Pharmacotherapy for Weight Management

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Abstract

Weight management means lifestyle modification, behavioral therapy, pharmacotherapy and surgery. Drugs have wide ranging side effects and contraindication for its widespread use. Orlistat and sibutramine are the most popular in the present day context. Anti depressants especially fluoxetine is a valuable adjunct for therapy of obesity. There are many newer concepts in weight management and these are mainly hormonal and receptor based, thereby reducing the uncalled adverse effects of drugs like orlistat and sibutramine. Anti-obesity vaccine, an immunotherapy to be looked out for.

Introduction

Definition

Obesity is a chronic disease characterized by excessive body weight and unhealthy distribution of fat that pre-disposes to various diseases and leads to increased mortality and morbidity. It is a combination of excessive calorie intake, inadequate exercise along with medical and genetic predisposition. It is one of leading public health problems affecting children and adults especially in developed countries. A leading non-communicable disease considered as a potential threat in reducing life expectancy by predisposing an individual to coronary vascular disease, diabetes, infertility, arthritis etc.

Schematic Illustration of consequence of obesity (Table 1)

Obesity is a chronic metabolic disorder with many acquired and inherited factors. It is also considered as a mild inflammatory disease leading to significant morbid conditions.

Acquired

- Excessive intake of food
- Unhealthy eating
- Lack of physical activity

Inherited

- Cohen’s disease
- Carpenter’s disease

Table 1: Schematic Illustration of consequence of obesity

<table>
<thead>
<tr>
<th>Consequence</th>
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<tbody>
<tr>
<td>Obesity</td>
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<tr>
<td>a. Excessive weight</td>
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<td>↓</td>
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<tr>
<td>b. Fat topography</td>
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<td>↓</td>
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<tr>
<td>Increased prevalence of disease</td>
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<tr>
<td>E.g. Diabetes</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Coronary Heart Disease</td>
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<tr>
<td>Increase Morbidity</td>
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<td>Increase Mortality</td>
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History

It was long known to the Greeks, Soranus advocated massage, laxatives, exercise, fiber diet. The age old method of use of diuretics and laxatives still continues popularly. But this methodology surely has no effect on body fat. These are seemingly without any adverse effects but can cause hypokalemia, affect heart and other muscle adversely.

Pyruvate rich food such as red apples, red wine, cheese have not yet been established as an anti-obesity agent. It was noted in 1900’s that hypothyroidism leads to obesity and supplementation

Table 2: Common diseases associated with obesity

1. Genetic
   - Lawrence Moon Biedl syndrome
   - Morgan Stuart syndrome
   - Carpenter’s syndrome
   - Cohen’s syndrome
2. Hypothalamic
   - Trauma
   - Inflammatory – Meningitis, TB, Syphilis
   - Infiltration – Histiocytosis X, Sarcoidosis
   - Leukemic dystrophy
3. Physical disability
   - Spina bifida
   - Paraplegic
4. Mental retardation
5. Down’s syndrome
6. Hunters disease
7. Endocrine
   Pituitary:
   - Lauren dwarf syndrome
   - Kallaman’s syndrome
   - Cushing disease
   - Thymus
   - Hypothyroidism
8. Metabolic
   - Diabetes Mellitus
   - Insulinoma
   - Mesidioblastone
   - Beckuth – Weedonan syndrome
   - Decrun’s disease
Dinitrophenol uncoupled oxidative phosphorylation lead to products of heat rather than ATP in the mitochondria which lead to dramatic rise in body temperature and fizzle out of the market for its weight reducing propensity. Digitalis was also tried and discarded anti-obesity drug. 1930’s brought anorectics which still hold sway over celebrities and general public, alike.

Incidence

In USA, 1.5 billion people are obese. 30,000 deaths were related to obesity or indwelling obesity. World over obesity totally amounts to 250 million. According to WHO in the year 2000, 55% of adult population was obese, of which men and women constitute about 21% and 21.4% respectively.

