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Pharmacotherapy of Obesity

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INTRODUCTION

Obesity has emerged as a global public health crisis and obesity rates have sharply increased over past 30 years. Global data suggests 500 million adults have obesity worldwide. India ranks third after United States and China in having highest number of obese people. US accounts for thirteen percent and India along with China accounts for 15% of the total obese population worldwide.

Obesity in Indian population is different from rest of the world as we have "Thin Fat" Indian phenotype, indicating that the proportion of body fat, abdominal obesity, subcutaneous fat, and intraabdominal fat is more in Indian overweight and obese phenotype.

A significant difference in prevalence of obesity is seen in urban and rural population in India. In Urban men aged 15-49 years prevalence is 26.5% and women is 25% as compared to rural population where prevalence is 5.6% and 7.4% respectively. The increasing prevalence of obesity in adolescent population has been documented in a study of adolescents (aged 14-18years) studying in public schools of Delhi in which 29% were overweight or obese.

DEFINITION

World Health Organization (WHO) defines overweight and obesity as "An abnormal or excessive fat accumulation that presents a risk to health."

CLASSIFICATION (TABLE 1)

Although BMI is used as a measure of obesity, it has certain limitation in stratifying risk of an Indian patient. It does not consider change in body composition, gender and central obesity all of which have a role in predicting comorbidities and mortality.

WHO has lowered the obesity cut off for Asians/Indians still there is need to have separate cutoff for Indians to redefine obesity as Indians are known to have higher percentage of body fat even at a lower BMI as compared to matched Caucasians.

COMPLICATIONS

Obesity is not only associated with cardio metabolic diseases but also linked to malignancies, osteoarthritis, psychosocial ailments like depression and low self-esteem.

Various diseases predisposed by obesity is enumerated in Table 2.

With an increase in the morbidity and mortality associated with obesity comes its cost in terms of economic burden to patient's family and country. So in order to tackle this complex problem, early recognition of obesity and associated comorbidities should be done by education and awareness and early institution of treatment.

EVALUATION AND MANAGEMENT

It includes thorough history including history of drug intake to rule out medication induced weight gain and detail physical examination.

Work up is depicted in Table 3

MANAGEMENT

I. LIFE STYLE THERAPY

1. Meal Plan

   A healthy meal plan with reduced caloric intake is must for weight reduction and a daily deficit of at least 500-750 kilocalories is likely to help in weight loss.

   Meal plans can include a Mediterranean diet, DASH, low carbohydrate, low fat diet and a high protein or a vegetarian diet, the stress being on reducing the total caloric intake.

2. Physical Activity

   Along with a healthy meal plan, physical activity

Table 1: Classification of obesity based on BMI

Classification	For Europoid-WHO (1998) BMI (kg/m2)	Classification	For Adult Asians WHO (2008) BMI (kg/m2)
Underweight	<18.5	Underweight	<18.5
Normal	<18.5-24.9	Normal	<18.5-22.9
Over weight	>25	Over weight	>23
Preobese	25-29.9	At risk	23-24.9
Obese I	30-34.9	Obese I	25-29.9
Obese II	35-35.9	Obese II	>30
Obese III	>40		

Table 2: Diseases Predisposed by Obesity

Cardiovascular	Coronary artery disease, Corpulmonale, Varicose Veins, Congestive heart failure, Pulmonary embolism
Endocrinal	Metabolic syndrome, Type2 Diabetes, Dyslipidemia, Poly cystic ovarian syndrome
Gastrointestinal	Gastroesophageal reflux disease, Nonalcoholic fatty liver disease, Cholelithiasis, Hernias,
Musculoskeletal	Hyperuricemia and gout, Osteoarthritis
Respiratory	Dyspnea, Obstructive sleep apnea, Hypoventilation syndrome, Pickwickian syndrome, Asthma
Genitourinary	Urinary stress incontinence, Obesity related glomerulopathy, Male hypogonadism
Neurological	Stroke, Idiopathic intracranial hypertension, Meralgia paresthetica, Dementia
Psychological	Depression/ low self-esteem, Social stigma
Integument	Lymphedema, Striae distensae, Cellulitis, Intertrigo,carbuncle, Acanthosis nigricans Acrochordons, Hidredenitis supurativa, Stasis pigmentation
Cancers	Breast cancer, Uterine cancer, Cervix, Esophagus, Pancreas, Kidney, Prostate, Colon cancer

should be prescribed to obese individual as a part of life style therapy. Individual must be encouraged to reduce sedentary behavior. The goal is aerobic activity of ≥ 150 min/week performed in 3-5 daily sessions per week which may be achieved in progressive increments over a period .Addition of resistance training, 2-3 times per week helps in preserving muscle mass. Resistance exercises using major muscle groups in single set repetitions are evidenced to help in fat loss. Physical activity must be tailored to an individual taking into account their physical and health status.

