REVIEW ARTICLE

Pharmacological management of obesity: Past, present and future

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ABSTRACT

Obesity is the problem of children, adolescents and the elderly because it is a problem that affects all ages. Obesity leads to many metabolic disorders diabetes, hyperlipidemia, hypertension, angina, depression, indigestion and arthritis. There were several studies and reviews presented on the treatment modality in literature for obesity. But there are no comprehensive reviews on anti-obesity drugs till date. In the present review, we are presenting the pharmacological management of obesity. The literature search carried out using electronic search engines through PubMed, Biological Abstracts, BIOSIS PREVIEWS, Current Contents®/Clinical Medicine, Current Contents®/Life Sciences, EBSCO, ScienceDirect, Ingenta, Springer, Wiley Interscience, J-STAGE, Google scholar and Scifinder from 1990 to September 2013. Based on this search, we are presenting a brief review on pharmacological management of obesity, with a focus on the drugs used in the past, present and future. From this search, it is revealed that some of the drugs approved earlier for treating obesity were withdrawn from the market (Phentermine, Dexfenfluramine, Fenfluramine and Sibutramine). Some of the older drugs are introduced in combination form (Phentermine + Topiramate (Qnexa), Empatic, Concave). Most of the adrenergic and serotonergic drugs possesses adverse effects like increasing heart rate and hypertension. Similarly, some new drugs came into the market for treating obesity (Lorcaserin, Orlistat,) and few are in clinical trials in different phases of drug development (APD-365, CD-945,598, MK-0364, ATL-962, GT-389-255, AOD9604, Leptin, Peptide3-36, obinepitide and TM30338). The drugs that are under clinical trials were subjected for evaluating the safety and efficacy. We have to see in the future how many of these drugs are going to be available for treating obesity.

Key words: Orlistat, obesity, pharmacological interventions, management

INTRODUCTION

Obesity is defined as an excess fat deposition due to long term change in the energy balance resulting in increasing energy input, lowering physical activity and decreases in energy output, or both. There are many factors governing obesity such as, sedentary movement, unhealthy diet and eating habits, family life-style, pregnancy, lack of sleep, certain medications, age, social and economic issues, medical problems and genetics.[1] Some of these factors are corrected by exercise, changing diet and a change of life-style. The factors that are not able to be corrected are subjected to pharmacological interventions. Therapeutic agents can help the weight loss with decreasing the consumption of foods or inhibiting absorption of food or increasing energy expenditure.

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Over the last 10 years, there has been a rapid explosion in our knowledge of the mechanisms involved in regulating feeding behavior and cellular mechanisms involved in

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energy expenditure. Rich harvests of potential new drug targets have arisen from this research, which may offer hope of safe and effective treatments for obesity. Till date, there is no literature citation on a comprehensive review of pharmacological management of obesity drugs. Hence, we have taken up this challenge to review drugs employed in the treatment obesity. We also presented the future candidate drugs for treating obesity.

METHODOLOGY OF REVIEW

We searched electronic databases through PubMed, Biological Abstracts, BIOSIS PREVIEWS, Current Contents®/Clinical Medicine, Current Contents®/Life Sciences, EBSCO, ScienceDirect, Ingenta, Springer, Wiley insterscience, J-STAGE and Google scholar, from January 1990 to September 2013. The electronic searches were carried out using key words obesity, pharmacological management of obesity, anti-obesity drugs, adverse effects of anti-obesity drugs, pharmacotherapy of obesity and also employed the different pharmacological classes of drugs such as, Neuropeptides, β_3 receptor agonists, Serotonergic agonists and Leptins.

Potential articles were examined to determine if they met the following eligibility criteria:
(1) Were published in peer-reviewed journals between 1990 and 2013? (2) Were written in English and involved pre-clinical and clinical experimentation? and (3) discussed the pharmacokinetics (PKs) and pharmacodynamics (PDs) parameters of anti-obesity drugs, related side-effects, adverse effects as related to treatment approaches and treatment outcomes?. Articles not meeting these criteria were not included in the review.

We searched full length articles and abstracts in different databases mentioned above . Based upon these results, we selected the most appropriate and relevant data concerned with Pharmacological categories for treatment of obesity. We also considered the PKs (what the body is doing on the drug? Absorption, distribution, metabolism and elimination) and PDs (how the drugs are acting? mechanism of action) of drugs and presented in short nut shell. This review is presented in brief to explore, what are the classes of drugs used in the treatment of obesity? How these drugs are classified? What are their actions? How these drugs are acting (PDs)? What are their shortcomings? or side-effects or adverse events? What are new drugs used in obesity? What type/class of the drugs will be used for treatment of obesity in the future? Based on this search, we were presenting a brief review on pharmacological management of obesity, taking into consideration drugs used in the past, present and the drugs under clinical trials (drugs of the future). Pharmacological interventions used for obesity are classified as follows.

