Current Management of Obesity in an Infertile Female-Recent Advances and Future Prospective Drugs

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Abstract: With obesity having grown to epidemic proportions, nearly half of women of reproductive age are overweight and obese and this is a major public health problem. Due to unfavourable ovarian stimulation protocols, higher gonadotropin consumption and poor results most insurance companies are reluctant to sponsor treatment for such patients .Since diet and exercise are inadequate treatments and bariatric surgery maybe too extreme, treatment in the model of other chronic diseases by combination therapies has prompted the development of novel combination therapies like Qysmia (topiramate/phentermine)/Contrave (Bupropion SR/Naltrexone SR) which simultaneously target multiple physiological pathways that regulate energy homeostasis to overwhelm endogenous compensatory mechanisms as opposed touse of monotherapies to maintain weight loss. The only concern is the slight risk of teratogenicity with topiramate hence it is better to use contraception while using topiramate/bupropionSR/naltrexoneSR. In obese diabetics the GLP-1 receptor agonists like exenatide/liraglutide remain the drugs of choice incombination with insulin, while combination of lixisenatide and insulinglargine are in the pipeline for the future.

Keywords: Obesity, infertility, Qnexia, topiramate, phentermine, contrave, bupropion SR, Naltrexone SR, Combination drugs.

INTRODUCTION

Obesity is emerging as a major public health problem in low socioeconomic countries like India as well as industrialized world [1, 2]. Although in the 20th century most populations in which obesity became a health problem were in north America, Europe, recent data show that largest increases in obesity are in developing countries such as Mexico, China and Thailand [3, 4].

To understand why obesity is reaching epidemic proportions worlwide one has to consider the multiple aetiological factors and the pathways controlling regulation of food intake and energy expenditure [5, 6] (Figures **1**, **2**). Dysregulated energy homeostasis stems from a societal reduction in physical activity, an increase in accessibility and overindulgence in energy dense foods combined with a myriad of genetic, social and economic factors. This also includes drug addiction and variable food adulterations all over the world [7-10]. The side effect of H. pylori eradication along with free use of proton pump inhibitors as antacid therapy contributes in increasing the obesity incidence [11, 12].

Obesity is associated with a number of chronic conditions including dyslipidaemia, hypertension, type2 diabetes mellitus (DM), heart failure, coronary artery disease, reproductive disorders including genital tract cancers along with decreased sexuality (more so in the female partner). Although the roles of rimonabant and topiramate were extensively discussed in our previous article the recent withdrawl of rimonabant from US and European markets because of its depressive side effects leading upto suicide and simultaneous withdrawl of sibutramine from world market has left us with very few medical options regarding obesity treatment. We had been using topiramate since 2004 [13, 14]. The recent concept of using combination therapies with the introduction of few combination therapies like topiramate/phentermine, bupropion/ naltrexone or bupropion/zonisamide has prompted us to review the management of obese women who require treatment for infertility. Over weight (BMI>25Kg/m2) and obese (BMI>30Kg/m2) women have increased anovulatory infertility andincreased miscarriage rates. The live birth rate following IVF/ICSI is alsoreduced and so is the response to ovarian stimulation [15].

Diet and lifestyle modifications remain the cornerstone of weightloss therapy but are limited by a lack of longterm success for most obese patients [16, 17]. Most studies that report shortterm weight loss after low calorie diet treatment acts disappointing in the

