A Review on Obesity and its Management

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ABSTRACT
Obesity may be considered a chronic pathological condition resulting from complex interactions between cultural, psychological and genetic factors. During the past 30-40 years, a markedly increased emphasis on its control has, in part, resulted from evidence of risks to the health of the obese by a spectrum of metabolic disorders, including non-insulin dependent diabetes mellitus, hypertension, hyperlipidemia, hypercholesterolemia, cardiovascular disease and gall bladder disease. However, as both moralizing exhortations and non-pharmacological treatments usually lead to no more than limited loss of weight, their supplementation by anorectic drugs is receiving much attention. Several such drugs are available, and many more are being developed, partly because the drugs that are recommended at present typically cause weight loss for only a few months. Drugs with anti-obesity properties due specifically to this effect or to effects on the absorption or metabolism of specific dietary constituents may provide new therapeutic avenues independent of appetite suppression.

Key Words: Anorectic drugs, Anti-obesity properties, Appetite suppression, Genetic factors, Hypertension, Hyperlipidemia, Hypercholesterolemia, Obesity.
INTRODUCTION

OBESITY

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. People are considered obese when their Body Mass Index (BMI), a measurement which compares their weight and squared height, exceeds 30 kg/m². Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. Obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, medications or psychiatric illness. [2,3]

Effect of obesity on health [4,5,6,7]

- Cardiology - Ischemic heart disease: Angina and Myocardial Infarction, Congestive heart failure.
- Dermatology - Stretch marks, Acanthosis nigricans, Lymphedema, Cellulitis, Hirsutism.
- Endocrinology and Reproductive Medicine - Diabetes mellitus, Infertility, Menstrual disorders.
- Gastrointestinal - Gastroesophageal reflux disease, Fatty liver disease.
- Neurology - Stroke, Meralgia paresthetica, Migraines, Low back pain.
- Psychiatry - Depression in women, Social stigmatization.
- Respiratory - Obstructive sleep apnea, Asthma.
- Rheumatology and Orthopedics - Gout, Poor mobility, Osteoarthritis, Low back pain.
- Urology and Nephrology - Erectile dysfunction, Urinary incontinence, Chronic renal failure, Buried penis.

Anti-obesity

Anti-obesity medication or weight loss drugs are all pharmacological agents that reduce or control weight. [9]

These drugs alter one of the fundamental processes of the human body, weight regulation, by either altering appetite, metabolism, or absorption of calories. [10] The main treatment modalities remain dieting and physical exercise. Only one anti-obesity medication, orlistat (Xenical), is currently approved by the FDA for long term use. It reduces intestinal fat absorption by inhibiting pancreatic lipase. Rimonabant (Acomplia), a second drug, works via a specific blockade of the endocannabinoid system. [10,11]

Drug used in treatment of obesity. [12,13,14,15,16,17,18,19]

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Mechanism</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of 19th century</td>
<td>Thyroid hormone</td>
<td>Increases metabolic rate</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>1920s</td>
<td>Dinitrophenol</td>
<td>Mitochondrial uncoupling</td>
<td>Cataracts, neuropancreatic, Cardiac failure</td>
</tr>
<tr>
<td>1930s</td>
<td>Amphetamines (phentermine, diethylpropion**, phendimetrazine)</td>
<td>Dopamine-noradrenaline-reuptake inhibitor, releaser, Sympathicomimetic drugs</td>
<td>Addiction, myocardial Infarction, stroke</td>
</tr>
<tr>
<td>1950s</td>
<td>Phenylpropanol amine</td>
<td>Sympathomimetic</td>
<td>Stroke</td>
</tr>
<tr>
<td>1960s</td>
<td>Rainbow pills (mixture of digitalis, Amphetamine, and Diuretics)</td>
<td>Mixed</td>
<td>Fatalities due to narrow therapeutic index of digitalis</td>
</tr>
<tr>
<td>1990s</td>
<td>Fen-phen(mixture of Fenfluramine and Phentermine**)</td>
<td>5-HT-reuptake inhibitor and releasing agent with sympathomimetic</td>
<td>Valvulopathy</td>
</tr>
<tr>
<td>Currentl y used</td>
<td>sibutramine**</td>
<td>5-HT-noradrenaline-reuptake inhibitor</td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td>Currentl y used</td>
<td>Orlistat</td>
<td>Gastric lipase inhibitor</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Currentl y used</td>
<td>Rimonabant</td>
<td>CBI antagonist</td>
<td>Depressive symptoms, Anxiety</td>
</tr>
<tr>
<td>Currentl y used (epilepsy)</td>
<td>Topiramate</td>
<td>Antiepileptic drug targeting multiple protons</td>
<td>Memory impairment, Depressive symptoms</td>
</tr>
<tr>
<td>Currentl y used (epilepsy)</td>
<td>Zonisamide</td>
<td>Antiepileptic drug targeting multiple protons</td>
<td>Memory impairment</td>
</tr>
<tr>
<td>Currentl y used (depression and smoking)</td>
<td>Bupropion</td>
<td>Dopamine-noradrenaline-reuptake inhibitor</td>
<td>Dry mouth, insomnia</td>
</tr>
<tr>
<td>Currentl y used (depression)</td>
<td>Fluoxetine</td>
<td>5-HT-reuptake inhibitor</td>
<td>Nausea, diarrhea</td>
</tr>
</tbody>
</table>

[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19]
### Catecholaminergic Drugs

Catecholaminergic agents have been the largest group of clinically used anti-obesity drugs since the observation in the 1930s that the use of sympathomimetic agents such as amphetamine to treat asthma caused anorexia and weight loss [20][27].

