Milestones in Drug Therapy
MDT

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Pharmacotherapy of Obesity

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Preface

In the last 10 years obesity has rapidly moved from being a 'cinderella' branch of general medicine which was largely viewed by health professionals and policy makers as more of a cosmetic than a medical problem, to becoming recognised as an epidemic that now rivals smoking for its adverse effects on health. These include increased risks for many major common diseases including diabetes, cardiovascular disease, respiratory disease, joint disease and many common cancers. Not surprisingly this has led to a race amongst researchers and the pharmaceutical industry to discover new, safe and effective treatments for this common disorder.

The first section of this book sets the scene with a chapter by Xavier Pi-Sunyer on the medical need for obesity drugs in a context of the many medical conditions that can be improved by weight loss. Obesity treatment has a long history and many of the older treatments have been withdrawn or have had their use restricted considerably because of concerns over safety and/or efficacy. In the current challenging regulatory environment it is therefore important to recall the salutary lessons from this early experience of the treatment of obesity which has been expertly reviewed by George Bray. Other than the medical need, the other reason for the explosion in drug development in obesity relates to very rapidly developments that have occurred over the last 10-15 years in our understanding of the regulation of energy balance. This has led to the identification of many new molecular targets with understanding of their role in normal physiology and in the pathophysiology of obesity and related conditions. The prospect the new drugs for obesity can be rationally designed on the basis of sound science is now becoming a reality.

Some of this new science has led to the development of new drugs, three of which have been approved in much of the world in the past 10 years. These include the intestinal lipase inhibitor orlistat, the centrally acting serotonin and noradrenaline reuptake inhibitor sibutramine and the cannabinoid 1 receptor blocker rimonabant.

Preclinical and clinical pharmacology, clinical efficacy and trial data for these drugs is reviewed in section 2, providing the basis for the current pharmacotherapy of obesity.

The final section deals with three broad areas that are the target for much of future drug development. These include drugs acting on the central nervous system, use of peripheral gut hormones and other signals, reviewed by Owais Chaudri, Kirsty Smith and Stephen Bloom and finally peripheral thermogenic targets reviewed by Jonathan Arch and John Clapham.

It is hoped that this book provides the reader with a comprehensive account of the past, current state of the art and likely future developments for pharmacotherapy in obesity.

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Why drugs?

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Introduction

Drug therapy for obesity has had a difficult past history. A number of drugs have had addictive or toxic properties that have required discontinuation. Pharmacotherapy for obesity has an important role in those persons who have failed behavioral weight loss attempts or as an adjunct to those attempts. The interest in pharmacotherapy for obesity is an outgrowth of the now general recognition that it is a chronic disease that cannot be cured, but can be treated. Treatment, however, will generally be a life-long affair. The focus on drug therapy is due to the frequent failure of non-pharmacological weight loss programs.

At present, only two drugs, sibutramine and orlistat, are approved for long-term use in the US and in much of the rest of the world. The development of new drugs that could help treatment and prevention is greatly needed. The risk/benefit ratio is important in deciding the usefulness of drugs. Drugs are helpful because the defense of baseline body weight by the body is very forceful, no matter what that baseline weight is. Energy expenditure falls and hunger greatly increases when weight is lost. Because of these very strong and sustained defensive biological reactions to weight loss, maintaining weight loss over time becomes increasingly difficult.

There are a large number of possible agents that could be developed. There are a wide variety of neurotransmitters, gut peptides, and other small molecules that are active in food intake and energy expenditure that can be copied or blocked.

It is probable that in the future, as our knowledge base increases, drugs will be developed that will be useful for some persons and not others, according to their individual genomic make-up. That would usher in an era of personalized medicine in the weight loss field.

It is important to accelerate the development of drugs that are safe and effective. Success in this endeavor could prevent a great deal of disease and improve quality of life.