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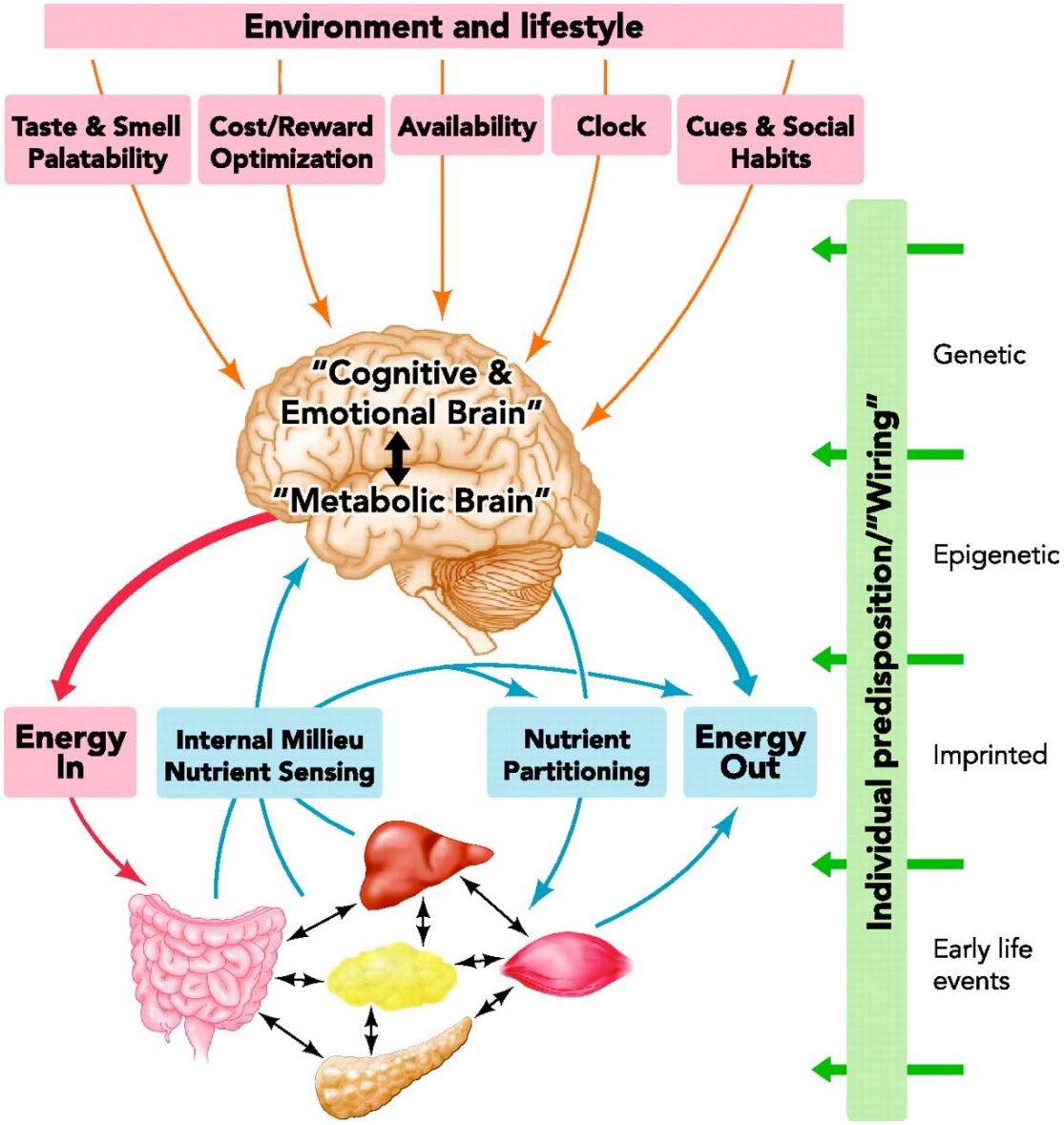


Figure 1: Schematic diagram showing the major factors determining neuaral control of appetite and regulation of energy balance-with permission from ref 5 -Zheng and Berthoud HR. The brain monitors the internal milieu through a number of hormonal and nutrient sensing mechanisms and is under constant influence of the environment and lifestyle through the senses and mainly the cognitive and emotional brain. The two streams of information are integrated to generate adaptive behavioural (food intake) and autonomic/endocrine responses determining nutrient partitioning, energy expenditure, and overall energy balance. Any of the peripheral and central signaling steps are subject to individual predisposition through either genetic/epigenetic, or nongenetic early life imprinting mechanism.

longterm. Most patients regain the weight lost partially or completely within 3-5 years after treatment. Long term studies present even less favourable profile [18]. Gosseling and Cote have followed women for 11 years after weight lossand showed that 49. 5% had regained or even surpassed their previous weight [19]. When obese patients fail to achieve adequate weight control with diet and lifestyle medications alone, interventions such as surgery may be indicated.