#### Ephedrine and Norephedrine (Phenylpropanolamine)

The adrenergic agent phenylpropanolamine (DL-norephedrine) has been marketed as an over-the-counter (OTC) treatment in the USA. It is readily absorbed from the gastrointestinal tract and has a half-life (11/2b) of 3.9–4.6 hours in man [28].

#### Diethylpropion

Diethylpropion is a phenylethylamine derivative (1-phenyl-2-diethylamine-1-propanone hydrochloride) with only slight sympathomimetic and stimulant properties. [29]

#### Mazindol

The non-phenylethylamine catecholaminergic drug mazindol has moderate stimulant activity but negligible abuse potential. In animal experiments, blockade of the hypophagic effect of mazindol by L-methyl-p-tyrosine and the dopamine receptor blocker pimozide indicates that the action of the drug on appetite depends on dopaminergic properties. [30].

#### Bromocriptine

Another dopaminergic drug, the D2 dopamine agonist bromocriptine, has, in a fast release formulation (Ergoset®), given encouraging results in a small, double-blind trial, which somewhat unusually had a slight preponderance of male subjects (drug 5 M, 3 F; placebo 5 M, 4 F). [31]

#### β 3-Adrenoceptor Agonists

As indicated above, an important problem when catecholaminergic drugs are used to treat obesity has been how to achieve selective sympathetic arousal, so that metabolism and lipolysis are stimulated without the undesirable effects of cardiovascular stimulation. As recently reviewed, β-agonists have been developed which stimulate lipolysis and thermogenesis much more potently than atrial contraction (β 1-receptor mediated) or inhibition of smooth muscle activity (β 2-receptor mediated) and act via β 3-adrenoceptors. [32]

### Some Newer Developments

However, much pharmacological research on appetite is now being driven by systematic studies of the biochemistry of appetite and obesity and, as indicated below, may be leading towards new and more effective drug treatments.

#### Orlistat

Orlistat, a hydrogenated derivative of lipstatin, a lipid produced by Streptomyces toxytricini, has been recommended for approval as an...
anti-obesity drug in the USA and Canada (May 1997). It inhibits gastrointestinal lipases and thus reduces the absorption of fat, typically by one-third. Several clinical trials are under way. [34]

Leptin

There has been considerable interest in the possible use in obesity of the protein leptin (OB protein), the product of the OB gene which is defective in ob/ob obese mice. Daily i.p. injection of leptin decreased food intake, body weight, fat and diabetic symptoms, and increased energy expenditure. [35]

Drugs Acting at Neuropeptide Receptors

Numerous neuropeptides have effects on food intake. This observation has led to recent interest in the possible use of drugs acting at peptide receptors in the control of obesity. [36]

Neuropeptide Y (NPY)

Attention has been paid to NPY since its intrahypothalamic injection of NPY in rats was found to elicit feeding with unsurpassed potency. Research on its role in appetite control has been encouraged by the finding that NPY occurs at high levels in ob/ob obese mice, and that when these are made deficient in NPY, their obesity and diabetes are attenuated. These results suggest that NPY antagonists may have anti-obesity potential. [37, 38]

Other Peptides

Feeding is suppressed when the peptides cholecystokinin and glucagon-like peptide-1 are injected centrally into rats. The latter compound is claimed to be the most potent known inhibitor of feeding when given by this route. Another peptide, galanin, increased fat intake by rats, and intrahypothalamic injection of galanin antagonists had the opposite effect, implying that orally effective antagonists would be candidate anti-obesity drugs. [39, 40, 41, 42, 43, 44, 45]

ANTI-OBEITY DRUGS (WITHDRAWN OR CURRENTLY RESTRICTED FOR USE) [39, 40, 41, 42, 44, 45]

