td>heart disease</td>
<td></td>
</tr>
<tr>
<td>thyroid disease</td>
<td></td>
</tr>
<tr>
<td>Women:</td>
<td></td>
</tr>
<tr>
<td>breast feeding?</td>
<td></td>
</tr>
<tr>
<td>pregnant? (run lab test)</td>
<td></td>
</tr>
<tr>
<td>Motivation</td>
<td></td>
</tr>
<tr>
<td>Financial concerns</td>
<td></td>
</tr>
<tr>
<td>Food Groups</td>
<td>1200 Calories</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Starch/breads/cereals</td>
<td>3-4</td>
</tr>
<tr>
<td>Meat/fish/poultry (1 oz/serving)</td>
<td>4-5</td>
</tr>
<tr>
<td>Vegetables</td>
<td>2 (at least)</td>
</tr>
<tr>
<td>Fruits</td>
<td>3</td>
</tr>
<tr>
<td>Fats</td>
<td>3</td>
</tr>
<tr>
<td>Dairy/milk</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 5

Example of an informed Consent

INFORMED CONSENT FOR FENFLURAMINE/PHTERMIN OR DEXFENFLURAMINE

By this document I acknowledge that I am giving informed consent for medications to help in my weight loss.

I understand that the long-term consequences of these medications have not yet been fully discovered and that there may be unfortunate health risks. I understand primary pulmonary hypertension occurs in a small number of patients taking these medications. But when it does occur it can lead to the need for a heart-lung transplant or death. I agree to contact the clinic immediately if any of the following symptoms occur: shortness of breath, fainting, chest pain or swelling (edema) in my legs.

I understand that the use of the medications is just one part of a weight loss program and that I must continue to modify my eating habits and increase my daily exercise so that my caloric intake (the calories that I eat) is less than my caloric expenditure (the calories burned by activity) to aid in the loss of weight.

I understand that I may possibly need to continue with these medications for the rest of my life while continuing exercise and diet therapy or all the weight loss may be regained.

I understand that if the medications are unsuccessful or are stopped for any reason that I may need to go gradually off them by a tapering dosage.

I understand that I must come in to the office to have periodic medical evaluation and follow-up with the health educators for my diet and exercise program.

I also understand that the manufacturers of these drugs suggest that a 10% to 15% weight loss is the average amount of weight lost when taking these medications. (This means that a person who weighs 200 pounds will lose between 20-30 pounds.) I also understand that this means that after the initial weight loss it is common for further weight loss to stop. At this point the medications are often needed to maintain this loss.

Understanding that the long-term consequences of the use of these medications are not yet known, I hereby give my informed consent to receive fenfluramine (Pondimin) and phentermine (Ionamin) or dexfenfluramine (Redux) to assist in weight loss.

Signed: ___________________________ Date: ____________

Witness: __________________________ Date: ____________