Obesity being a chronic condition, treatments aimed at management of obesity is similar to the principles of management of other chronic conditions eg hypertension and type 2 DM. Just as diseases like hypertension and diabetes are not expected to be cured with medication we try to palliate them with medication. Hence the same principle applies for medications used to treat obesity and promote weight loss. The longterm success of single drug therapies for obesity are limited by the counterregulatory adaptive mechanisms of the human body especially the processes in the central nervous system that regulate energy intake and homeostasis [20]. Hence combination drug therapies which could more effectively overcome endogenous compensatory

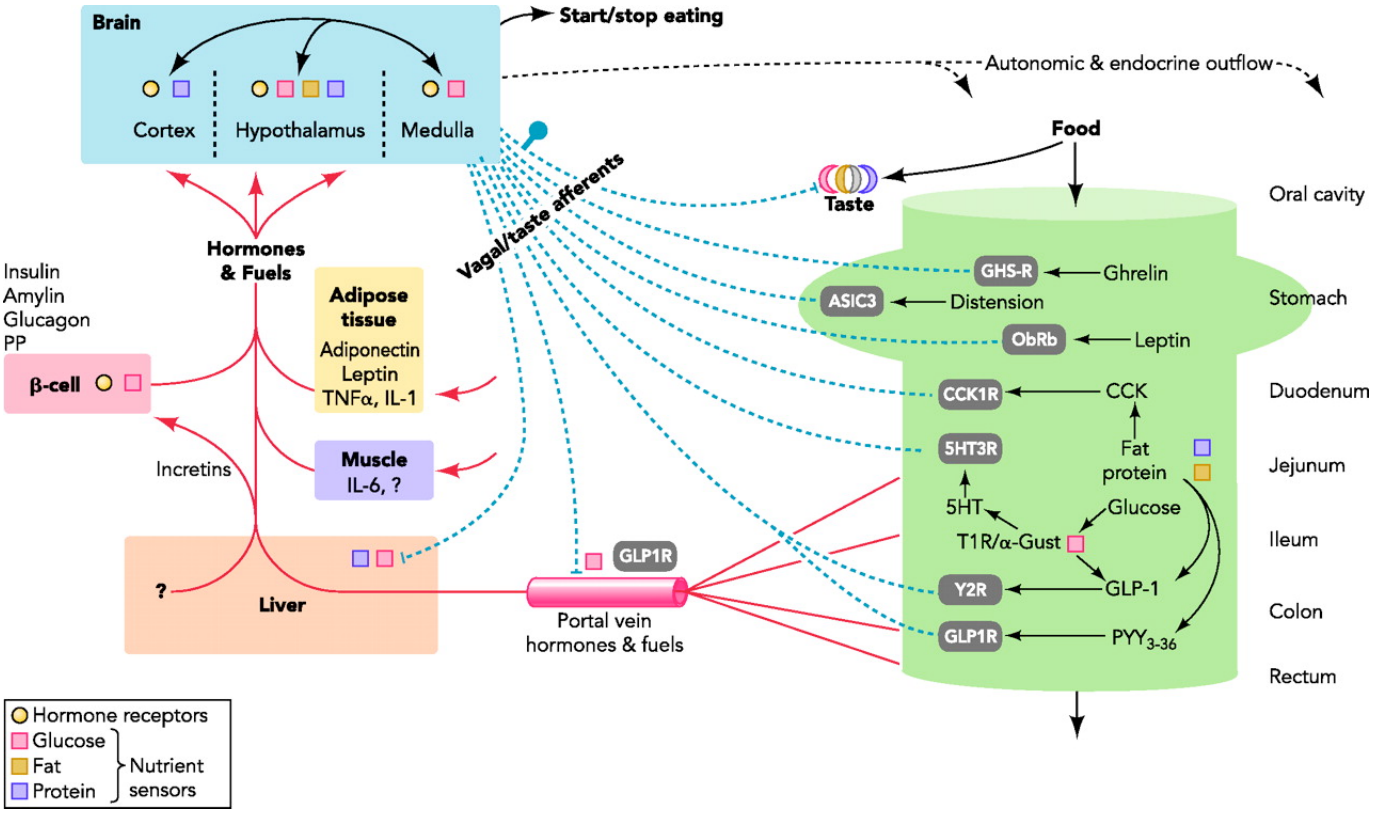


Figure 2: Nutrient sensing by the brain with permission from ref 5 Berthoud HR. Simplified schematic diagram showing the major pre and postabsorptive transduction sites and mechanisms for the detection of ingested food and its macronutrient components. Nutrient information is sent to the brain through vagal and taste afferents (heavy broken lines). Specific receptors expressed by vagal afferent naurons are showed in rectangular boxes. Specific sensor mechanisms demonstrated for glucose, amino acids, and lipids/fatty acids are shown by gray striped, and white squares, respectively.

mechanisms are preferred over single drug usage. Hence a combination of drugs that target multiple physiological pathways that regulate energy homeostasis may thus achieve a favourable longterm weight outcome than monotherapies [21].