3. Behavioral Intervention

Behavioral therapy enhances adherence to a healthy meal plan and an exercise routine.

Behavioral therapy consists of:

1. Self-monitoring of weight, food and caloric intake and physical activity
2. Setting of goals for self which are reasonable but clear.
3. Education regarding meal plan physical activity and obesity
4. Stimulus control

Table 3: Work Up for Obesity

History	Physical Examination	Investigation
Medical causes Drugs PCOS Family history of obesity Binge eating or bulimia	Measure height and weight BMI Waist circumference Thyroid Oropharynx Acanthosis	Comprehensive metabolic profile LFT Fasting blood glucose TSH Lipid profile PCOS workup if history suggestive

5. Mobilization of social support
6. Stress reduction
7. Behavioral contracting
8. Cognitive behavioral therapy
9. Systematic problem solving

A multidisciplinary team consisting of (nurses, dieticians, educators, physical instructions and psychologist) for behavioral therapy enhances its effectiveness. Therapy should be intensified in case 2.5% weight is not achieved during the first month of treatment, as early weight loss is a predictor of successful long term weight loss. Behavioral intervention must take into account the patients cultural and socio-economic background and educational status.

II. PHARMACO THERAPY

Drugs are indicated as an adjunct to life style and behavioral changes in individuals to achieve a sustainable reduction in body weight. Pharmacotherapy may be instituted in patients with a BMI of ≥30kg/m2 or at ≥27/m2 when one or more co-morbid conditions exist that may benefit with weight loss.

Factors considered while choosing pharmacotherapy:

1. Willingness
2. Current medication and possible drug to drug interaction
3. Diabetes/prediabetes
4. Medical history of other co-morbid conditions in patient

Recent advances and approval of antiobesity drugs has opened the way to much more directed treatment approaches than ever before. Table 4 gives list of drugs, their mechanism side effects and contraindications.

Orlistat: Until recently Orlistat, a reversible pancreatic gastric lipase inhibitor was the only drug approved for use in chronic weight management. In a 2-year, multicenter, randomized, double-

Table 4: Drugs for Obesity

Drug	Dosage	Mechanism of action	Status	Side effects	Contraindications
Phentermine resin (ADIPEX)	(37.5 mg/d) Lonamin (30-37.5 mg/d)	Norepinephrine-releasing action	Approved in 1960s for short term use(3mo)	Headache ,nausea, dry mouth, fatigue, Constipation Insomnia, dry mouth, dizziness, constipation, dysgeusia Palpitation, tachycardia, hypertension, euphoria, psychosis Urticarial, impotence	Anxiety, heart disease, uncontrolled hypertention, seizure, MAO inhibitors, pregnancy and breast feeding, hyperthyroidism, glaucoma, drug abuse, sympathomimetic amines
Diethylpropion (TENUATE)	(75 mg/d)	Norepinephrine-releasing action	FDA Approved in 1960s for short term use(3mo)	Same as phentermine	Same as phentermine
Orlistat prescription (120mg) (XENICAL)	120 mg TID	Pancreatic and gastric lipase inhibitor	FDA approved in 1999 for chronic weight management	Decrease absorption of fat soluble vitamins, steatorrhoea, oily spotting, fecal urgency and incontinence	Chronic malabsorption syndrome, pregnancy and, breast feeding, levothyroxine, warfarin, antiepileptic drugs
Orlistat, Over –the-counter (60 mg)	60-120 mg TID	Pancreatic and gastric lipase inhibitor	FDA approved in 1999 for chronic weight management	AS stated above	As stated above
Lorcaserin (10 mg) (BELVIQ)	10 mg BID	5HT2c receptor agonist	FDA approved in 2012 for chronic weight management	Headache, nausea, dry mouth, dizziness, fatigue, constipation	Pregnancy and, breast feeding, Use with caution: SSRI, SNRI/ MAOI, triptans, buproprion, dextromethorphan
Phentermine (P)/ topiramate (T) (OSYMIA)	3.75 mgP/23 mgT ER QD (starting dose) 7.5 mg P/46 T ER daily (recommended dose) 15 mg P/92 mg P/T ER daily (high dose)	GABA receptor modulation (T) plus norepinephrine releasing agent (P)	FDA approved in 2012 for chronic weight management	Insomnia, dry mouth, dizziness, parasthesia, constipation, dysgeusia	Pregnancy and, breast feeding, hyperthyroidism, glaucoma, MAO inhibitor, sympathomimetic amines
Naltrexone/ Bupropion (CONTRAVE)	32 mg / 360 mg 2 tablet QID (high dose)	Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone)	FDA approved in 2014 for chronic weight management	Constipation, Headache, nausea vomiting, dizziness	Uncontrolled hypertention, seizure, anorexia nervosa or bulimia, drug or alcohol withdrawl, MAOI
Liraglutide (VICTOZA)	3 mg injectable	GLP1 agonist	FDA approved in 2014 for chronic weight management	Nausea, vomiting, pancreatitis	Medullary carcinoma of thyroid, MEN2 history