"Diseases desperate grown
by desperate appliance are reliev'd
or not at all" Shakespeare, Hamlet IV.III.9

Historical context

Drug therapy for obesity has been fraught with problems over the years. Early drugs such as amphetamines were found to be addictive and therefore unacceptable [1] (Tab. 1). In the 1950s, phentermine and diethylpropion were developed for weight loss. These drugs, however, were only tested and approved by the FDA for short-term use (less than 3 months) [2] (Tab. 2). Their effect also was modest and they produced significant side effects. In the late 1960s, phentermine was tested for a somewhat longer period (36 weeks) with modest effects [3]. In the 1970s, fenfluramine was introduced, again only approved for short-term use. The weight loss results were, however, somewhat better. In the 1980s, dexfenfluramine, the active component of d,l fenfluramine, was approved and a number of trials demonstrated its efficacy in weight loss [4–7]. It was in this decade that the combination of phentermine and fenfluramine was first tried long-term [8, 9]. Subjects were treated for up to 3.5 years. The obese volunteers were treated with diet, exercise, and behav-

Table 1. History of drug approval by FDA

1950s	1970s	1980s	1990s
Phentermine*	Fenfluramine*	Dexfenfluramine*	Sibutramine†
Diethylpropion*			Orlistat†

* approved for short-term use only
† approved for long-term use

Table 2. Drugs approved for use in the USA

Drug	Drug enforcement administration schedule
Amphetamine†	II
Phenmetrazine†	II
Benzphetamine HCL*	III
Phendimetrazine tartrate*	III
Phentermine HCL*	IV
Diethylpropion HCL*	IV
Mazindol*	IV
(d,l) Fenfluramine‡	IV
Dex fenfluramine‡	IV
Phenylpropanolamine HCL‡	—
Sibutramine	IV
Orlistat	—

† Not recommended for treatment of obesity
‡ Use discontinued
* Approved for short-term use only

ior modification, and were randomized to experimental drugs or placebos. At 60 weeks, patients on continuous treatment had lost 15.8 kg. Individuals who took medication constantly for 3.5 years had persistent weight loss. The efficacy of this combination was thus much greater than had been the case when any of the drugs which were available were used alone, and as a result it was used extensively throughout the world. In the late 1990s reports of toxicity began to surface. These included heart valve abnormalities [10, 11] and primary pulmonary hypertension [12–15]. The fenfluramines were therefore withdrawn from the market.

There was then a lull in the availability of new drugs until the 1990s, when sibutramine and orlistat were introduced. These two drugs are now approved for at least 2 years of use, and in fact physicians are using them for longer periods. Sibutramine is a serotonin and nor-epinephrine re-uptake inhibitor which reduces food intake by enhancing satiety. The drug has been tested in a number of randomized clinical trials and has been found to reduce weight with an average of a 4–8 kg weight loss [16–18]. The other drug is orlistat. Orlistat is an inhibitor of intestinal lipase which impairs fat absorption by the gut. The net effect is to decrease absorption of dietary fat calories. This drug has undergone 2-year clinical trials with no significant side effects except for a small reduction in blood levels of fat soluble vitamins (within the normal range) [19–21]. It is of about the same effectiveness as sibutramine over a 1 year period. In a 1 year placebo-control study, 55% of orlistat-treated patients lost more than 5% and 25% lost more than 10% of their body weight compared to 33% and 15%, respectively, achieving the same mean weight loss in the placebo-treated group. The side effects of this drug are steatorrhea, with soft and more frequent stools. An attempt to use the two drugs in combination did not improve weight loss [22].

There is a school of thought that the modest effect of presently approved drugs and their resultant very low sales are all to the good and that obesity should be treated strictly by diet and exercise and not by drugs. There has been a strange dichotomy in many physicians' and regulators' thinking that, while it is reasonable to have long-term drug therapy for metabolic conditions like high blood pressure, dyslipidemia and diabetes mellitus, it is not acceptable for obesity. This stems from an attitude that obesity is a matter of self-discipline and not a matter of biologic susceptibility. But as more and more is known about the etiology of obesity, it is clear that the enhanced eating behavior and the diminished activity are to a large extent genetically determined [23, 24], and that while environment certainly plays a part, biology is also extremely important.

Why use a drug?

The rationale for the use of a drug for a specific condition includes: (i) the condition predisposes to or exacerbates a disease, (ii) amelioration of the condition improves the disease state or risk, and (iii) the intervention has an accept-

able safety profile. Pharmacotherapy for obesity has a role in those who have failed conservative weight loss attempts and is often effective when included in a long-term multi-modal plan.

The interest in pharmacotherapy for obesity is an outgrowth of the now general recognition that it is a chronic disease with genetic underpinnings. The new thinking stresses that a chronic disease cannot be cured but can be treated, and that treatment is a life-long affair and will require medication for life rather than medication for a short period of time. The model for obesity then is diabetes mellitus and hypertension, where chronic medication is an accepted modality of treatment and a cure is not the anticipated result.