1. Adrenergic agents
   - Indirectly acting drugs: Phentermine, amphetamine, dexfenfluramine, fenfluramine
   - Mixed acting (directly and indirectly): Ephedrine.
2. Monoamines: Bupropion, Tesofensine, Lorcaserin,
3. Serotonergic Agents: Fluoxetine, Sertraline, Sibutramine, Venlafaxine
4. Cannabinoids: Taranabant, TM38837
5. Neuropeptides (hormones): Neuropeptide-Y (NPY), Glucagon like peptide, Cholecystokinin (CCK), Oxyntomodulin, Melanocortins, Orexigenic peptide (Orexines A and B)
6. Pancreatic Lipase Inhibitors: Orlistat, Lipstatin, Ebelactone-A, FL386, Caulerpenyne
7. Thermogenic and energy expenditure drugs: Ephedrine, Caffeine, β_3 receptor agonist
8. Fixed dose combination: Pramlintide + Metreleptin; Naltrexone + Bupropion, Phentermine + Topiramate and Zonisamide + Bupropion
9. Drugs that Reduces Food Intake: Phenylpropanolamine, Amphetamine, Phentermine and Diethylpropion.

Adrenergic agents

These agents act by increasing catecholamine release from nerve endings terminating in the para-ventricular nucleus of the hypothalamus, a brain area central to feeding behavior.[2] As a consequence of noradrenaline release, activation of postsynaptic α1- and β_1-adrenoceptors reduces appetite. Brief adrenergic agents PK and PD profile is presented in Table 1.

Phentermine, an analog of amphetamine indirectly acting adrenergic agent with reduced abuse liability, has been available as mono therapy for obesity since the early 1960s [Table 1]. It is restricted to short-term - treatment in conjunction with calorie restriction[3,4] one reason being that treatment is limited by this agent due to intolerance to its central nervous system (CNS) stimulatory activity.[3] Other agents used in obesity like amphetamine, dexfenfluramine/fenfluramine are banned by Food and Drug Administration (FDA) these are listed in Table 1 with their PK/PD and other activities.

Phenylpropanolamine is chemically related to ephedrine mixed acting (directly and indirectly) adrenergic agent and is available as an over-the-counter remedy for colds, hay fever and in some countries, obesity. Like ephedrine, which is described in the section of "Agents, which enhances thermogenesis and energy expenditure", because it has some thermogenic activity.[5,6]

Monoamines

The monoamines consist of a group of chemically related compounds that act as neurotransmitters in both the central and peripheral nervous system. Some

Table 1: Pharmacological profiles of adrenergic, monoamine, serotonergic and cannabinoids agents

Pharmacological class of drug	Name of the drug	Pharmacodynamic	Pharmacokinetics	Therapeutic use	Adverse reactions	Approval year	Reference
Adrenergic drugs	Phentermine	Catecholamines tend to suppress hunger signals and appetite. The drug seems to inhibit reuptake of noradrenaline, dopamine and serotonin through inhibition or reversal of the reuptake transporters	Rapidly absorbed orally, hepatic metabolism, half-life is 16-31 h	Appetite suppressant	Headache, insomnia, irritability, palpitations and nervousness	USFDA-1959	[8,10]
	Amphetamines* Dexfenfluramine*/ Fenfluramine*	The drug seems to inhibit reuptake of noradrenaline, dopamine and serotonin through inhibition or reversal of the reuptake transporters	Well absorbed orally, largely distributed, excreted in urine	Depression of appetite, reduced food intake	Tremor, hyperactive reflexes, irritability, insomnia, anxiety and suicidal/ homicidal tendencies	Banned in 1997 by FDA/EMEA	[6,8,10]
	Ephedrine	Sympathomimetic which stimulates both alpha and beta adrenergic receptors, and also releases noradrenaline from storage site	Well absorbs intramuscularly/ subcutaneously, small quantities are metabolized in the liver, but the majority of ephedrine is excreted unchanged in the urine. The plasma half-life of ephedrine is 3-6 h	Increase energy expenditure	Angina, palpitation, nausea, anxiety, prostatic hypertrophy	Under clinical studies	[5]
Monoamine	Bupropion	Weak inhibitor of the neuronal uptake of norepinephrine and dopamine	Oral absorption, 84% bound to plasma protein, metabolized by cytochrome P450 IIB6 isoenzyme, excreted in urine and feces	Depression of appetite, reduced food intake	Hypertension, insomnia, agitation, dry mouth	Under review by USFDA/ EMEA	[6-9]
	Tesofensine	A triple monoamine reuptake inhibitor in development for treating obesity	-	Treatment of obesity	Diarrhea, constipation, nausea	Phase-III	[10]
	Lorcaserin	Lorcaserin binds to and activates $5HT^{2C}$ with greater affinity and potency than for $5HT^{2A}$ and ^{2B}	Oral absorption is rapid, metabolized to sulfate metabolite, 38% blood radio activity. Excreted in urine as un changes	Treatment of obesity	Valvular heart disease, psychiatric disorders, hypoglycemia and decrease of heart rate	USFDA/ June-2012 Under review by EMEA	[8,10]
Serotonergic drugs	Fluoxetine	Selective serotonin reuptake inhibitor	Well absorbed orally, large volume of distribution in the body, undergoes hepatic first-pass metabolism, excreted in urine	Depression of appetite, reduced food intake	Agitation, dermatological reaction, nervousness, Hypertension	Under clinical studies	[6,15]
	Sertraline	Selective serotonin reuptake inhibitor	Absorbed from GIT, widely distributed in the body, hepatic metabolism, N-methylation is the takes place, 0.2% of an oral dose being excreted unchanged in urine	Suppression of appetite	Hypertension, agitation, dermatological reaction, nervousness	Under clinical studies	[6,11]

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Table 1: Contd...