Qsymia™ (PHEN/TPM), combines immediate release phentermine hydrochloride (PHEN) and delayed release topiramate beads(TPM)in a timed release capsule form. This was approved by FDA in July 2012 and marketed in september 2012 but the european medicine agency(EMA) rejected the marketing authorization of PHEN/TPM due to the longterm cardiovascular and central nervous side effects, teratogenic potential of topiramate and the possibility of continuation in patients in whom this combination is not recommended. A longterm trial is awaited regarding the cardiovascular outcomes before European medicine agency approves(latest february 2013 report).

TOPIRAMATE (Tp)

Tp is an anticonvulsant incidentally discovered to cause weight loss in contrast to other antiepileptic drugs [22]. It is a sulfamated monosaccharide and, it has positive modulatory effect on GABA receptors. Although this effect is expected to promote weight gain, it has been reported that activation of GABA(A) receptors by Tp may decrease nightmares and sleep deprivation induced feeding [23]. Peripherally Tp has been shown to be insulin sensitizing *in vitro*, with direct effects on adipocytes and it enhances insulin sensitivity at level of tissue disposal. It also inhibits hepatic glucose output (HGO) and suppresses lipolysis in adipose tissue. It also causes skeletal muscle insulin sensitization, and increases high molecular weight adiponectin (A Crp 30) [24], along with increase in phospho AMPK in skeletal muscle. Also Tp has been found to be effective for weight reduction and improvement in glycaemic control in obese subjects with type 2 diabetes treated with metformin monotherapy and hence should prove effective in controlling hyperinsulinemia in obese PCOS patients [25]. Central actions of Tp include effects on hypothalamic CRH and galanin [26]. It was also found to have effects on NPY as well as Y1 and Y5 receptors, CRH, glucocorticoids in rats when its weight loss characteristics were being examined [27, 28]. Tp is a neurostabilizer which acts *via* modifications of

