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 as obese when their Body mass index (BMI), a measurement which compares their weight and squared height, exceeds 30 kg/m^2. [1] 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 , Dementia , Multiple sclerosis.
- Oncology - Breast, Ovarian, Esophageal, Colorectal, Liver, Pancreatic, Prostate, Kidney.
- Psychiatry - Depression in women, Social stigmatization
- Respirology - Obstructive sleep apnea , Asthma increased complications during general anaesthesia
- 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. [8] These drugs alter one of the fundamental processes of the human body, weight regulation, by either altering appetite, metabolism, or absorption of calories. [9]The main treatment modalities remain dieting and physical exercise.Only one anti-obesity medications 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]

Year	Drug	Mechanism	Side effects
End of 19th century	Thyroid hormone	Increases metabolic rate	Hyperthyroidism
1920s	Dinitrophenol	Mitochondrial uncoupling	Cataracts,neuropathy, Cardiac failure
1930s	Amphetamines (phentermine, diethylpropion*+ , Phendimetrazine)	Dopamine-noradrenaline-reuptake inhibitor,releaser, Sympathicomimetic drugs	Addiction,myocardial Infarction, stroke
1950s	Phenylpropanolamine	Sympathomimetic	stroke
1960s	Rainbow pills (mixture of digitalis, Amphetamine and Diuretics)	Mixed	Fatalities due to narrow therapeutic index of digitalis
1990s	Fen-phen(mixture of Fenfluramine and Phentermine*+)	5-HT-reuptake inhibitor and releasing agent with sympathomimetic	Valvulopathy
Currently used	sibutramine*+	5-HT-noradrenaline-reuptake inhibitor	Tachycardia,hypertension
Currently used	Orlistat	Gastric lipase inhibitor	Diarrhea
Currently used	Rimonabant	CB1 antagonist	Depressive symptoms, Anxiety
Currently used (epilepsy)	Topiramate	Antiepileptic drug targeting multiple protiens	Memory impairment, Depressive symptoms
Currently used (epilepsy)	Zonisamide	Antiepileptic drug targeting multiple protiens	Memory impairment
Currently used (depression and smoking)	Bupropion	Dopamine-noradrenaline-reuptake inhibitor	Dry mouth,insomnia
Currently used (depression)	Fluoxetine	5-HT-reuptake inhibitor	Nausea,diarrhea

Currentl y used (ADHD)	Atomoxetine	noradrenaline-reuptake inhibitor	Dry mouth,palpitations

- * Approved by the U.S Food and Drug Administration for weight loss
- + Drug Enforcement Aministration schedule 4

Alternative medicine [20, 21 ,22]

Product	Claim	Effectiveness	Side effects
Conjugated linoleic acid	Reduces body fat	Possibly effective	Upset stomach, nausea, loose stools
Green tea extract	Decreases appetite, and increases metabolism, fatcell death	Insufficient evidence to evaluate	Dizziness, insomnia, agitation, nausea, vomiting, bloating, gas, diarrhea
Lipoic acid	Increases glucoseabsorption in musclesrather than fat		
ECA Stack	Increases metabolism	Effective in Humans	severe skin reactions, irritability, nervousness, dizziness, trembling, headache, insomnia, profuse perspiration, dehydration, itchy scalp and skin, vomiting, hyperthermia, irregular heartbeat, seizures, heart attack, stroke, or death.
Raspberry ketone	Increases norepinephrine-inducedlipolysis	No clinical evidence in humans	

Serotonergic drug

The serotonergic drug fenfluramine has been extensively used as an appetite suppressant. [23]

Sertraline

Another SSRI, sertraline, has been the subject of limited study as an appetite suppressant. [24].

Drugs Acting at Specific 5-HT Receptor Subtypes

As drugs with agonist activity at 5-HT2C receptors cause hypophagia in rats, highly selective agonists at these sites have been suggested as potential anti-obesity agents [25].

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 [26] [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 (t1/2b) 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 a-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. [33].

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 . [34].

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. [35].

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. [36].

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. [37, 38].