Table 3: Drugs inducing obesity

<table>
<thead>
<tr>
<th>Drugs inducing obesity</th>
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<tbody>
<tr>
<td>Sulfonylureas</td>
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<td>Insulin</td>
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<tr>
<td>Oestrogen</td>
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<td>Oral contraceptive pills</td>
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<td>Alcohol</td>
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<td>Steroids</td>
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<tr>
<td>Cyproheptadine</td>
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<tr>
<td>Valproate</td>
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<tr>
<td>Tricyclic antidepressants</td>
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<td>Phenothiazine</td>
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</tbody>
</table>

Table 4: Investigations for an Over-weight Individual

a. Clinical assessment:
   1. Skin fold thickness with a spring loaded calliper
      - Biceps
      - Triceps
      - Subscapular
      - Suprailliac
   2. Normal body fat content: Males – 20 %, Females – 30%
   3. Index of intra-abdominal fat content: Ratio of waist circumference to height: Males> 0.95, Females> 0.8
      - Sagittal diameter of abdomen at L₄ L₅
      - Males ≥ 94cms = 37 weeks
      - Females ≥ 80 cms = 32 weeks
b. Laboratory investigations:
   2. Lipid profile – Apolipoproteins, chylomicrons.
   3. LFTs
   4. S. GGT analysis (for alcoholic liver disease)
   5. Kidney functions – S. Urea, S. Creatinine, S. Electrolytes
   6. CCK MB.
   7. Urine analysis
   8. ECG
   9. Thyroid function tests.
   10. Isotopic measurement of whole body potassium content
   11. Impedance analysis.
   12. Abdominal fat can be measured by any CT or MRI
   13. Hydrostatic weighing.
   14. Dual Energy X-Ray Absorptiometry (DEXA)

with thyroid hormone was tried and continues to be used in addition to other agents not only for weight management but also in immortality clinics.

Assessment of Obesity

Degree of obesity may be assessed early by the body mass index which is taken as a reliable indicator for many disease states

\[
\text{BMI} = \frac{\text{Weight in kilograms}}{(\text{Height in meters})^2}
\]

Significant obesity of males > 30 and females > 28.6.

The fat distribution also predicts the complications of obesity. Fat distribution above the hips (gynecoid, pear type) rather than abdomen (apple type) has a propensity of cardiovascular disease and diabetes mellitus.

Essential obesity is multifactorial e.g. Racial and inheritance traits determine multifaceted of obesity. Persons with tendency for obesity have lower energy requirements.

Moreover, obesity is observed predominantly in certain diseases (Table 2). Also drug intake can aid to the tendency of developing obesity (Table 3). All of the antecedent complications of obesity appear frequently and consequently, leading to morbidity and mortality.

Investigations

There should be constant investigations, post clinical assessment or screening of obese individuals to pick up vital information of impending diseases so that drugs can be prescribed to the specific cause. Various methods can be employed to determine the obesity status starting from the simple clinical assessment like skin fold thickness, intra-abdominal fat content index17 to lab investigations like S.SGPT, S.SGOT. Apart from these various radiographic and research oriented tools like CT, MRI, impedance analysis, Dual Energy X-Ray Absorptiometry (DEXA), Hydrostatic weighing can be utilized in research institutions. Comprehensive list of investigations (Table 4).

Sometimes stocky and muscular body have a BMI that appear to be in a higher range, but this is innocuous. So a constant array of investigations is indicated to know progress of disease and development of the complications. When obesity occurs with the continuing years many complications appear virtually ruining every aspect of our body (Table 5).

The treatment of obesity borders on the main equation of

a. Calorie intake reduction.
b. Excessive calorie expenditure.