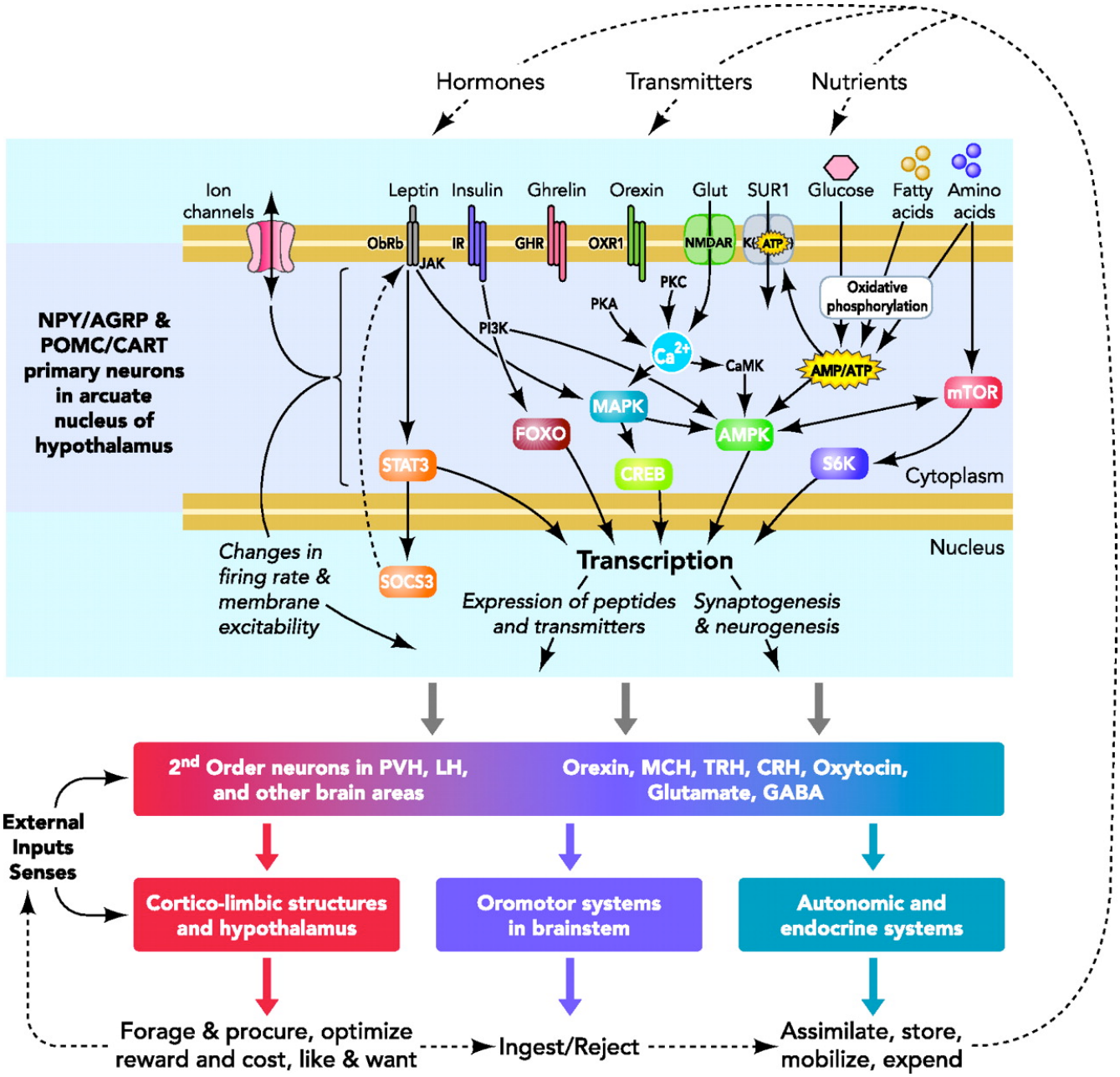


Figure 3: Hypothalamic regulator of energy balance-with permission from ref. [5], Berthoud HR. Highly schematic diagram depicting the major purported intracellular signaling pathways in a hypothetical arcuate nucleus neuron that integrates nutrient, hormonal and neurotransmitter signals and activates downstream neural networks leading to behavioral, autonomic, and endocrine responses. ObRb, long fotm of leptin receptor, IRinsulin receptor; GHR, ghrelin receptor; OXR1, orexin type-1 recceptor; Glut, glutamine; NMDAR, NMDR-glutamatereceptor; SUR1, sulfonylurea receptor; JAK, janus kinase; AMPK, adenosine monophosphate-dependent kinase; Mtor, mammalean target of rapamycin; PKA, protein kinase A.

excitatory voltage activated Na and Ca channels, antagonism of alpha amino-3 hydroxyl-4 isoxazole propionic acid kainite (AMPA-Kainate) receptors and enhancement of GABA-mediated inhibitory currents. Although exact mechanism of action is not clear, animal experiments suggest an increased energy expenditure, decreased calorie intake, of which in humans decreased calorie intake as an appetite suppressant appears to be associated with a significant amount of weight loss [25, 29, 30]. Also AMPK/KA receptor antagonism may lead to a reduction in compulsive addictive food craving as suggested by improvement in binge eating disorders [31, 32]. Tp is a potent inhibitor of carbonic anhydrase isoenzymes and thereby inhibiting lipogenesis [33, 34]. This effect may also contribute to Tp induced hypophagia due to altered taste sensitivity [35]. Although Tp has many favourable metabolic effects and constant demonstration of weight loss efficacy in randomized controlled trials its development as a monotherapy for

obesity has been hindered by a dose dependent neuropsychiatric and cognitive adverse effects such as memory and concentration impairment, language difficulty and mood changes [36]. Several of the adverse effects of Tp maybe related to its inhibitory effect of carbonic anhydrase (CA) [37, 38]. Paraesthesias of the distal extremities and preriorbitally are potential side effects as they are with other drugs with CA inhibitor activity which possibly maybe corrected by potassium supplementation. Also metabolic acidosis can occur due to CA inhibitor activity and type3 renal tubular acidosis [27, 38, 39]. This can usually be resolved by reducing the dose of Tp and administration of sodium bicarbonate if needed. Nephrolithiasis is also more common and incidence can be reduced by supplementation of potassium citrate [27, 39]. In the Qnexia trial only 34 pregnancies were reported with drug being discontinued immediately as soon as pregnancy became known. Of the 19 pregnancies no teratogenicity was reported but in a retrospective study by FDA on Tp for use of Tp in epilepsy an incidence of cleft lip /palate was found to be high and hence considered a risk factor for use in pregnant patients and also it affects contraception efficacy.

