Pharmacotherapy of Obesity

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MDT

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Contents

List of contributors ........................................... VII

Preface ......................................................... IX

F. Xavier Pi-Sunyer
Why drugs? .................................................. 1

George A. Bray
Some historical aspects of drug treatment for obesity .......... 11

Joanne A. Harrold and John P.H. Wilding
Regulation of energy balance – towards rational drug design in obesity .................................................. 21

John P.H. Wilding
Intestinal lipase inhibitors ..................................... 47

John P.H. Wilding
Sibutramine .................................................... 59

Muhammad Khan and John P.H. Wilding
The endocannabinoid system as a target for obesity treatment .... 69

Owais B. Chaudhri, Kirsty L. Smith and Stephen R. Bloom
Using the body’s natural signals – gut hormones .................... 81

John C. Clapham and Jonathan R. Arch
Influencing energy expenditure and substrate utilisation ............ 101

Index ............................................................... 117
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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 Obesity treatment has a long history and many of the older treatments have been withdrawn or have had their use restricted considerably because of concerns over safety and/or efficacy.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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September 2007
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

<table>
<thead>
<tr>
<th>1950s</th>
<th>1970s</th>
<th>1980s</th>
<th>1990s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine*</td>
<td>Fenfluramine*</td>
<td>Dexfenfluramine*</td>
<td>Sibutramine†</td>
</tr>
<tr>
<td>Diethylpropion*</td>
<td></td>
<td></td>
<td>Orlistat†</td>
</tr>
</tbody>
</table>

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

Table 2. Drugs approved for use in the USA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug enforcement administration schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine†</td>
<td>II</td>
</tr>
<tr>
<td>Phenmetrazine†</td>
<td>II</td>
</tr>
<tr>
<td>Benzphetamine HCL*</td>
<td>III</td>
</tr>
<tr>
<td>Phendimetrazine tartrate*</td>
<td>III</td>
</tr>
<tr>
<td>Phentermine HCL*</td>
<td>IV</td>
</tr>
<tr>
<td>Diethylpropion HCL*</td>
<td>IV</td>
</tr>
<tr>
<td>Mazindol*</td>
<td>IV</td>
</tr>
<tr>
<td>(d,l) Fenfluramine‡</td>
<td>IV</td>
</tr>
<tr>
<td>Dex fenfluramine‡</td>
<td>IV</td>
</tr>
<tr>
<td>Phenylpropanolamine HCL‡</td>
<td>—</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>IV</td>
</tr>
<tr>
<td>Orlistat</td>
<td>—</td>
</tr>
</tbody>
</table>

† 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-