The goal can be achieved only through

a. Diet restriction
b. Exercise

Table 5: Complications of obesity

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<thead>
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<th>Complications of obesity</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<tr>
<td>Coronary Artery Disease</td>
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<tr>
<td>Type 2 Diabetes Mellitus</td>
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<td>Gall Stones</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Arthritis</td>
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<tr>
<td>Infertility</td>
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<tr>
<td>Pregnancy complications – neural tube defects, pre-eclampsia, perinatal mortality</td>
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<tr>
<td>Stress incontinence</td>
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<tr>
<td>Depression</td>
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Infact there is no substitute for this mantra. But to add to this venture three options are available.

a. Non-pharmacological measures

b. Surgery

c. Pharmacotherapy

a. Non-pharmacological measures:

1. Lifestyle changes:
   - It requires the motivation to resist temptation and the desire to continue when the going gets tough. It is difficult to take off weight and keep it that way. It is not as simple as it seems. Help may be obtained from psychiatrist, psychologist or any other trained professional.
   - A simple easily modifiable flow chart for weight management (Table 6)

2. Psychological therapy
   - Hypnosis: Hypnosis by a psychologist helps to aid the suggestibility that remain with the patient to help overcome temptation and maintain weight loss.

3. Dietary therapy
   - A low fat low carbohydrate nutritionally balanced diet is advocated. It is also advised not to sleep immediately after meals as there is lesser tendency for fat deposition.

4. Physical activity:
   - Warm up exercises, high energy impact activities for calorie expenditure, stretches, yoga, abdominal workouts. Regular exercises to lose and maintain weight is necessary. Cycling, skipping, brisk walking are other useful exercises.

5. Behaviour therapy:
   - Lifestyle modifications cannot be made without a behavioural change and such a change does contribute to weight management. Some of the methods are
     - Improving self esteem
     - Enhance self confidence
     - Understanding health
     - Changing to healthy food stuff
     - Changing to healthy food practices
     - Recording daily diet
     - Recording daily weight
     - Rewards for losing weight
     - Selling realistic short term goals
     - Avoiding crash diet
     - Adopting moderate and sustained weight loss program
     - Enlisting social support network involving family, friends, colleagues
     - Joining and supporting other people in a similar situation

b. Surgery:
   - Weight loss surgery: Consists of gastric bypass (Roux en y type) and banding surgery to aid weight loss in those with BMI > 36. Although it leads to 60% of weight loss, it can be maintained by reduced calorie intake and exercise. It may end up in complications like gall stone formation, malabsorption and other nutrition deficiency.
   - Wiring of teeth is advised.
   - Cosmetic surgery: Abdominoplasty or apronectomy are various surgeries undertaken to immediately prune the misshapen body.

c. Pharmacotherapy

Anti-obesity Drugs

The availability of drugs for any disease condition, itself brings with it a sense of relief. Drugs are last ditch effort in maintaining optimal weight. Weight creeps on insidiously, so also it should be taken off in a slow and steady manner rather than suddenly. Drugs aid in management. The physician takes a judicious decision after completely reviewing the investigations, patient’s needs and status.

Drugs alter the fundamental metabolic process of the human body and thereby regulate weight. The benefits are out weighted by their adverse effects. Anti-obesity drugs are long term solution for obesity. Combination of drugs may be effective by regulating multiple pathways and possibly inhibiting feedback pathways. The comprehensive list of drugs presently available is charted in Table 7.

The mechanistics of drugs in weight management is represented in Table 8.
Table 7: Anti obesity drugs

