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A Review on Recent Advances in Drug Development and Pharmacotherapeutic Approaches for Obesity

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Abstract
Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. A crude population measure of obesity is the body mass index (BMI) . A person with a BMI of 30 or more is generally considered obese. A person with a BMI equal to or more than 25 is considered overweight.
Obesity is a well-established risk factor for hypertension, hyperlipidemia, type II diabetes, coronary heart disease, stroke, obstructive sleep apnea, asthma, orthopedic disorders, and certain cancers. Despite this risk, the prevalence of obesity continues to increase worldwide, and there is a growing demand for safe and effective antiobesity drugs. Previous antiobesity drugs or anorexigens, particularly centrally acting agents, have poor safety records. Life-threatening safety issues led to the withdrawal of aminorex in 1968, fenfluramine and dexfenfluramine in 1997, and phenyl propanolamine in 2000. Many of the safety issues, such as valvulopathy with fenfluramine and pulmonary arterial hypertension with aminorex, were initially not predicted by routine preclinical toxicology studies. . Meridian(Sibutramine) was approved by FDA in 1987,Xenical (orlistat) was approved by FDA in 1999, Recently Qsymia (phentermine & topiramate), Belviq(lorcaserin) was approved by FDA in 2012. This review covers the current state of antiobesity drugs and their safety concerns, and highlights new therapeutic targets and also highlights the threats associated with the surgical treatment of obesity as how liposuction surgery recently claim life of JNTU assistant professor.

INTRODUCTION

DEFINATION: In clinical practice, body fat is most commonly and simply estimated by using a formula that combines weight and height. The underlying assumption is that most variation in

Weight for persons of the same height is due to fat mass, and the formula most frequently used in epidemiological studies is body-mass index (BMI).Obesity is associated with a wide range of metabolic and cardiovascular conditions that substantially increase the risk of stroke, coronary heart disease and myocardial infarction. The combination of widespread consumption of the energy-dense Western diet with an increasingly sedentary lifestyle has increased the global prevalence of obesity and the associated causes of mortality and morbidity. The WHO reported that in 2008, 500 million adults were obese globally, which is expected to rise to 700 million by 2015.

Approximately two-thirds of US adults are overweight or obese and the obesity rate in English men increased from 13.2% in 1993 to 23.1% in 2005 and in English women from 16.4 to 24.8% during the same period. Diet and exercise remain the most commonly prescribed strategies for weight loss, but have proved unsuccessful for many affected individuals. Therefore, industrial interest in the development of effective pharmacological therapies has been sustained. The rising prevalence of obesity is a worldwide problem affecting not only the developed world but also developing nations such as South Africa. Excess body fat deposition is caused by an imbalance between energy intake and energy expenditure and there are many genetic and environmental factors that can influence this balance.

The present article will describe these factors and discuss the complex interaction between the environment and the human genome that may underlie the current obesity epidemic.

A famous ancient proverb states: eat breakfast like a king, lunch like an ordinary person, and your dinner like a beggar. These words of wisdom have long been discarded. Modern life has brought with it more food with high caloric density and better taste. New technology has made life easier and less active, and the result is a worldwide epidemic of obesity and its associated disorders. Obesity involves both increased fat cell size and occurs when energy intake is greater than energy expenditure.

This balance between energy input and energy output can be affected by many factors including the quality and quantity of dietary intake, environmental and genetic inputs and physiological and psychological status.

The prevalence of obesity in male and female adolescents and adults in different South African ethnic groups

ETHINIC GROUP	Age:13-19yrs		Age: 15-95yrs	
	Male	Female	Male	Female
African	1.9	5.3	7.7	30.5
European	4.8	7.7	19.8	24.3
Coloured	2.8	3.8	9.1	28.3
Indian	---	---	8.7	20.2

Data given as % values. *Data taken from reference number 6; **data taken from reference number 4

EPIDEMIOLOGY

Calorie Intake

Food intake can be affected by many factors, including the price, portion size, taste, variety, and accessibility of foods. The method by which the food is prepared is also important. There are also strong cultural influences on the types of food consumed with some societies abstaining from particular types of food or only eating food if it has been prepared in a specific manner.