The reason that there has been interest in pharmacotherapy for the treatment of obesity is that the attempt to lose weight and particularly to keep it off has been fraught with failure. Data from a number of studies have shown that in behavioral modification programs weight is lost for only the first 4–6 months [25]. After this, weight tends to plateau and then begins to increase. At the end of 4–5 years at a maximum, all of the weight has been regained [26, 27]. There is thus a powerful incentive to find drugs that can improve the success rate in the loss of weight and particularly in the maintenance of this loss.

Risk/benefit ratio

Given the widespread and growing prevalence of obesity, the development of new drugs that could help in treatment and prevention of this condition is greatly needed. What are the characteristics of an ideal anti-obesity drug? It needs to be safe and effective. Safety is pre-eminent since such a drug would be taken by a great number of persons. The risk/benefit ratio is therefore extremely important. What are the risks of using the drug as compared to the risks of not using the drug and either maintaining the elevated weight or actually increasing it? To calculate this for a given drug, one needs to know: (i) how much a given weight gain decreases health and longevity, (ii) whether and how much a given weight loss improves the two, and (iii) how much weight loss warrants treatment with a drug given its side effects. The answer is only known reasonably well on the first of the questions. Obesity reduces health [28], increases mortality [29], and reduces longevity [30, 31]. We know that weight loss reduces many risk factors associated with obesity [25], but we do not know if it actually decreases the incidence of many of the eventual comorbid diseases themselves, although it seems self-evident that it should. So we do not have firm answers to these questions. This is because it is expensive and tedious to do the long-term trials that would be necessary to measure 'events' such as the onset of myocardial infarction, or stroke. We generally only have shorter term studies that have measured risk factors and have shown them to be improved after a period of weight loss [32]. Thus, it has been difficult to judge when an individual drug is worth using. Also, some drugs may just lower weight while others may have additional independent effects on

some of the risk factors for diabetes and cardiovascular disease. Some may improve certain risk factors but not others. Some may have more unpleasant side effects than others.

Weight change effects on energy balance

As previously mentioned, it is very difficult to lose weight, and it is even more difficult to keep it off. An individual's body defends the highest weight that has been attained. As soon as one begins to lose weight, two phenomena occur: first, energy expenditure decreases and, second, the urge to eat increases.

Energy expenditure changes

The data on energy expenditure is clear. Early human studies showed that with hypocaloric dieting energy expenditure dropped 10–15% from baseline. Later studies have confirmed this [33]. The mechanisms for this are not totally clear, but the thyroid gland, the sympathetic nervous system, as well as central nervous system changes are involved.

The thyroid makes L-thyroxine (T_4), which is metabolized to L-triiodothyronine (T_3). These two thermogenic hormones help to maintain the normal resting metabolic rate. As calorie intake decreases and weight is lost, the thyroid switches from producing T_3 to producing reverse T_3 (rT_3). Unlike T_3, which is thermogenic, rT_3 is not, so that the stimulus to energy production decreases [34]. Figure 1 shows the thyroid hormone products.

A second hormone that influences energy expenditure is leptin. Leptin is secreted from fat cells and is active in the central nervous system [35–38]. As weight is lost, fat cells decrease in volume and leptin production drops [39].

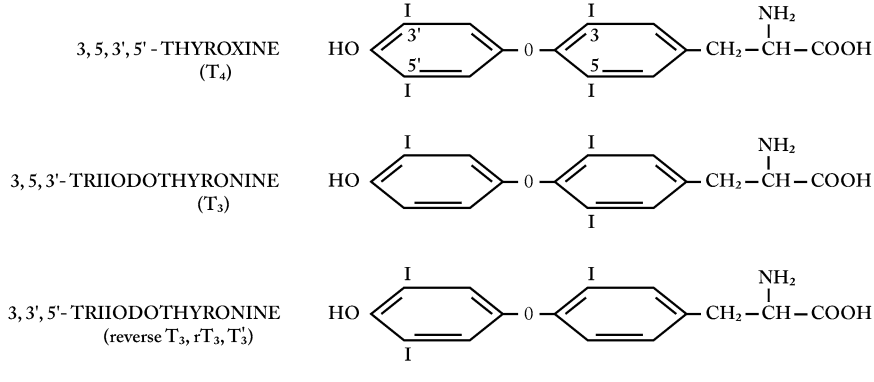

Figure 1. Chemical structures of L-thyroxine (T_4), L-triiodothyronine (T_3), and reverse T_3 (rT_3). From Hershman JM (1980) *Endocrine pathophysiology*. Lea & Febinger, Philadelphia.