1. Diet Supplements: Fiber diet Hydrogel
2. Reduced fat absorption: Orlistat
3. Reduced carbohydrate absorption: Acarbose
4. Appetite Suppressants:
   - Sympathomimetic: Benzphetamine
     Phendimetrazine
     Diethyl propranolol
     Mazindol
     Phenylpropanolamine
   - Serotonergic: Dexfenfluramine
     Fenfluramine
   - Both sympathomimetic and serotonergic: Phenteramine
     Phendimetrazine
5. Antidepressants:
   a. Tricyclic antidepressants:
      - NA and 5HT receptor reuptake inhibitor: Doxepin
        Trimipramine
      - NA receptor inhibitor: Amoxetine
   b. Selective Serotonin Reuptake Inhibitor:
      Sertraline
      Fluoxetine
   c. Atypical:
      Mirtazapine
      Buspropione
6. GABA potentiator and glutamate receptor antagonist: Topiramate
7. Opioid antagonist: Naltrexone
8. Anti-diabetic drug:
   Metformin
   Pramlintide
   Exenatide
9. Cannabinoid receptor antagonist:
   Rimonabant
10. Leptin and neuropeptide Y
11. Cholecystokinin receptor antagonist
12. Breakthrough treatment options:
    OB receptor modulating drugs
    Neuropeptide inhibitors
    Insulotropin
    Cytokine regulators
    Uncoupling protein Z
    B3 agonists
    Dopamine antagonists

Individual Agents

A brief description of each of the agents will be described with supporting evidence.

Table 8: Schematic representation of general mechanism of action of anti-obesity drugs

Orlistat

Mechanism of action: Reduces fat absorption from the intestine by inhibiting pancreatic lipase and reduces triglyceride hydrolysis.

Low fat diet is generally advised.

Adverse effects: Steatorrhoea (oily stools).

Newer analogues have lesser degree of steatorrhoea. A well balanced low calorie diet is advocated with vitamin supplements especially fat soluble vitamins A, D, E and K.25 Orlistat on long term treatment basis had lesser mortality and morbidity incidence and was particularly useful to the patients with impaired glucose tolerance.26,27

Sibutramine

Mechanism of action: Centrally acting sympathomimetic amine that enhances satiety by inhibiting non-selective uptake of nor adrenaline, serotonin and dopamine. It mainly acts on \( \beta_1 \), 5HT\(_{2a} \) and 5HT\(_{2c} \). In addition, peripheral D\(_3\) receptor are stimulated enhancing metabolic rate, thermogenesis and reduces energy expenditure.28

Efficacy of the drug was found to be better when life style modification was implemented along with the drug intake.29

Adverse effects: Hypertension, serotonin syndrome,30 dry mouth, insomnia, headache, constipation, seizures, fatal pulmonary hypertension may occur.31

Metformin

Biguanide used in type II diabetes mellitus is also used for weight reduction. It is the drug of choice in obese patients with type II diabetes when its found to be associated with heart failure or polycystic ovarian disease.32

Mechanism of action: It activates cAMP-activated protein kinase and suppresses hepatic gluconeogenesis activity.

Adverse effects: Lactic acidosis, Gastro-intestinal upset.

Exenatide

Mechanism of action: It is long acting analogue of the hormone GLP-1, which the intestine secretes in response to the presence of food which in turn is responsible for the delaying of gastric emptying time and gives the sense of satiety. It is often noticed that obese individuals are deficient in GLP-1 which
should not be mixed in the same syringe. For the effective weight reduction, the drug has to be taken for at least but the benefits of glycemic control was found to be higher than weight loss.

**Adverse effects:** Injected twice daily and severe nausea during initial therapy. **Oxyntomodulin:** It is pro-glucagon gene product with actions similar to exenatide.

**Amylin:** It is a hormone co-released with insulin reduces glucagon secretion. It is advocated as a therapeutic agent, surprisingly.

**Pramlintide**

**Mechanism of action:** It is a synthetic analogue of amylin secreted by pancreas. It produces a feeling of satiety and delays gastric emptying. It inhibits hepatic gluconeogenesis by inhibiting glucagon synthesis and thereby reduces blood glucose levels. Treatment started with 60µg and increased as needed. Injected subcutaneously twice a day prior to food intake.

It is advocated for obese diabetic with type 1 or type 2 with uncontrolled sugar levels.

**Adverse effects:** Apart from redness, pain at injection site, it causes hypoglycemia, headache, abdominal pain, fatigue, weight loss.

**Drug interactions:** Atropine, acarbose, miglitol that slow gastric emptying and absorption. Insulin and pramlintide should not be mixed in the same syringe.