PHENTERMINE(PHEN)-PHEN is one of the centrally acting appetite suppressant drugs which was approved for shortterm (upto 3 months) treatment of obesityin a dose range 15mg-37. 5mg by USA in 1939 and remains available today. It is a noradrenergic drug. Its effects on food intake are *via* enhancement of norepinephrine release and possibly *via* blockade of reuptake as well. It does not appear to enhance dopamine release [40], therefore its addiction potential is believed to be less than that of amphetamine [41]. Its side effects of insomnia, irritability, nervousness, constipation, headache, dryness of mouth are typical of sympathomimetic side effects of which most important include palpitations, tachycardia and hypertension [42]. It is primarily metabolized by liver and mainly excreted by urine with a half life of 19-24h.

Four pivotal phase 3trials have been published within last two years. EQUATE/EQUIP/CONQUER/ SEQUEL/FORTRESS (Fetal outcome retrospective topiramate exposure study) [43]-THE EQUATE trial (n=756) compared high dose PHEN/TPM (15mg phentermine/92 mg of topiramate controlled release and mid docse PHEN/TPM (7. 5mg/46mg) with placebo along with a respective single agent PHEN and TPM components x28weeksin adults with BMI>27KG/M2. The EQUIP trial (n==1267) compared high (15/92mg) as well as lowdose (3. 75/23mg) PHEN/TPM with placebox56 weeksin obese individuals(BMI>35Kg/m2 [44]. The CONQUER trial (n==2487) compared fulldose and mid dosePHEN/TPM with placebo x56weeks including obese and overweight adults (BMI-27-45Kg/m2) who had to have 2 or more weight related comorbidities [45]. The most recent study SEQUEL was an extension of the CONQUER study. SEQUEL, was designed to evaluate longterm efficacy /safety of PHEN/TPM combination in obese subjects with cardiometabolic disease for an additional 52 weeks (total 2yrs) [36] reviewed in shin *et al.* 2013 [46] and Cosentino*et al.* 2013 [47]. Atotal of 676(78. 1%) of 866 eligible subjects continued in extension study 84% completed the study and 79. 3%in the high dosePHEN/TPM group and 75. 2 %in the middose PHEN/TPM7. 5/46mg) group lost>5% mean weight loss over a 2 year periodcompared to placebo. The percentage achieving atleast 10% weight loss in maximum dose group was 53. 9% and 50. 3% in the 7. 5/46mg group [46]. All these were statistically significant, better than placeboand also demonstrated a clinical reduction of 76% in new onset of DM.

Both obesity and drug addiction can be defined as disorders in which salience value of one type on reward (food and drugs respectively) becomes abnormally enhanced related to and at the expense of others. Both have powerful reinforcing effects partly mediated by dopamine increases in the limbic system that, under certain circumstances or in vulnerable individuals could overwhelm brain homeostatic control mechanisms [48-51]. New brain imaging discoveries show overlapping brain circuits and that obese and drug addicted individuals suffer from impairments in dopaminergic pathways that regulate neuronal systems associated not only with reward sensitivity and incentive motivation, but also with conditioning (memory/ learning), impulse control (behavioral inhibition), stress reactivity and interoceptive awareness [52].

Hence the newer development of Bupropion SR (400mg) immediate release/naltrexone SR (48mg) (NB) is a most likely combination to be effective. Although the FDA advisory panel voted 13to 7 in favour of approval for this in December 2010, the FDA declined to approve the drug in early 2011 going against the advisory panel recommendation and is requiring a large scale study evaluating CVS sideeffects before reapproval is reexamined. Surprisingly bupropion which is associated with increased CVS risks is used by millions of US people for treatment of mild depression and smoking cessation.

Still it warrants strong attention either by its own or a trial of further 3 drugs namely bupropionSR, naltrexoneSR and topiramate decreasing the dosages of all 3 drugs and further potentially reducing sideeffects but attacking the reward circuitry simultaneously with drugs like bupropion and topiramate which affect weight loss is essential and naltrexone ascertains non development of tachyphylaxis to the weight reducing effect of these drugs.