A high fat diet enriched with saturated fatty acids is the common diet in developed countries whilst in poorer countries the majority of people derive their calories from a vegetarian diet.

Diet may affect body weight by controlling satiety and metabolic efficiency, or by modulating insulin secretion and action. Thus, the calorie dense diet common in the western world may predispose to obesity via elevated postprandial insulin levels resulting from the high carbohydrate intake which leads to increased triglyceride storage in the adipose tissue depots. High insulin levels may also provoke a vicious metabolic cycle.

Insulin induces hunger by depleting the glucose levels of the blood, and this promotes further food intake which leads to greater insulin secretion. Ultimately, this cycle will lead to weight gain and chronic hyperinsulinaemia. It has also been observed that obese subjects have an increased preference for fatty foods13 which will also enhance insulin output and triglyceride storage.

Genetic factors

Genetic factors may act as determinants of BMI by affecting energy balance. More than 300 genes, markers, and chromosomal regions have been found to be associated with various human obesity phenotypes and it has been estimated that 30–70% of the variance in BMI in humans can be explained by genetic factors. The first monogenic human obesity syndrome, congenital leptin deficiency was reported in 1997.The discovery of the leptin gene has dramatically changed our understanding of the role that adipose tissue plays in the regulation of energy balance and appetite .

Leptin acts within the arcuate nucleus of the hypothalamus to decrease the expression of orexigenic signals and increase the levels of anorexigenic signals and thus reduce food intake. A number of other forms of monogenic obesity have been discovered and each of the affected genes has been shown to be expressed in the hypothalamus and to play a part in the control of appetite. However, these gene mutations explain only a very small proportion of cases of human obesity.

The common form of obesity is a polygenic disease and it is thought that each of the polymorphisms involved contributes in only a small way to the phenotype and this may explain why it has been very difficult to unravel the genetic etiology of human obesity. However, recent advances in gene screening techniques have allowed geneticists to perform high throughput, whole genome analyses and uncover a number of new gene loci that may play a part in causing increased adipose tissue deposition.

Most of these genes are thought to be expressed in the CNS and to be involved in controlling food intake. The genetic variant with the strongest association to the polygenic form of obesity lies close to the FTO (fat mass and obesity associated) gene. This association has been confirmed in a number of large population studies, however the exact function of the FTO gene remains a mystery although expression studies have demonstrated that this gene is expressed in a wide range of tissues with high expression in the brain.