**Rimonabant**

**Mechanism of action:** It is an approved but infrequently used drug. It is a cannabinoid CB1 receptor antagonist. It selectively acts on CB1 receptor in brain and peripheral organs. It potentiates satiety feeling along with increase peripheral glucose uptake in muscle. It increases insulin sensitivity and reduces lipogenesis in liver. They not only cause weight loss but in addition reverse metabolic effects of obesity.

Some studies concluded that it suppresses appetite and weight reduction. The experimental evidence proves that its action manifests by silencing RIP140 a nuclear hormone co-repressor, which regulates fat accumulation.

**Adverse effects:** Severe depression and predisposes to neurodegenerative diseases e.g. Alzheimer’s disease, amyotrophic sclerosis.

**Mazindol**

Nonamphetamine, an indole derivative. It acts peripherally by increasing metabolic rate and preferred as an adjunct with other anti-obesity drugs, to enhance overall effectiveness. Mazindol is found to be effective in initial weeks of treatment and their response tends to decline later. So it’s used as a short term treatment regimen.

**Phendimetrazine**

Sympathetic agonist that shows potential as anti-obesity agent because of lesser tendency for addiction liability. Few cases of cardiac ischemia and interstitial nephritis have been reported. Other adverse effects are hyperpyrexia, mydriasis, arrhythmias, rhabdomyolysis. Cardiomyopathies are noted on long term usage which is reversible on discontinuation.

Fenfluramine has tendency to produce heart valve damage and fatal pulmonary hypertension due to action on 5HT2a receptors. Combinations approved are

| a. SSRI + phentermine |
| b. Topiramate + phentermine |
| c. Buproprion + zonisamide |
| d. Buproprion + naltrexone |

**Peptide YY3-36**

It is secreted neuro-endocrine cells of ileum and colon, acts via neuropeptide Y receptors leading to suppression of pancreatic secretion and inhibition of gastric motility along with increased water and electrolyte absorption. Its concentration is found to be reduced in obese individuals. Peripheral infusion or nasal spray before meals, with high plasma concentration found to be effective in reducing weight. It brings about appetite suppression.

**RNAi Therapy**

The ribonucleic acid interface (RNAi) is a nuclear hormone co-repressor and helps to maintain lean profile thought out their life. Development of ribonucleic acid interface series is the only long term approach to obesity. The experimental evidence proves that a high dose of diazoxide along with calorie restriction and life style modification brought about significant insulin suppression and weight reduction. But efficacy of diazoxide is better in non-obese than obese individuals and therefore dosages based weight of an individual played an important role.

**New Hydrogel – diet Pill**

It consists of bio-degradable polycellulose that imbibes water which is flushed out in a few hours giving dieters a feeling of satiety and has no major adverse effects except for flatulence, it is a good alternative to drugs with higher adverse effects like sibutramine.

**Diazoxide**

Affects potassium channels and enhances potassium release leading to suppression of insulin secretion. It is used in treatment of obesity and hyper insulin states. A 6 month study concluded that a high dose of diazoxide along with calorie restriction and life style modification brought about significant insulin suppression and weight reduction. But efficacy of diazoxide is better in non-obese than obese individuals and therefore dosages based weight of an individual played an important role.

**Naltrexone**

An opioid antagonist often used to reduce craving, as with substances of abuse. It selectively antagonizes opioid receptors in central nucleus of amygdala and paraventricular nucleus of hypothalamus leading to diet selection and regulation of food intake. Certain studies showed that Buproprion action was potentiated with use of naltrexone. So the combination is preferred rather than the monotherapy.

**Topiramathe**

Antiepileptic, has promising effect by an unknown mechanism. Acts mainly by inactivating sodium channel, potentiates GABA and some glutamate receptors. It has got varied uses. Apart from treatment of nocturnal and binge eating disorders, it is also used in treatment of SSRI induced weight gain. Topiramathe has a wide range of use.