Pharmacological class of drug	Name of the drug	Pharmacodynamic	Pharmacokinetics	Therapeutic use	Adverse reactions	Approval year	Reference
Serotonergic-noradrenaline reuptake inhibitor	Venlafaxine	Inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake	Well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine is only major active metabolite. Renal excretion	Reduce food intake	Carcinogenesis, Mutagenesis, impairment of fertility	Under review of USFDA/ EMEA	[16]
	Sibutramine*	an inhibitor of the reuptake of 5-HT, norepinephrine and dopamine	Orally absorption, Rapid and extensive distribution into tissues, metabolized by the liver by cytochrome P450. Major excreted by urine and feces	Depression of appetite, reduced food intake	Hypertension, palpitation, migraine, laryngitis, insomnia	EMEA1990 FDA1998 (withdrawn EMEA/ FDA2010)	[39-41]
Cannabinoids	Rimonabant (Acompia/Zimulti)	A selective cannabinoid CB_1 receptor antagonist	Rapidly absorbed on oral administration, maximum plasma concentration reached in 2 h after of 20 mg, Both hepatic and CYP3A, anhydrolase pathway	Reduction of weight	Nausea, depression, anxiety, abdominal discomfort	Further clinical studies/ under review by USFDA/ EMEA	[25-27]
	Taranabant	A CB-1 inverse Agonist being investigated as a potential treatment For obesity due to its anorectic effects	Oral rapid absorption, plasma taranabant has biphasic disposition, elimination half-life 38-69 h	Depression of appetite, reduced food intake	Depression, anxiety, abdominal discomfort, nausea	Phase III	[28,29]
Cannabinoid (new agent)	TM38837	Inverse inhibitor of the CB1 receptor cannabinoid receptor	-	Treatment of obesity and metabolic disorders	-	Phase-I	[28-30]

*Banned drugs-USFDA: United states food and drug administration, EMEA: European medicine agency, GIT: Gastrointestinal tract, FDA: Food and drug administration

members of the group, particularly adrenaline, are also important hormones and play a role in integrating metabolic responses to stress and other stimuli. In general, effects of monoamines depend on actions at G-protein-coupled receptors although there are also a few examples of interaction at ion gated channels. Within the CNS monoamine projections show many of the signs expected of a neurotransmitter that acts in a modulatory role. Cell bodies are typically relatively small in number and concentrated into rather few anatomical locations. However, they typically have extremely broad innervation patterns. Neurotransmitter release may occur at specialized axonal sites, in addition to synaptic release, generating paracrine effects. Their PKs and PD profile presented in Table 1.

Bupropion

Bupropion is used in the treatment of depression and as a smoking cessation aid. It acts primarily by inhibiting the reuptake of dopamine and possibly noradrenaline and has relatively little effect on 5-hydroxytryptamine (5-HT) reuptake. Bupropion tends to cause weight loss in depressed patients if they are overweight, but weight gain if they are on brief Pharmacological interventions to underweight subject[6,7] There are some reports that bupropion strongly promotes weight loss in non depressed obese patients[8,9] [Table 1].

Tesofensine

Tesofensine is an inhibitor of noradrenaline, dopamine and serotonin reuptake [Table 1]. It is also acting indirectly by stimulating the cholinergic system. This compound was originally developed for treatment of Alzheimer's and Parkinson's diseases, but little efficacy was noted in clinical trials for these indications, persistent weight loss was evident.[10-12] In future, this drug may be available for the treatment of obesity.

Lorcaserin

Lorcaserin is a selective serotonin receptor ($5\text{-}HT_{2C}$) agonist that received the U.S. FDA approval in June 2012 for chronic weight management [Table 1]. The efficacy of this drug in reducing body weight and improving metabolic parameters of obese patients has been demonstrated in phase-3 clinical trials. The available evidence indicates that this drug does not show any heart valve abnormalities and the treatment improves the risk factors for type 2 diabetes and cardiovascular diseases. Nevertheless, the drug's manufacturer will be required to conduct

postmarketing studies, including a long-term cardiovascular outcomes trial to assess the effect of Lorcaserin on the risk for major adverse cardiac effects such as heart attack and stroke.[12,13]

Serotonergic agents

Serotonergic agents include fenfluramine, its dextrorotatory stereoisomer dexfenfluramine, fluoxetine and sertraline. These agents act by causing release or by inhibiting the reuptake of serotonin 5-HT and by stimulating hypothalamus 5-$HT_{1B/D}$ and 5-HT_{2C} receptors.[11,12] These drugs are presented with their mechanism and PK behavior in Table 1.