Obesity as a medical problem

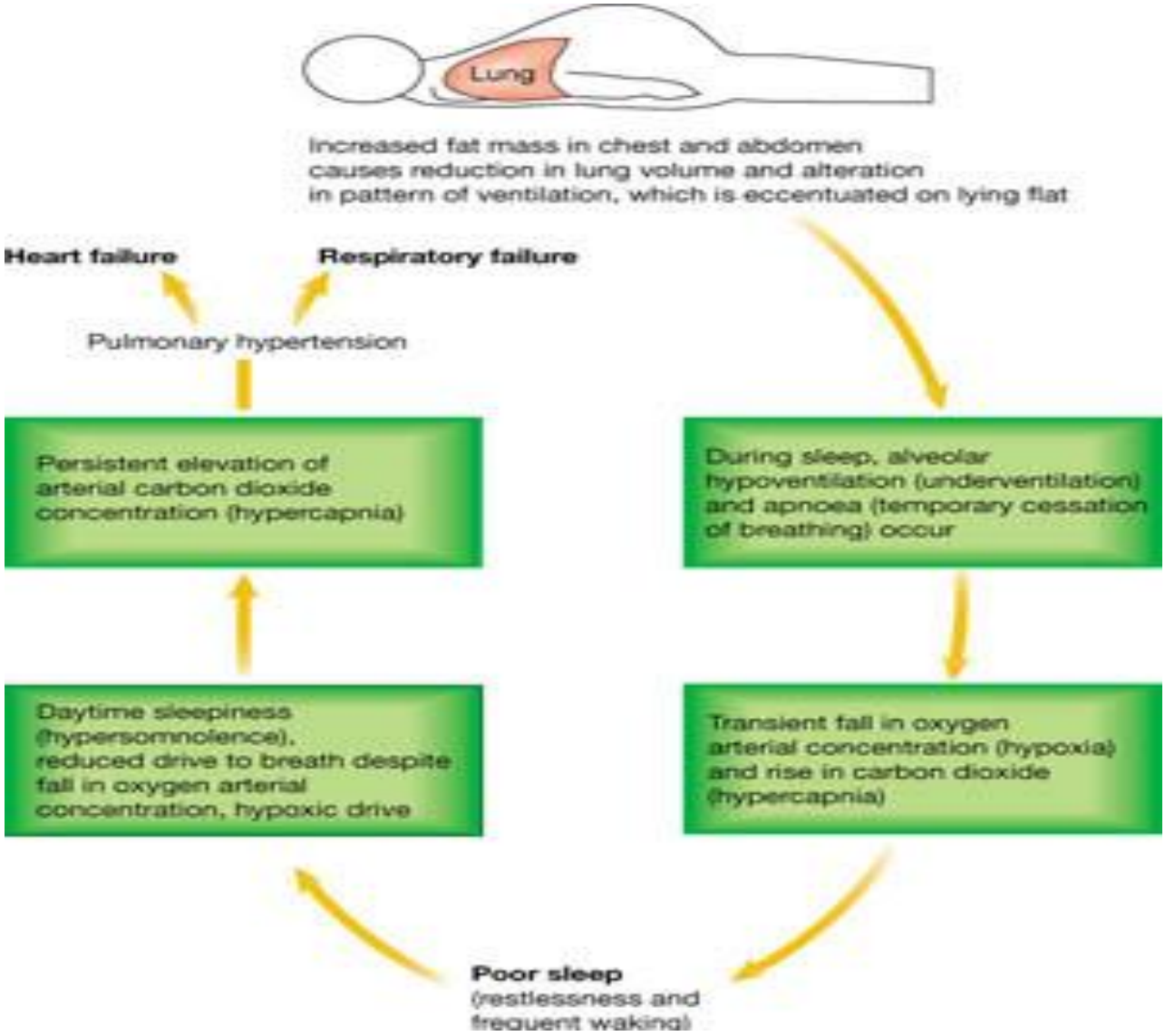
Increasing body fatness is accompanied by profound changes in physiological function. These changes are, to a certain extent, dependent on the regional distribution of adipose tissue. Generalized obesity results in alterations in total blood volume and cardiac function, whereas the distribution of fat around the thoracic cage and abdomen restricts respiratory excursion and alters respiratory function. The intra-abdominal visceral deposition of adipose tissue, which characterizes upper body obesity, is a major contributor to the development of hypertension, elevated plasma

insulin concentrations and insulin resistance, diabetes mellitus and hyperlipidaemia.

Obesity and type 2 diabetes mellitus

Obesity is characterized by elevated fasting plasma insulin and an exaggerated insulin response to an oral glucose load. Overall fatness and the distribution of body fat influence glucose metabolism through independent but additive mechanisms. Increasing upper body obesity is accompanied by a progressive increase in the glucose and insulin response to an oral glucose challenge with a positive correlation being observed between increasing upper body obesity and measures of insulin resistance. Post-hepatic insulin delivery is increased in upper body obesity leading to more marked peripheral insulin concentrations that, inturn, lead to peripheral insulin resistance .Different fat depots vary in their responsiveness to hormones that regulate lipolysis and this also varies according to fat distribution.In both men and women, the lipolytic response to noradrenaline is more marked in abdominal than gluteal or femoral adipose tissue. Cortisol may also contribute to this enhanced lipolysis by further inhibiting the antilipolytic effect of insulin. These factors contribute to an exaggerated release of free fatty acids (FFAs) from abdominal adipocytes into the portal system. FFAs have a deleterious effect on insulin uptake by the liver and contribute to the increased hepatic gluconeogenesis and hepatic glucose release observed in upper body obesity. Insulin insensitivity is confined not only to adipocytes — the process being accentuated by insulin resistance of skeletal muscle.The elevation in plasma FFA concentration, particularly postprandially when they are usually suppressed by insulin, leads to an inappropriate maintenance of glucose production and an impairment of hepatic glucose utilization (impaired glucose tolerance).