ANTI-OBESITY DRUGS (WITHDRAWN OR CURRENTLY RESTRICTED FOR USE) [39 ,40,41,42,43,44,45].

DRUG	MECHANISM OF ACTION*	STATUS	ADVERSE EFFECTS.
Dinitrophenol	Thermogenesis(uncouples oxidative phosphorylation)	Introduced in 1933 with no regulatory controls;1938 FDA acquired greater power to prosecute;end of the official clinical use in 1938	Heat,sweating,dermatitis ,agranulocytosis, hepatoxicity, cataracts, neuropathy, hyperthermia,metabolic collapse,and death
Amphetamines	NE,DA, and 5HT (weak) releaser	Introduced in 1936,desoxyephedrine(approved by the FDA for obesity in 1944);for short-term use only;banned or restricted	Abuse potential dependency and,hypertension,tachycardia,insomnia, nervousness,psychosis,dehydration and case reports of PAH
Phenylpropanolamine	NE,DA and 5HT releaser	Introduced in 1939(US);OTC(1976) as nasal decongestant and antiobesity(1979);withdrawn in 2000	Hypertension,intracranial hemorrhage and hemorrhage stroke (espically women),arrhythmias,myocardial infarction,cardiac arrest,PAH,seizures,and death
Diethylpropion(amfepramone)	NE releaser, and also NE and DA reuptake inhibitor	Inrtroduced in 1959;withdrawn in 2000(Europe);still available in the USA and Australia for short-term use	Psychosis,nervousness,insomnia,transient ischemic attack,and case reports of PAH
Phentermine	NE and DA reuptake inhibitor	Inrtroduced in 1959(USA);withdrawn in 2000(Europe);still available in the USA and Australia for short-term use	Hypertension,tachycardia;nervousness;euphoria;insomnia;and case reports of ischemic stroke,ischemic colitis;and nephritis
Fenfluramine	5 HT releaser and reuptake Inhibitor	Introduced in 1963(Europe) and in 1973(USA);withdrawn in 1997	Valvulopathy,PAH,neuropsychiatric syndromes,depression,and dizziness PAH
Aminorex	5HT releaser and reuptake inhibitor;also potent monoamine oxidase inhibitor	Introduced in 1965(Europe);withdrawn in 1968	PAH
Mazindol	Similar to ampheta	Introduced in	Nervousness,atrial fibrillation,insomnia,syn

	mine(NE reuptake inhibitor)	1970;discontinued in 1993(Australia);withdrawn in 2000(Europe)	cope and case reports of PAH
Dexfenfluramine	5 HT releaser and reuptake Inhibitor	Introduced in 1985 in Europe and in 1996 (USA);withdrawn in 1997	Valvulopathy ,PAH, depression, and case reports of psychosis

*DA 5 dopamine; NE 5 norepinephrine; OTC 5 over-the-counter

PROCESS MEASURE TO JUDGE THE SUCCESS OF ANTI-OBESITY DRUG TREATMENT [46 , 47, 48 ,49]

Measures	Immediate benefits	Long term benefits
Physical measures	Weight loss, Reduction in waist circumference,Improvement in comorbidities	Reduced breathlessness,Decreased sleep apnoea,Reduced angina,Reduced blood pressure
Metabolic measures	Decreased fasting blood glucose and plasma insulin,Improvement in fasting lipid profile,Decreased HbA1c(if diabetic)	Reduction in doses of concomitant medications
Functional measures	Increased mobility,Decreased symptoms,Improved well being and mood,Improved health-related quality of life	Reduced time away from work,Increased involvement in social activites,Decreased number of consultations with health professionals

LIMITATION OF CURRENT KNOWLEDGE

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) andContrave (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.Another 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 miceAnother approach is to induce a sense of satiety by occupying space in the gastric and intestinal cavities. One clinical trial involves ahydrogel made of indigestible, food-grade materials. Another pilot study uses pseudobezoars. [53, 54]

RESEARCH

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 aminergic mechanisms are contraindicated in patients taking other aminergic drugs such as reuptake and monoamineoxidase 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

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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