Unlike fenfluramine, which elicits the release of 5-HT, fluoxetine and sertraline are selective serotonin reuptake inhibitors (SSRIs) approved for the treatment of anxiety and depression. They are not approved as anti-obesity agents, but are used off-label. Their use in obesity has been reviewed recently.[12] SSRIs have been shown to induce weight loss via suppression of appetite;[13] they may also improve the insulin sensitivity.[14]

Fluoxetine

Fluoxetine selectively inhibits serotonin uptake *in vitro* and *in vivo*. It enhances serotonergic function, leading to a decrease in food intake in the beginning (with the first dose) and thus a decrease in body weight [Table 1]. Fluoxetine suppress stress-induced eating, selectively, suppress carbohydrate consumption and also suppress insulin-induced hyperphagia.[12,14-16] It is widely used clinically for the treatment of depression without being associated with pulmonary hypertension or cardiac valvular damage. A number of short-term clinical trial studies of fluoxetine treatment reported that it produced a dose-related decrease in body weight.[17,18]

Sertraline

Sertraline inhibits CNS neuronal reuptake of serotonin and also blocks $5HT_{1b}$ and $5HT_{2c}$ receptors [Table 1]. Sertraline is a SSRIs approved for the treatment of anxiety and depression.[14] Sertraline is not approved as anti-obesity agents, but is used off-label. Its use in obesity have been reviewed recently.[16] SSRIs have been shown to induce weight loss via suppression of appetite; they may also improve insulin sensitivity.[15,19-21]

Venlafaxine

It is a phenylethylamine derivative. Venlafaxine inhibits synaptosomal reuptake of both serotonin (5-HT) and noradrenaline (norepinephrine); the drug is a relatively weak inhibitor of dopamine reuptake [Table 1].[22,23] Its potency in inhibiting serotonin reuptake is approximately 5 times that of its noradrenaline reuptake inhibitory activity. Venlafaxine has no significant affinity for adrenergic, muscarinic cholinergic or histamine H_1 receptors. Venlafaxine found to be effective in obese women and binge eating disorder.[23,24]

Cannabinoids

Cannabinoid system is a crucial mechanism in the regulation of feeding and metabolism. It is involved in central and peripheral mechanisms regulating such behavior, interacting with many other signaling systems with a role in metabolic regulation [Table 1].[25] Anandamide cannabinoid agonist activates both the known cannabinoid receptors CB1 and CB2.[26] CB2 receptors are present peripherally is not involved in regulation of energy balance whereas CB1 receptors are predominantly localized in the brain, hypothalamus, neurons and astrocytes.[27] Cannabinoid agonists promote food intake and cannabinoid antagonist (CB1 receptor antagonist) rimonabant, block food intake and employed in the treatment of obesity. It not only causes weight loss, but also alleviates metabolic syndrome by changing the lipid and glucose metabolism, which is not observed with other anti-obesity drugs currently available.[28,29]

Neuropeptides (hormones)

The potential of the neuropeptide receptors as targets for anti-obesity drugs are greatly enhanced if the neuropeptide plays a physiological role in the regulation feeding. This class of drugs affects food intake when injected into the hypothalamus, a lateral brain ventricle, or the third ventricle [Table 2].[30] Peptide plays a role in feeding. Peptides that stimulate food intake called orexigenic peptides and those that decrease intake are denoted as anorectic peptides. It is easier to identify antagonists of peptide receptor than agonists. Some neuropeptides (e.g. NPY) alter both food intake and metabolic rate and the two effects synergies in their influence on body weight.[31,32] The leptins, (glucagons like peptide, oxyntomodulin and CCK. CCK derives from procholecystokinin which is closely related to progastrin), that gives rise to gastrin and delays gastric emptying time and thus increases satiety leads to weight reduction.

Pancreatic lipase inhibitors

This class of drugs is used for the weight control by the inhibition of lipase leading to decreasing the dietary fat absorption Table 2.

Orlistat (tetrahydrolipstatin)

It is a potent and specific inhibitor of intestinal lipases. The inhibition of lipases prevents the digestion of long-chain triglycerides, which reduces about 30% of the intestinal absorption of fats by inhibition of triglyceride hydrolysis.[33-36] In a double-blind placebo-controlled Orlistat act on the gut and is poorly absorbed into the

Table 2: Brief pharmacological profile of neuropeptides, pancreatic lipase inhibitors, combination therapies