SLEEP-BREATHING ABNORMALITIES IN OBESITY



An increased amount of fat in the chest wall and abdomen has a predictable effect on the mechanical properties of the chest and the diaphragm and leads to an alteration of respiratory excursions during inspiration and expiration, reducing lung volume and altering the pattern of ventilation to each region. In addition, the increased mass of fat leads to a decrease in compliance of the respiratory system as a whole. All of these changes are significantly exaggerated when an obese person lies flat. The mass loading effect of fat requires an increased respiratory muscle force to overcome the excessive elastic recoil and an associated increase in the elastic work of breathing. The obesity-related changes in respiratory function are most important during sleep62,63 .

During rapid eye movement (REM) sleep, there are decreases in voluntary muscle tone with reduced arterial oxygen saturation and a rise in carbon dioxide. These changes affect all individuals but are especially marked in obese subjects. Irregular respiration and occasional apnoeic episodes often occur in lean people during

REM sleep, but obesity, with its influence on respiratory mechanics, increases their frequency and may result in severe hypoxia with resultant cardiac arrhythmias. Studies of obese men and women have demonstrated that the obstruction occurs in the larynx and is associated with loss of tone of the muscles controlling tongue movement. Relaxation of the genioglossus muscle allows the base of the tongue tofall back against the posterior pharyngeal wall occluding the pharynx. This results in a temporary cessation of breathing (apnoea) and associated transient fall in arterial oxygen saturation concentration (hypoxia). It is not uncommon to observe low oxygen saturation values during REM sleep in some obese men while their awake arterial gases are normal64. By contrast, premenopausal obese women show relatively minor alterations during sleep with a decrease in arterial oxygen saturation of less than 7% without apnoea. After the menopause, the changes seen in obese women become more marked with the reduction in oxygen saturation during sleep being >7% and being accompanied by apnoeic episodes.

A minority of obese patients develop a situation characterized by amarked depression in both carbon dioxide (hypercapnic) and hypoxic respiratory drives, accompanied by abnormal and irregular pattern of breathing during sleep and (eventually) in the waking state. Characteristically, such individuals show frequent and prolonged episodes of sleep apnoea: sleep is disturbed with frequent awakening related to the resumption of breathing after an apnoeic episode. Daytime somnolence soon intervenes and is accompanied by persistent hypoxia/hypercapnia, pulmonary hypertension (superimposed upon an increased circulatory volume) and rightsided cardiac failure. Such changes constitute the clinical manifestation of the obesity–hypoventilation syndrome (formerly known as the Pickwickian syndrome).

Herbs Recommended for Obesity

Evidences are emerging to support that an increasing consumption of herbs are effective strategy for obesity control and weight management. Usage of plants and plant products has potential to keep the increasing preva-lence of metabolic syndrome in control. There are few drugs in the market to prevent/manage obesity but there are the costs, efficacy and side effects to consider. For centuries people across the countries have been using natural products as plant based dietary supplements for weight control. Here are some examples.

List of herbs indicated for obesity in *ayurveda* text books. Botanical name	Sanskrit/official name	Part(s) used
Acacia arabica	Babbula	Gum, bark, leaf, fruit-pods
Acacia catechu	Khadira	bark, heartwood, flower
Achyranthus aspera	Apamarga	Root, seed, leaf, whole plant
Aconitum heterophyllum	Ativisha	Root, rhizome
Acorus calamus	Vacha	Rhizome
Adathoda vasica	Vasa	Leaf, root, flower
Aloe vera	Kumari	Leaf, root
Alstonia scholaris	Saptaparna	Bark, latex, flower
Ananas comosus	Ananas	Fruit
Anthocephalus chinensis	Kadamba	Bark, leaf, fruit, root
Azadirachta indica	Nimba	All parts
Berberis aristata	Daruharidra	Root, stem, fruit
Betula utilis	Burja	Bark, nodes

The Probable Reasons for Obese Person to Prefer Herbal Products for Weight Management

1) Health benefits of weight loss without any side ef-fects.