blind, placebo-controlled study by Rossner et al in patients with BMI 28 to 43 kg/m2 were randomized to placebo or Orlistat (60 or 120 mg) three times a day, combined with a hypo caloric diet during the first year and a weight maintenance diet in the second year of treatment to prevent weight regain. Orlistat-treated patients lost significantly more weight ($p<0.001$) than placebo-treated patients after 1 year (6.6%, 8.6%, and 9.7% for the placebo, and Orlistat 60 mg and 120 mg groups, respectively. During the second year, Orlistat therapy produced less weight regain than placebo ($p = 0.005$) for Orlistat 60 mg; $p<0.001$ for Orlistat 120 mg). It has also been documented to produce significant improvement in metabolic parameters.

Lorcaserin- It is a highly selective agonist of 5HT2C receptor, the activation of which leads to increased satiety. Recommended for use in obese nondiabetic and diabetic individuals in a dose of 10mg BD. In a multicentric placebo controlled trial by Smith SR et al. in nondiabetic overweight and obese patients, on lifestyle modification therapy, addition of Lorcaserin in a dose of 10 mg twice daily was associated with ≥ 10% loss in body weight in significantly more patients vs placebo group after 52 weeks of therapy($p<0.001$). Also in patients who achieved ≥5% weight loss during the first year on therapy, that loss was maintained more in patients on Lorcaserin during second year on therapy (67.9%) vs placebo(50.3%$P<0.001$). Locarserin was also documented to have a beneficial effect on insulin resistance, blood glucose and insulin levels significantly more so in the first year as compared to placebo.

In the BLOOM-DM trial in diabetic patients with (HbA1C between 7% and 10%) addition of Lorcaserin (10 mg once or twice daily for a year) in conjunction with the antidiabetic drugs(metformin and/or sulfonylurea) has been studied to causes ≥5% weight loss 37.5% and 44.7% respectively vs 16.1% in the placebo group in the first year. Improvement in HbA1C (1%) levels along with blood glucose was seen without any significant changes in blood pressure, triglyceride, LDL-C or HDL-C levels. Lorcaserin interacts with MAO- inhibitors and SSRI, though it has a low rate of adverse effects. Europe has not yet approved the use of Lorcaserin, labeling it as a drug with carcinogenic potential on long term use along with concerns regarding depression and valvulopathy.

Phentermine/Topiramate controlled release combination (PHEN/TPM CR) - phentermine acts on the hypothalamus to cause release of norepinephrine and dopamine. Topiramate primarily an antiepileptic drug (AED) causes weight loss by decreased caloric intake together with increased energy expenditure. Using an extended release combination of the two drugs allows for lower dosages of both components and lesser side effects.

In the 56 week EQUIP trial 66.7% patients with obesity (BMI ≥35kg/m^2) receiving 15/92mg of PHEN/TPM CR lost ≥ 5%of body weight, as also 44.9% of those receiving 3.75/23mg of PHEN/TPM CR vs 17.3% of placebo patients.

The SEQUEL trial documented that after 108 weeks, the addition of PHEN/TPM CR to a standardized lifestyle modification led to substantial weight loss. The percentage changes in body weight from baseline were 1.8%, 9.3%, and 10.5% in subjects treated with placebo, PHEN/TPM CR 7.5/46, and PHEN/TPM CR 15/92, respectively (ITT-LOCF). Importantly, both doses of PHEN/TPM CR were significantly more effective than placebo regardless of baseline BMI and were similarly effective at baseline BMI values extending from 30 to 40 kg/m^2. In those subjects with class III obesity (BMI ≥40 kg/m^2), the 15/92 dose produced an even more pronounced degree of weight loss, exceeding that observed with 7.5/46.