Pharmacological class of drug	Name of the drug	Pharmacodynamic	Pharmacokinetic	Therapeutic use	Adverse reactions	Approval year	References
Neuropeptides	NPY	Inhibition of NPY synthesis by antisense oligodeoxy nucleotides or blockade of NPY action by NPY antibody	NPY1-36 rapidly breaking in serum into 3 main fragments with the following order of efficacy: NPY3-36, NPY3-35, >NPY2-36	Suppression of food intake	-	Under clinical studies	[30]
	Melanocortins	These are peptide analogue into the cerebrospinal fluid or into the ventromedial hypothalamusin nanomolar or subnanomolar doses induces a long-lasting inhibition of food intake	Not clear	Suppress appetite and increase energy expenditure	-	Under clinical studies	[31]
Leptins	Gulcogon like peptide	GLP-1 receptors modulates body weight	-	Effects on gastric emptying and on satiety	Gastrointestinal side effects, including nausea	Under clinical studies	[32,33]
	Orexines (A and B)	Stimulates glucose uptake in 3T3-L1 adipocytes		Increase energy expenditure			[34]
	Oxyntomodulin	An intestinal hormone which inhibits gastric acid secretion	-	Delay gastric emptying	-	Under clinical studies	[33,34]
	Cholecytokinin	Activated by the endogenous peptide cholecystokinin-4 and gastrin	-	Delay gastric emptying	-	Under clinical studies	[35]
	Orlistat	A reversible inhibitor of lipases	Oral absorption, 99% bound to plasma proteins, metabolism within the gastric intestinal wall, unabsorbed drug excreted in feces	Reduce fat absorption decrease body weight	Diarrhea, flatulence, bloating, abdominal pain and dyspepsia	1997-US-FDA 1998-EMEA	[36-38]
	Lipstatin	Irreversible active site inhibitor	Not clear still under clinical studies	Reduce fat absorption decrease body weight	Flatulence, bloating, abdominal pain and dyspepsia	-	[35,39]
Natural inhibitors of pancreatic lipase	Ebelactone-A	A direct inhibitor of lipases, affecting Interfacial quality	Not clear still under clinical studies	Decrease body weight	Headache, insomnia, irritability, palpitations, nervousness	-	[40]
(New Agent)	FL386	Inhibitor of lipases Natural constituent in Japanese diet	Not clear still under clinical studies	Treatment of obesity	-	Under clinical studies	[41-42]
	Caulerpenyne	Inhibitor of lipases Natural constituent in Japanese diet	Not clear still under clinical studies	Treatment of obesity	-	Under clinical studies	[41-42]
Leptin+long acting amylin analogue	Pramlintide+ metreleptin (Amylin)	GLP-1 receptors modulates body weight	-	Treatment of obesity	Gastro Intestinal side effects, including nausea	Phase-II	[5,40]

Contd...

Table 2: Contd...

Pharmacological class of drug	Name of the drug	Pharmacodynamic	Pharmacokinetic	Therapeutic use	Adverse reactions	Approval year	References
Opiate antagonist+ NA/DA reuptake inhibitor	Naltrexone+ bupropion (Contrave)	Lowering motility of GIT, neuronal uptake of norepinephrine and dopamine	-	Treatment of obesity	Nausea and headache, high dose can cause hepatotoxicity, dry mouth, agitation	Submitted to FDA approval	[5,43,55]
NA/DA releasing agent+ anticonvulsant	Phentermine+ topiramate (Qnexa)	Multiple mechanism	-	Treatment of obesity	Nausea, hepatotoxicity, dry mouth, agitation	FDA/ July-2012	[5,8,43,55]
Anticonvulsant+ DA/NA reuptake inhibitor	Zonisamide+ bupropion (Empatic)	Multiple mechanism	-	Treatment of obesity	Seizures, nausea, insomnia	Phase-II	[43,44]

USFDA: United states food and drug administration, EMEA: European medicine agency, GIT: Gastrointestinal tract, NPY: Neuropeptide-Y, GLP-1: Gulcogon like peptide, FDA: Food and drug administration

systemic circulation.[37] Orlistat was approved by United States Food and Drug Administration in the year 2007 for the long term management of obesity.[38] Orlistat is effective in combination with exercise, diet and behavioral changes, resulted in significant improvement in weight management in obese adolescents.[39-43] However, more clinical studies should be performed to determine its safety and efficacy.[44] Orlistat long-term use causes decrease in fat absorption results in a deficiency of the fat-soluble vitamins (vitamin A, D, E and K). The other lipase inhibitors like natural inhibitors of pancreatic lipase and some new agents are under clinical studies mentioned in the given Table 2 with detail emphasis on pharmacological action and relative adverse effects.

Thermogenic and energy expenditure drugs

Ephedrine and Caffeine or their combination is employed for the treatment of obesity for their thermogenic effect [Table 1]. It is generally accepted that ephedrine/caffeine mixtures are more effective than either agent alone[45-47] Ephedrine act, directly via release of noradrenaline from sympathetic nerve endings[47] stimulates β_3 receptors whereas caffeine (methylxanthines) act by inhibition of cyclic nucleotide phosphodiesterase and subsequent augmentation of cyclic adenosine monophosphate levels raised by ephedrine-induced receptor activation.[48] Liraglutide (a long term acting gulcogon like peptide [GLP-1] receptor agonist), alone or in combination with metreleptin is also employed for the treatment.[49]