2) Less demanding than accepted lifestyle changes, such as exercise and diet.

3) Easily available without a prescription.

4) More easily accepted than a professional consulta-tion with a physician or a nutritionist.

5) 100% natural origin and perception that natural means safe

Remarks on Available Information about Herbal Treatment for Obesity

For many of the herbal weight loss products, there is lit-tle published information and there have been no clinical trials or the level of evidence is limited. Some of the herbal products fall under an acceptable level of evidence viz., clinical trials and with no scientific background or scientific rational.

compiles available clinical trial literature on various herbal products which have weight reducing ef-fects. Few of the products, which underwent clinical trial, have significant weight

reduction as an overall result. The other products have shown comparatively good re-sults in pre clinical studies but lack clinical studies. There are several products in the market claimed to have remarkable weight reducing effects, however there is no supporting published pre clinical and clinical data evi-dences.

THERAPEUTIC APPROACH TOWARDS OBESITY

- A successful weight-loss drug should reduce energy intake and/or increase energy expenditure without adverse side effects. Which aspect of energy balance could best be targeted by drugs? Most energy expenditure is due to the basal metabolic rate (BMR). Drugs that target the BMR, such as dinitrophenol and thyroid hormone, successfully reduce body weight but are associated with serious side effects.Drugs that target the BMR, such as dinitrophenol and thyroid hormone, successfully reduce body weight but are associated with serious side effects . Energy expenditure does not fluctuate extensively during the day, except when performing physical exercise. By contrast, energy intake is highly variable during the day . Thus, drugs that target energy intake, such as phentermine and sibutramine, act on the more dynamic part of the energy balance equation. Initiation of energy intake is triggered by habits (e.g., eating three times a day), by different types of internal and external cues that trigger (palatable) food intake, and by social pressure (e.g.,to participate in the consumption of a snack or a high-calorie drink).
- In the 19th century, preparations containing thyroid hormone were used as anti-obesity drugs . Thyroid hormone increases the BMR and thus increases energy expenditure. Side effects include symptoms of hyperthyroidism, such as restlessness and sleep problems, as well as increased risk of heart failure.Another drug that increases energy expenditure, dinitrophenol, was used to lose weight a century ago. It uncouples oxidative phosphorylation from the generation of ATP in mitochondria, so that heat rather than ATP is generated. It was a successful weight loss drug, but overheating was a risk, which resulted in deaths. Both treatments demonstrate the efficacy of drugs to lose weight by increasing BMR.
- Amphetamines are sympaticomimetics that reduce feeding and increase locomotor activity. Amphetamines have been successfully used as weight-loss drugs since the 1930s, but were abandoned because of their cardiovascular side effects and addictive properties,although phentermine is still prescribed for the first weeks duringweight loss programs. As a monotherapy, phentermine is one of the safer amphetamines and results in bodyweight loss of 3–4 kg more than for placebo after 3-month treatment .

Phentermine was combined with fenfluramine in FenPhen, a popular weight-loss drug 20 years ago with efficacy of up to 10% bodyweight loss. This successful drug was abandoned because it often induced pulmonary Hypertension.

- Sibutramine a noradrenalin and serotonin reuptake inhibitor, was introduced in the late 1990s as a weight-loss drug . Although on average it leads to bodyweight loss of 4–5 kg over 1 year, it was withdrawn in 2010 because of cardiovascular side effects,which resulted in increased heart attacks and strokes.

- **FDA APPROVED DRUGS**

Thyroid hormone preparations used to lose weight

Dinitrophenol causes weight loss by generating heat

First amphetamines introduced

FDA approval of sibutramine.

Off label use of combination of fenfluramine and phentermine (fen-pen)

FDA approval of sibutramine.

FDA approval of orlistat

2006

EMA approval of rimonabant.