**Antidepressants:** They most inhibit the receptors of biogenic amines NA, 5HT at neurons and potentiate their action. Common antidepressants preferred are buproprion and diethylpropion.

Drugs that were initially used for obesity and later
withdrawn from use by the FDA are fenfluramine, dexflurane, phenylpropanolamine and troglitazone.

Sertraline
An SSRI often used in the treatment of nocturnal and binge eating disorders. It is also used in bulimia nervosa treatment.

New Concepts
As obesity is considered to be a mild chronic inflammatory disease, along with weight reducing drugs anti-inflammatory drugs is also advocated. Since obesity has a tendency to develop leptin insensitivity, to overcome the resistance, ciliary neurotrophic factor, a glial cytokine was developed. It brought about weight loss in individuals with diet and leptin resistance induced obesity via melanocortin independent pathway. However, the trial had to be called off since the patients developed antibodies against ciliary neurotrophic factor.61

The unexpected fall out of anti-obesity drugs could be in the prevention of HIV, influenza and hepatitis which rely on metabolic processes for enhancing viral load. Rimonabant may also be given to maintain smoking cessation and has potential to improve short term memory, anti-inflammatory and anti-hyperalgesic effect. Since obesity is associated with depression, tri-cyclic anti-depressants can be given. But they have an added disadvantage of weight gain on long term dosage. Various trials are being carried out to provide better drug, some of them are worth a mention.

Olestra
It is polyester of sucrose used as a fat substitute which is neither digested nor absorbed and therefore has no role in production of energy. It is considered as a tool for weight loss and maintenance. On a long term usage, it is associated with decreased absorption of fat soluble vitamins and steatorrhoea.

Atomoxetine
A central nor-epinephrine uptake inhibitor. A 10-week, double-blind, clinical trial found it to be effective in reducing binge eating episode along with weight and body metabolic index. Another 12-week, double-blind, randomized controlled trial with 30 obese women (average BMI = 36) concluded that atomoxetine reduced 5% of body mass when compared to placebo with minimal adverse effects.

Melanin-concentrating Hormone Receptors (MCHR)
MCHR are G protein-coupled receptors involved in regulation of appetite. MCHR1 antagonists bring reduced food intake and elevation of body metabolic rate. GW-803,430 and T-226,296 drugs come under this group and presently under trial.

Melanocortins
Melanocortin receptor 4 antagonists bring about anorectic effects by mediating its action by leptin-melanocortin pathway similar to MCHR antagonists except for the latter’s thermogenic effects.

P57
A steroidal glycoside, Hoodia gordonii plant extract brings about appetite suppression by increasing ATP content in hypothalamus. Apart from these, clinical trials are being done on 5HT6 receptor ligands, human steroidal hormone RF1051, amylose inhibitors AZM-140, β adrenergic receptor agonists L755,507 and SB 418790, Cholecystokinin A agonists GI 181771, corticotropin releasing factor agonists NBI-30326, leptin promoters and leptin receptor agonists may serve a potential benefit in years to come.

Anti-obesity Vaccine
An innovative unexpected method in weight management and is said to be ideal to yoyo dieters, the cycle of repeated loss and regain of weight which inhibits a naturally occurring hormone ghrelin for regulating energy balance in the body, this immunotherapy comes to the rescue. It is expected to reduce fat stores inspite of not reducing food intake.

Anti-cellulite Cream
Anti-cellulite creams are said to increase the metabolism of the local area using local energy and leads to increased blood circulation, sweating that is helpful in burning and dissolving fats.

Most commonly the herbal ingredients used in anti-obesity creams are myrica cerifera, cyperus rotundus, prunes amygladus, ocimum sanctum, piper nigrum

Conclusion
Obesity can be adequately managed by just dietary restriction and lifestyle modification. It is only rarely that drugs are to be used. Moreover, only a befitting patient that is cleared of contraindications can be given drugs.

Surgery is rarely used for weight management in Indian scenario.

Lifestyle modifications and behavioural therapy has an integral part to play in weight management.

References