Sibutramine, similar to that producing thermogenesis and show stimulation, this stimulation is due to a CNS activation of the sympathetic nervous system that richly innervates brown adipose tissue and a consequent stimulation of the β_3-adrenoceptors on brown adipocytes[50] Sibutramine was withdrawn in 2010 from the American and European market due to high risk of the cardiovascular system.[51]

Combination therapies for the treatment of obesity

The new agents are currently under investigation as single or in combination therapy, including 5HT/dopamine/noradrenalin reuptake inhibitor (testofensine) and polytherapies such as bupropion, a norepinephrine and dopamine reuptake inhibitors, with the opioid antagonist (naltrexone) or with an antiepileptic agent (zonisamide) that exerts dose-related biphasic dopaminergic and serotonergic activity. A new mechanism of action is also under investigation, targeting satiety signals emanating from the gut and adipose tissue, through the molecules like accented (a GLP-1 receptor agonist), pramlintide (analog of Amylin, released by B-cells of the pancreas).[52] These are given in the Table 2.

Drugs that reduces food intake

The control of food intake and body weight is modulated by multiple mechanisms. This may allow homeostatic responses to counter the effects of modulating any one of these mechanisms, amine neurotransmitter, like adrenaline/noradrenaline, dopamine serotonin, or amino acid neurotransmitter like γ-amino butyric acid receptors or the cannabinoid receptors and some peptides that decrease appetite or elicit a feeling of satiety.[53]

THE OTHER INTERVENTIONS AND TREATMENTS

Alternative medications (herbal system)

The use of modern medicine has become a popular means to overcome excess weight gain. Although these drugs generally are effective, exerts severe adverse toxicities may limit their overall usefulness. A nutritional based intervention is being hailed as an inexpensive alternative to aid weight loss and weight management.[54] Medicinal herbal supplements are being extensively utilized due to cost-effective

and exert less to no toxic side-effects in comparison with chemical synthesized drugs.[54] According to recent preliminary test reports suggests that herbs with a long history of remedial use with less severe toxicity might be effective in reducing appetite and promoting significant weight loss are encouraging.[56] Evidences are emerging to support that increasing consumption of herbs are effective strategies for obesity control and weight management. Usage of plants and plant products has potential to keep the increasing prevalence of metabolic syndrome in control.[57] The allopathic drugs, which are available in the market to prevent/manage obesity are expensive, but herbs are less cost-effective and possess more side-effects. For centuries people across the countries have been using natural products as plant based dietary supplements for weight control.[56]

Most supplements and alternatives have insufficient evidence to support or oppose its use. Non-prescription products for weight loss are heavily promoted by media, the popular products are pyruvate which is found in red apples, cheese and red wine, has not been scientifically studied.

Future perspective

The last 30 years have seen great increases in the incidence of obesity all over the world, but limited progress in the development of new anti-obesity drugs. The older agents have come under the scanner and increasing pressure from regulatory agencies, lead to withdrawal of sibutramine, fenfluramine and dexfenfluramine from the market. Fortunately, the future seems to offer more hope for rational drug design. For research scientists, there are now numerous molecular targets for anti-obesity drugs such as central receptors for biogenic amines, cannabinoids and hypothalamic neuropeptides; the peripheral β3-adrenoceptor, lipase inhibitors, lipid metabolism modulators, gut hormone, pancreatic hormone and uncoupling proteins; and dominating all obesity research is leptin Ð a tantalizing, but frustrating, obesity target. From among these mechanisms, where are new classes of anti-obesity drugs most likely to come? Since it has already shown efficacy in humans and is in Phase III clinical trials, topiramate, apparently acting through biogenic amines, is a front-runner. Some of these drugs (APD-365, CD-945,598, MK-0364, ATL-962, GT-389-255, AOD9604, Leptin, Peptide3-36, obinepitide and TM30338) in phase III clinical trial drugs may be future drug for treating obesity. The developmental pipeline for anti-obesity drugs is not empty and in the future, we will perhaps see even more compounds reaching approval, such as tesofensine, or bupropion in combination with either naltrexone or zonisamide.

CONCLUSION

Obesity treatment by pharmacological interventions reduces body weight and decreases the health risks factors associated with obesity. However, most of the anti-obesity drugs are found to possess major side-effects with such as palpitation, tremors, hyperactive reflexes, hypertensive crisis with adrenergic drugs, monoamine, serotonergic drugs. Drugs approved for treatment of obesity are only for a short term, whereas a long-term is needed. Several studies revealed that orlistat to be a promising agent in weight reduction. But most of the studies indicate fatty stool and decrease in absorption of fat soluble vitamin, which can be overcome by vitamin supplement. Recent discoveries found more targeted sites for satiety behavior and food intake. Based on this, there are many new drugs at different stages of clinical trials, which have been mentioned in this review. An anti-obesity drugs which are void of CNS and cardiovascular adverse events are more acceptable and tolerated. Hence we presume that Novel, more efficacious and better tolerated treatments for obesity may become available in the near future.