2012

FDA approval of lorcaserin and qsymia

MECHANISM OF ANTI-OBESITY DRUGS

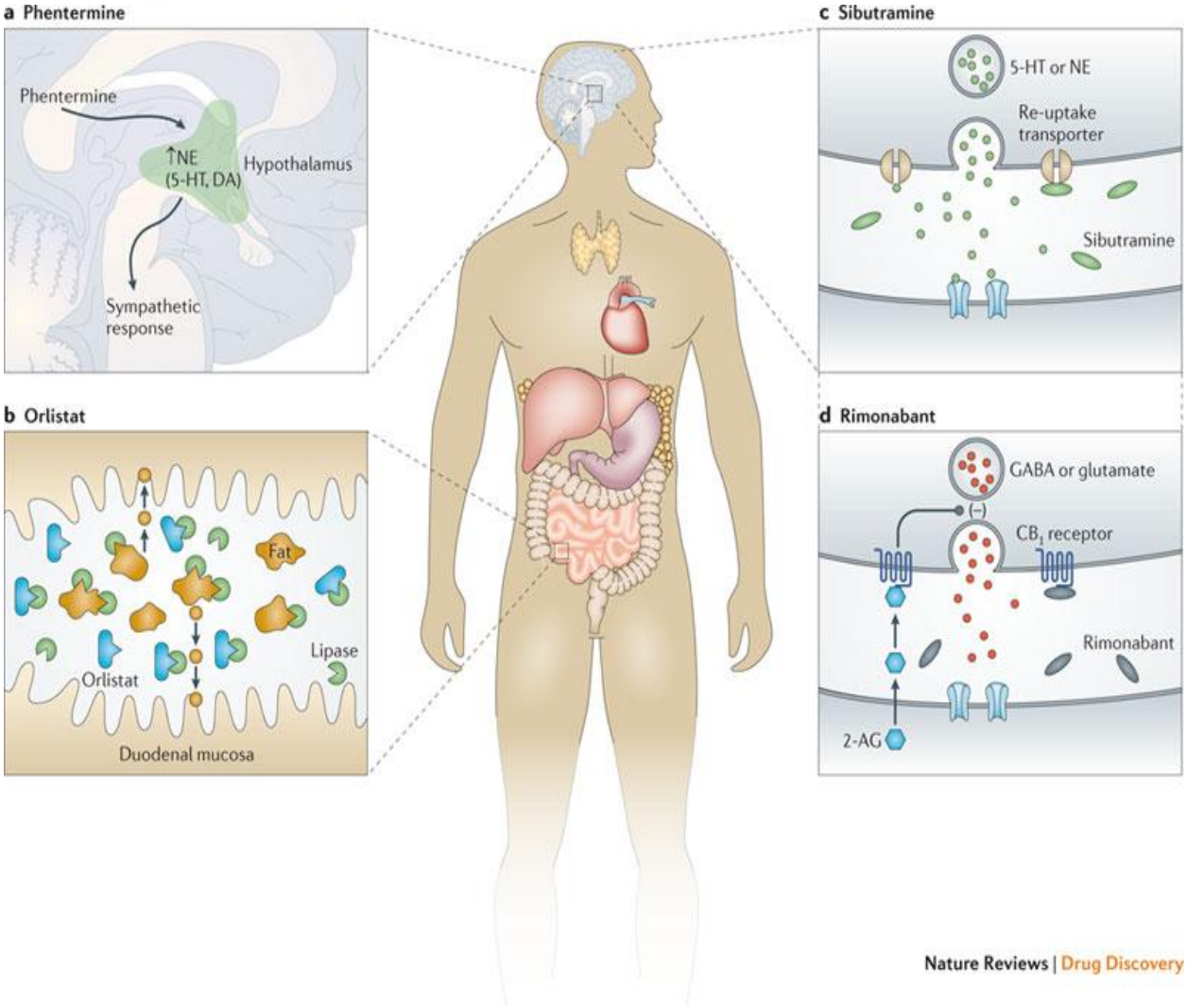


Table 1. Drugs With US Food and Drug Administration-Approved Indication for Obesity