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
<th>STATUS</th>
<th>ADVERSE EFFECTS</th>
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<tbody>
<tr>
<td>Dinitrophenol</td>
<td>Thermogenesis (uncontrolled oxidative phosphorylation)</td>
<td>Introduced in 1933 with no regulatory controls; 1938 FDA awarded greater power to prosecute</td>
<td>Heat, sweating, dermatitis, agranulocytosis, hepatotoxicity, cataretic, neuropathy, hyperthermia, metabolic collapse, and death</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>NE, DA, and 5-HT releaser</td>
<td>Introduced in 1936, desoxycortephrine approved by the FDA for obesity in 1944; for short-term use only; banned or restricted</td>
<td>Hypertension, intracranial hemorrhage and hemorrhage stroke (especially women), arrhythmias, myoccardial infarction, cardiac arrest, PAH, seizures, and death</td>
</tr>
<tr>
<td>Diethylpropion (amphetamine)</td>
<td>NE, DA releaser, and also NE and DA reuptake inhibitor</td>
<td>Introduced in 1959; withdrawn within 1979; withdrawn in 2000 (Europe); still available in the USA and Australia for short-term use</td>
<td>Psychosis, nervousness, insomnia, transient ischemic attack, and case reports of PAH</td>
</tr>
<tr>
<td>Phentermine</td>
<td>NE and DA reuptake inhibitor</td>
<td>Introduced in 1959 (USA); withdrawn in 1963 (Europe); still available in the USA and Australia for short-term use</td>
<td>Hypertension, tachycardia, nervousness, euphoria, insomnia, and case reports of ischemic stroke, ischemic colitis, and nephritis</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>5-HT releaser and reuptake inhibitor</td>
<td>Introduced in 1963 (Europe) and in 1973 (USA); withdrawn in 1997</td>
<td>Valvulopathy, PAH, neuropsychiatric syndromes, depression, and dizziness PAH</td>
</tr>
<tr>
<td>Aminorex</td>
<td>5-HT releaser and reuptake inhibitor; also potent monoamine oxidase inhibitor</td>
<td>Introduced in 1965 (Europe); withdrawn in 1968</td>
<td>PAH</td>
</tr>
<tr>
<td>Mazindol</td>
<td>Similar to amphetamine</td>
<td>Introduced in</td>
<td>Nervousness, atrial fibrillation, insomnia, syn...</td>
</tr>
</tbody>
</table>
The limitation of drugs for obesity is that we do not fully understand the neural basis of appetite and how to modulate it. Appetite is clearly a very important instinct to promote survival. In order to circumvent the number of feedback mechanisms that prevent most monotherapies from producing sustained large amounts of weight loss, it has been hypothesized that combinations of drugs may be more effective by targeting multiple pathways and possibly inhibiting feedback pathways that work to cause a plateau in weight loss. The damage was found to be a result of activity of fenfluramine and dexfenfluramine at the 5-HT2B serotonin receptor in heart valves. Newer combinations of SSRIs and phentermine, known as phenpro, have been used with equal efficiency as fenphen with no known heart valve damage due to lack of activity at this particular serotonin receptor due to SSRIs. There has been a recent resurgence in combination therapy clinical development with the development of 3 combinations: Qnexa (topiramate + phentermine), Empatic (bupropion + zonisamide) and Contrave (bupropion + naltrexone). [50, 51, 52]

**FUTURE DEVELOPMENT**

Other classes of drugs in development include lipase inhibitors, similar to orlistat. Another lipase inhibitor, called GT 389-255, is being developed by Peptimmune (licensed from Genzyme). This is a novel combination of an inhibitor and a polymer designed to bind the undigested triglycerides therefore allowing increased fat excretion without side effects such as oily stools that occur with orlistat. The development seems to be stalled as Phase 1 trials were conducted in 2004 and there has been no further human clinical development since then. In 2011, Peptimmune filed a potential long-term approach to anti-obesity medication is through the development of ribonucleic acid interference (RNAi). Similarly, another nuclear hormone receptor co-repressor, SMRT, has demonstrated an opposing effect in genetically engineered mice. Another approach is to induce a sense of satiety by occupying space in the gastric and intestinal cavities. One clinical trial involves hydrogel made of indigestible, food-grade materials. Another pilot study uses pseudobezoars. [53, 54]

**APPLICATION OF SCIENTIFIC KNOWLEDGE**

A number of drugs are in clinical trials including as of October 2009 Cetilistat and TM38837. [55]

**GENERAL COMMENTS AND CONCLUSIONS**

Clinical trials of anti-obesity drugs reveal significant degrees of success but also limitations. Loss of weight is greater than that attained by non-pharmacological methods alone but usually only sufficient for a partial reversal of obesity. This outcome, though associated with significant improvements in health, is obviously less than ideal. As already mentioned, maximal decrease of weight occurred typically in the first six months of clinical trials and then remained almost stationary despite continued drug treatment. These limitations imply a need for improved treatments and for the targeting of patients for treatment according to their degree of motivation to lose weight and their risk of obesity-related illness. Anti-obesity drugs that alter amineergic mechanisms are contraindicated in patients taking other amineergic drugs such as reuptake and monoamine oxidase inhibitors. Caution is stated to be necessary in patients with a history of major psychiatric illness, in pregnancy and lactation and in the presence of psychiatric illness.
antihypertensive and hypoglycemic medication. While the latter are beyond the scope of this review, it should be emphasized that, at present, pharmacologic treatments are primarily intended as supplementary to procedures that provide advice on diet and exercise and psychological stimuli for long-term lifestyle changes promoting control of appetite, weight loss, and resultant reduction of health risks in clinically obese patients. [56, 57, 58]

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