Weight loss is documented to occur in a dose dependent fashion along with reduction in waist circumference, decrease in blood pressure and improved fasting glucose and Lipid profile. Though the drug has not yet been approved for use in Europe due to its potential teratogenic effect.

Naltrexone SR/ Bupropion SR - Naltrexone is an opioid receptor antagonist primarily used to treat alcohol and opioid dependence. In addition it also reduces food craving. Bupropion is a reuptake inhibitor of norepinephrine and dopamine and is known to cause weight loss. This drug combination was shown to cause remarkable weight loss in patients of obesity with or without T2DM.

The COR-I trial documented a mean change in bodyweight of 1·3% in the placebo group, 6·1% in the naltrexone 32 mg plus bupropion 360 mg group ($p<0·0001$ *vs* placebo) and 5·0% in the naltrexone 16 mg plus bupropion 360 mg group ($p<0·0001$ *vs* placebo). 84 (16%) participants assigned to placebo had a decrease in bodyweight of 5% or more compared with 226 (48%) assigned to naltrexone 32 mg plus bupropion 360 mg ($p<0·0001$ *vs* placebo) and 186 (39%) assigned to naltrexone 16 mg plus bupropion 360 mg ($p<0·0001$ *vs* placebo). Significant improvement in weight and the cardio metabolic markers with a fall in HbA1c of 0.6% has also been documented in the COR-BMOD trial. The Gastro intestinal effects of nausea, vomiting, constipation may limit its tolerability and use. These may be mitigated by up titrating the dose weekly over a 4-week period.

This combination may cause increases in blood pressure and must be used with caution in hypertensives. It is not recommended for use in those with kidney and liver impairment.

Liraglutide: is GLP -1 receptor agonist and bears a strong homology to the native GLP-1. Liraglutide acts centrally on the GLP-1 receptor causing a

Table 5: Specific drugs can be selected for different meal related behavioral problems	
Increase appetite	Phentermine /Topiramate ER
Satiety problems	Lorcaserin
Craving problem	NaltrxoneSR/BuproprionER
Prediabetes/Diabetes	Liraglutide

reduction in food intake, reduction in production of hepatic glucose and reduced glucose uptake by the muscle. The peripheral GLP-1 receptors increase Insulin secretion, reduce glucagon secretion and slow the gastric emptying time. (Table 5) Liraglutide earlier approved for use in T2DM has now been approved for use in obesity at a dose of 3mg/day. Liraglutide in a 2 year trial was compared with Orlistat and placebo and has been shown to cause significant weight loss as compared to both (5.8 kg more than placebo and 3.8 kg more than Orlistat) at 3mg/day by Astrup et al. In the SCALE Diabetes randomized controlled trial patients with T2DM and overweight, Liraglutide caused significant weight loss with 54.3% of patients on Liraglutide (3mg/day) losing >5% body weight vs 21.4% of patients on placebo. Liraglutide was also documented to reduce fasting blood glucose, HbA1c, systolic blood pressure and the waist circumference. The benefits of Liraglutide induced weight loss has been studied in both nondiabetic obese individuals and patients of T2DM.The drug may be started at a dose of 0.6mg SC once a day and up titrated by 0.6mg weekly going up to a maximum of 3mg/day.

Criteria for stopping pharmacotherapy (drug failure):

Lorcaserin - stop if <5% loss at 12 week

Phentermine/Topiramate CR - at 12 weeks, can increase the dose to 11.25mg/69mg for 14 days, then 15mg/96; stop if <5% loss at 12 week on maximum dose

NaltrxoneSR/Bupropion SR - stop if <5% loss at 12 week

Liraglutide 3 mg - stop if <4% loss at 16 week

III. SURGICAL TREATMENT

Bariatric Surgery: It is indicated if BMI is ≥40kg/m^2 and failure to lose weight with diet, exercise and drug therapy

BMI>35kg/m^2 with comorbidities like diabetes mellitus ,dyslipidemia, impaired glucose tolerance with failed diet, exercise and drug therapy.

FUTURE THERAPY

Oxytocin is emerging as a treatment modality for metabolic disorders such as obesity and dysglycemia. Few RCTs have evaluated the effect of intranasal oxytocin on weight loss.

Combination of GLP-1 RAs with SGLT 2 inhibitors is also a potential option under consideration for management of obesity.

CONCLUSIONS

Obesity is not only a lifestyle disorder but a "disease" as along with it comes inevitable predisposition to various cardio metabolic disorders. So in order to control the epidemic, we need to keep in mind the lower cut off of BMI as Indians. A multidisciplinary approach should be exercised involving NGOs, the Government, schools, family and society to which education and awareness is key.

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