Generic Drug (Proprietary Name[s] Dose Frequency/d)	Mechanism of Action	Wholesale Price/mo, $[a]	1-y Weight Change Relative to Placebo, Mean (95% CI), kg[b]	Common Adverse Effects
Short-term approval[c]				
Phentermine 15-37.5 mg (Adipex-P, Fastin, Oby-Cap, Ionamin, Others; 1×)[d]	Noradrenergic causing appetite suppression	6-45	Not included	Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, and restlessness[e]
Diethylpropion 25 mg or 75 mg, SR (Tenuate, Tenuate Dospan, Tepanil; low dose, 3×; SR dose, 1×)[d]	Noradrenergic causing appetite suppression	47-120	Not included	Same as phentermine[e]
Phendimetrazine 17.5-70 mg or 105 mg, SR (Bontril; lower doses, 2-3×; SR dose, 1×)[f]	Noradrenergic causing appetite suppression	6-20	Not included	Same as phentermine[e]
Benzphetamine 25-50 mg (Didrex; 1-3×)[f]	Noradrenergic causing appetite suppression	20-50	Not included	Same as phentermine[e]
Long-term approval[c]				
Orlistat 60 mg (Alli) or 120 mg (Xenical; 3× within 1 h of a fat-containing meal)[g]	Lipase inhibitor causing excretion of approximately 30% of ingested triglycerides in stool	60 mg, 45 120 mg, 207	60 mg, −2.5 kg (−1.5 to −3.5) 120 mg, −3.4 kg (−3.2 to −3.6)	Oily spotting, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence[h]
Lorcaserin 10 mg (Belviq; 2×)[d]	Highly selective serotonergic 5-HT2C receptor agonist causing appetite suppression	240	−3.2 kg (−2.7 to −3.8)	Headache, dizziness, fatigue, nausea, dry mouth, cough, and constipation; and in patients with type 2 diabetes, back pain, cough, and hypoglycemia[h]
Phentermine plus topiramate-ER (Qsymia; 3.75 mg/23 mg for 2 weeks, increased to 7.5 mg/46 mg, escalating to a max of 15 mg/92 mg; 1×)[d]	Noradrenergic + GABA-receptor activator, kainite /AMPA glutamate receptor inhibitor causing appetite suppression	140-195	7.5 mg/46 mg, −6.7 kg (−5.9 to −7.5) 15 mg/92 mg, −8.9 kg (−8.3 to −9.4)	Paresthesias dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes[h]

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ER, extended release; GABA, γ-aminobutyric acid.

[a] Reference prices[9] as of March 8, 2013.

[b] Weight change data are relative to placebo using intent-to-treat analyses for each medication at 1 year. No studies for older noradrenergic agents met inclusion criteria for length of treatment, sample size, and attrition.

[c] Food and Drug Administration–approved for short-term (ie, a few weeks) or long-term use.

[d] Medications listed on Drug Enforcement Administration Schedule IV are associated with a lower risk of abuse than medications on Schedule III.

[e] Common adverse events for noradrenergic agents include those listed as common in Prescription Medications for the Treatment of Obesity[10] because adverse event frequency is not available in drug package inserts for these agents.

[f] Drug Enforcement Administration Schedule III medication.

[g] Orlistat is a non-Drug Enforcement Administration–scheduled drug.

[h] For orlistat, lorcaserin, and phentermine plus topiramate-ER, common adverse events are those listed in the drug package inserts[11-13] that are reported to occur more frequently than placebo and with more than 5% prevalence. See full prescribing information for all adverse effects, cautions, and contraindications.

FUTURE PROSPECTS

It is noticeable, working in east London, how the current generation of teenage Asians is much taller and more sturdily built compared with their parents. This observation is explained largely by improved nutrition. In contrast, Asian parents are becoming obese, a situation not seen 10 years ago, and are paying a serious medical penalty as a

consequence. This change in population anthropometry is not restricted to east London or to a particular ethnic group, but reflects a major global shift in body size. A sudden disproportionate rise in the number of people who are seriously obese is observed as the mean weight of a population rises69; a situation now faced by mostdeveloped and many developing nations.