REFERENCES

1. Gray LJ, Cooper N, Dunkley A, Warren FC, Ara R, Abrams K, *et al*. A systematic review and mixed treatment comparison of pharmacological interventions for the treatment of obesity. Obes Rev 2012;13:483-98.
2. Fantasia HC. New developments in the pharmacologic treatment of obesity. Nurs Womens Health 2013;17:53-62.
3. Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, *et al*. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. Synapse 2001;39:32-41.
4. Chaput JP, St-Pierre S, Tremblay A. Currently available drugs for the treatment of obesity: Sibutramine and orlistat. Mini Rev Med Chem 2007;7:3-10.
5. Arch JR, Ainsworth AT, Cawthorne MA. Thermogenic and anorectic effects of ephedrine and congeners in mice and rats. Life Sci 1982;30:1817-26.
6. Goldstein DJ, Potvin JH. Long-term weight loss: The effect of pharmacologic agents. Am J Clin Nutr 1994;60:647-57.
7. Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, O'Neil PM. Bupropion SR enhances weight loss: A 48-week double-blind, placebo-controlled trial. Obes Res 2002;10:633-41.
8. Greenway FL, Dunayevich E, Tollefson G, Erickson J, Guttadauria M, Fujioka K, *et al*. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. J Clin Endocrinol Metab 2009;94:4898-906.
9. Zernig G, De Wit H, Telser S, Nienhusmeier M, Wakonigg G, Sturm K, *et al*. Subjective effects of slow-release bupropion versus caffeine as determined in a quasi-naturalistic setting. Pharmacology 2004;70:206-15.
10. Thatte U. NS-2330 (Neurosearch). Curr Opin Investig Drugs 2001;2:1592-4.
11. Astrup A, Madsbad S, Breum L, Jensen TJ, Kroustrup JP, Larsen TM. Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients:

A randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1906-13.
12. Kennett GA, Clifton PG. New approaches to the pharmacological treatment of obesity: Can they break through the efficacy barrier? Pharmacol Biochem Behav 2010;97:63-83.
13. Smith SR, Prosser WA, Donahue DJ, Morgan ME, Anderson CM, Shanahan WR, *et al*. Lorcaserin (APD356), a selective 5-HT (2C) agonist, reduces body weight in obese men and women. Obesity (Silver Spring) 2009;17:494-503.
14. Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs: Effects on appetite expression and use for the treatment of obesity. Drugs 2007;67:27-55.
15. Maheux, P, Ducros, F, Bourque J, Garon J, Chiasson JL. Fluoxitine improves insulin sensitivity in obese patients with noninsulin-dependent diabetes mellitus independently of weight loss. Int. J Obes 1997;21:97-102.
16. Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, *et al*. Meta-analysis: Pharmacologic treatment of obesity. Ann Intern Med 2005;142:532-46.
17. McGuirk J, Silverstone T. The effect of the 5-HT re-uptake inhibitor fluoxetine on food intake and body weight in healthy male subjects. Int J Obes 1990;14:361-72.
18. Lucki I, Kreider MS, Simansky KJ. Reduction of feeding behavior by the serotonin uptake inhibitor sertraline. Psychopharmacology (Berl) 1988;96:289-95.
19. Nielsen JA, Chapin DS, Johnson JL Jr, Torgersen LK. Sertraline, a serotonin-uptake inhibitor, reduces food intake and body weight in lean rats and genetically obese mice. Am J Clin Nutr 1992;55:185S-9.
20. Wadden TA, Bartlett SJ, Foster GD, Greenstein RA, Wingate BJ, Stunkard AJ, *et al*. Sertraline and relapse prevention training following treatment by very-low-calorie diet: A controlled clinical trial. Obes Res 1995;3:549-57.
21. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, *et al*. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters *in vitro* and *in vivo*, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology 2001;25:871-80.
22. Horst WD, Preskorn SH. Mechanisms of action and clinical characteristics of three atypical antidepressants: Venlafaxine, nefazodone, bupropion. J Affect Disord 1998;51:237-54.
23. Malhotra S, King KH, Welge JA, Brusman-Lovins L, McElroy SL. Venlafaxine treatment of binge-eating disorder associated with obesity: A series of 35 patients. J Clin Psychiatry 2002;63:802-6.
24. Arias Horcajadas F. Cannabinoids in eating disorders and obesity. Mol Neurobiol 2007;36:113-28.
25. Rinaldi-Carmona M, Calandra B, Shire D, Bouaboula M, Oustric D, Barth F, *et al*. Characterization of two cloned human CB1 cannabinoid receptor isoforms. J Pharmacol Exp Ther 1996;278:871-8.
26. Guzman M, Sanchez C. Effects of cannabinoids on energy metabolism. Life Sci 1999;65; 657-64).
27. Doggrell SA. Is rimonabant efficacious and safe in the treatment of obesity? Expert Opin Pharmacother 2008;9:2727-31.
28. Christopoulou FD, Kiortsis DN. An overview of the metabolic effects of rimonabant in randomized controlled trials: Potential for other cannabinoid 1 receptor blockers in obesity. J Clin Pharm Ther 2011;36:10-8
29. Beck B. Neuropeptide Y in normal eating and in genetic and dietary-induced obesity. Philos Trans R Soc Lond B Biol Sci 2006;361:1159-85.
30. Kalra SP, Horvath TL. Neuroendocrine interactions between galanin, opioids, and neuropeptide Y in the control of reproduction and appetite. Ann N Y Acad Sci 1998;863:236-40.
31. Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. Endocr Rev 1999;20:68-100.
32. Drent ML, van der Veen EA. Lipase inhibition: A novel concept in the treatment of obesity. Int J Obes Relat Metab Disord 1993;17:241-4.
33. Liu YL, Ford HE, Druce MR, Minnion JS, Field BC, Shillito JC, *et al*. Subcutaneous oxyntomodulin analogue administration reduces body weight in lean and obese rodents. Int J Obes (Lond) 2010;34:1715-25.
34. Li J, Ma W, Wang S. Slower gastric emptying in high-fat diet induced obese rats is associated with attenuated plasma ghrelin and elevated plasma leptin and cholecystokinin concentrations. Regul Pept 2011;171:53-7.
35. Guerciolini R. Mode of action of orlistat. Int J Obes Relat Metab Disord 1997;21 Suppl 3:S12-23.
36. Zhi J, Melia AT, Eggers H, Joly R, Patel IH. Review of limited systemic absorption of orlistat, a lipase inhibitor, in healthy human volunteers. J Clin Pharmacol 1995;35:1103-8.
37. US Food and Drug Administration. FDA approves orlistat for obesity. [Press Announcement]. Available from: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01557.html. [Last accessed on 2007 Feb 07].
38. de la Garza AL, Milagro FI, Boque N, Campión J, Martínez JA. Natural inhibitors of pancreatic lipase as new players in obesity treatment. Planta Med 2011;77:773-85.
39. Day JW, Ottaway N, Patterson JT, Gelfanov V, Smiley D, Gidda J, *et al*. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. Nat Chem Biol 2009;5:749-57.
40. Amin KA, Nagy MA. Effect of Carnitine and herbal mixture extract on obesity induced by high fat diet in rats. Diabetol Metab Syndr 2009;1:17.
41. Cooke D, Bloom S. The obesity pipeline: Current strategies in the development of anti-obesity drugs. Nat Rev Drug Discov 2006;5:919-31.
42. Carter R, Mouralidarane A, Ray S, Soeda J, Oben J. Recent advancements in drug treatment of obesity. Clin Med 2012;12:456-60.
43. Filippatos TD, Derdemezis CS, Gazi IF, Nakou ES, Mikhailidis DP, Elisaf MS. Orlistat-associated adverse effects and drug interactions: A critical review. Drug Saf 2008;31:53-65.
44. Astrup A, Toubro S, Cannon S, Hein P, Madsen J. Thermogenic synergism between ephedrine and caffeine in healthy volunteers: A double-blind, placebo-controlled study. Metabolism 1991;40:323-9.
45. Astrup A, Breum L, Toubro S, Hein P, Quaade F. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial. Int J Obes Relat Metab Disord 1992;16:269-77.
46. Astrup A, Breum L, Toubro S. Pharmacological and clinical studies of ephedrine and other thermogenic agonists. Obes Res 1995;3 Suppl 4:537S-40.
47. Liu YL, Toubro S, Astrup A, Stock MJ. Contribution of beta 3-adrenoceptor activation to ephedrine-induced thermogenesis in humans. Int J Obes Relat Metab Disord 1995;19:678-85.
48. McGavigan AK, Murphy KG. Gut hormones: The future of obesity treatment? Br J Clin Pharmacol 2012;74:911-9.
49. Arterburn DE, Crane PK, Veenstra DL. The efficacy and safety of sibutramine for weight loss: A systematic review. Arch Intern Med 2004;164:994-1003.
50. Li MF, Cheung BM. Rise and fall of anti-obesity drugs. World J Diabetes 2011;2:19-23.
51. Li M, Cheung BM. Pharmacotherapy for obesity. Br J Clin Pharmacol 2009;68:804-10.
52. Gadde KM, Franciscy DM, Wagner HR 2nd, Krishnan KR. Zonisamide for weight loss in obese adults: A randomized controlled trial. JAMA 2003;289:1820-5.

53. Carek PJ, Dickerson LM. Current concepts in the pharmacological management of obesity. Drugs 1999;57:883-904.
54. Rueda-Clausen CF, Padwal RS, Sharma AM. New pharmacological approaches for obesity management. Nat Rev Endocrinol 2013;9:467-78
55. Yun JW. Possible anti-obesity therapeutics from nature: A review. Phytochemistry 2010;71:1625-41.
56. Mayer LE, Walsh BT. The use of selective serotonin re-uptake inhibitors in eating disorders. J Clin Psychiatry 1998;59 Suppl 15:28-34.
57. Najm W, Lie D. Herbals used for diabetes, obesity, and metabolic syndrome. Prim Care 2010;37:237-54.

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