The accompanying reviews in this *Nature* Insight on Obesity confirm the identity of several genes involved in the development of obesity in animal models and describe central neural pathways concerned in the regulation of energy balance. Such genes and neural pathways are likely to be important in the genesis of human obesity but they should not detract from the importance of environmental factors — the epidemic of obesity witnessed during the past 20 years has emerged from a relatively constant genetic pool. For the future, priority must be given for achieving a better understanding of susceptible genotypes for obesity and identifying different obese phenotypes.

The latter should enable particular treatments to be targeted at appropriate individuals who are at specific medical risk.The identification of major and minor genes involved in the aetiology and pathogenesis of obesity remains critically important for the immediate future. Nevertheless, the development and implementation of effective programmes that successfully encourage increased physical activity and healthy eating across populations remain paramount for the prevention of obesity and its associated diseases — this will require the active engagement of individuals and their governments.

CONCLUSIONS

Since the removal of drugs such as sibutramine and rimonabant from the market, the introduction of Qsymia and lorcaserin brings a new perspective for the pharmacological treatment of obesity. These drugs pave the road for the introduction of other anti-obesity drugs in the pipeline such as Contrave and Empatic. Because animal models have remarkably good predictive validity for the clinical efficacy of anti-obesity drugs, more drug candidates are likely to reach clinical testing in the near future.

Many of these novel drugs target multiple pathways involved in the regulation of energy balance. This reflects the redundancy in pathways involved in this important and fundamental physiological process. In addition, there is large variability in drug response, which may originate from individual differences in the cause of obesity and the difficulty in sustaining lifestyle changes. For the treatment of obesity, a personalized medicine approach in which the right drug is combined with personal lifestyle advice is expected to be more successful than one treatment for all. Now that multiple anti-obesity drugs are available, this has become feasible.

Pharmacological interventions in addition to lifestyle changes (diet and physical activity) and in some cases behavioural modifications are used to promote weight loss.At present, only two drugs

are currently approved and available for the long-term treatment of obesity—orlistat and sibutramine. However, there are several drugs and combination drug therapies undergoing Phase III trials that may be approved in the next few years. Pharmacotherapies have demonstrated a significant though modest decrease in weight compared to placebo over 1-2 years.

Unfortunately weight loss following pharmacological intervention is not sustained when therapy is discontinued with individuals regaining some or all of the weight that was originally lost. Obesity is often considered a chronic disease, hence it requires long-term therapy. Currently, there is a lack of high quality evidence from long-term studies of both the efficacy and safety of pharmacological interventions for obesity.

Serious safety concerns have resulted in thewithdrawal of some drugs that had originally received market approval whilst other drugs have been abandoned during Phase III evaluation. The maintenance of a large number of genetic variants within the genome that give rise to increased adipose tissue mass may be explained by the process of natural selection. It has been hypothesised that during human evolution there was selection for any genotype that favours energy storage because this would enhance survival during periods of famine. Famine is known to be an important and consistent occurrence during the evolution of the human species. However, this genotype is only advantageous under conditions of food scarcity and is deleterious in conditions where food availability is high and energy expenditure is low i.e. the prevailing environment! Thus, obesity is the result of an unfavourable interaction between our current environment and our ancient genome.

The process of natural selection is not fast enough to modify our genome in response to rapid changes in environmental conditions. This genomic inertia has led to many mass extinction events during the life course of planet Earth. The only solution to the problem of the obesity epidemic is therefore a rapid change in environmental conditions to better match our present genetic make-up. Such changes must occur at the individual level and be encouraged by changes at the population level. However, societal inertia is a major stumbling block and it is therefore possible that the ultimate demise of the human species will be the result of a clash between a highly evolved genome, sculpted by millennia of fine.

There are several plants described in *ayurveda* for weight management. But so far, no systematic and well designed screening is attempted to come up with an effective herbal weight loss product. A better understanding in the existing evidence based science on herbs will further guide a qualitative research in obesity management that will attract the end users by the effective benefits. True randomized, double blinded, placebo-controlled clinical trials using herbal products will demonstrate their poten-tial benefits. Significant weight loss after placebo sub-traction along with known mechanism of action is re-quired in order to generate conviction amongst users as effective agent for weight management.

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