Bupropion is an antidepressant (of aminoketone class) and is a dopamine reuptake inhibitor. Its structure closely resembles that of diethylpropion, an anorexiant and sympathomimetic agent currently used to prevent smoking. Bupropion has neuronal effects that lead to reduced energy intake and increased energy expenditure. Normallyproopiomelanocortin (POMC) producing neurons in arcuate nucleus release α MSH and β-endorphin. α-MSH mediates the anorectic effects of POMC activation, whereas β-endorphin provides autoinhibitory feedback in an opioid receptors on POMC neurons [53] (Figure **3**). Similar to endogenous signals that cause weight loss bupropion stimulates hypothalamic POMC neuron firing [54] with downstream effects to reduce food intake and energy expenditure. Yet 2 large long term trials showed only modest weight loss (1.7%-3.7%) placebo substracted changes from baseline that reached a plateau by 24 weeks. Hence it was considered that β-endorphin is one of the compensatory mechanisms that limits the long term efficacy of weight loss pharmacotherapy.

Opioid antagonism decreases shortterm food intake [55, 56] perhaps by blocking β-endorphin. Still the opioid antagonist naltrexone fails to produce consistent weight loss, even at large doses (300mg) [57-59]. **Naltrexone** blocks opioid receptor mediated autoinhibition, augmenting POMC firing in a synergistic manner [60]. Given the known effects of naltrexone and bupropion on alcohol addiction [61] and nicotine [62] respectively, NB is hypothesized to induce weight loss through sustained modulations ofmesolimbic reward pathways and goal oriented behaviors [63, 64] (Figure **4**).

Four pivotal trials comprising of Contrave obesity research (COR) programme have been performed, and 2 have been published. The COR-I assesses the safety and efficacy of BUP/NAL in 1742 healthy nondiabetic, obese patients and was published in 2010 [63]. COR-II is a56 week study designed to assess the safety and efficacy of combination in 1496 healthy, nondiabetic, obese patients [65]. 55. 6% vs 17. 5and 50. 5% vs 17. 1% experienced >=5% weight loss vs placebo at 28 weeks and 56 weeks respectively. NB32 (N=32mg, B=360mg/day) produced > improvements in various cardiometabolic risk markers. The most common adverse affect was nausea, which was mild to moderate and transient. NB was not associated with increased events of depression or suicidality vs placebo [65]. COR-Diabetes is a 56 weeks study designed to assess the safety and efficacy of NB in 505 obesesubjects with type2diabetes, COR-BMOD, aunique design to evaluate safety and efficacy of N/B alone or when combined with intense diet exercize and behavior modification in 793 patients over 56weeks published in2011. In COR-BMOD-participants were randomly assigned to 1:3 ratio to receive placebo and intensive weight loss behavioral modification (BMOD) or N/B (32/320mg) and intensive weight and behavioral modification. The placebo +BMOD group lost 5. 1% of initial body weight vs 9. 3% in the N/B with BMOD group. Depression and suicidalideation were more frequent in placebo group as compared to treatment group.

Role of Lorcaserin(Ln)-Although PHEN/TPM combination controlledrelease administration used 2 agents with differing mechanisms of action to provide additive weight loss, while using lower doses of both agents with different mechanism of action, potentially reducing side effects the PHEN/TPM controlled release has been shown to decrease weight at an average of 12. 2kg over 52-104 weeks of treatment. Of this formulation however estimated cost of this is going to be nearly 2200$/year, hence the need for a cheaper antiobesity drug which has also been allowed by FDA. Although the exact mechanism of action is not clearly understood it is believed to act as an agonist at central serotonin subset 2C(5HT2C) receptors located on hypothalamic POMC neurons. Agonists of the 5HT2C receptors is believed to reduce food intake And increase satietyleading to weight loss [66]. Ln shows high selectivity for 5HT2C receptor. Ln is similar in mechanism of action to fenfluramine and dexfluramine, except that it is free of any heart or heart valve side effects.

Three pivotal US trials have been recently published for Ln-BLOSSOM, BLOOM, BLOOM-DM (reviewed in Taylor *et al.* 2013) [67] In the BLOSSOM Trial [68] 4008 obese or overweight individuals with obesity related comorbid conditions were studied, of which 2224 (55. 4%)completed 1year trial. Patients were randomly assigned in a 2:1:2ratio to receive Ln10mgbd (n-=1608), Ln 10mgod (n=801) or placebo (n=1601).

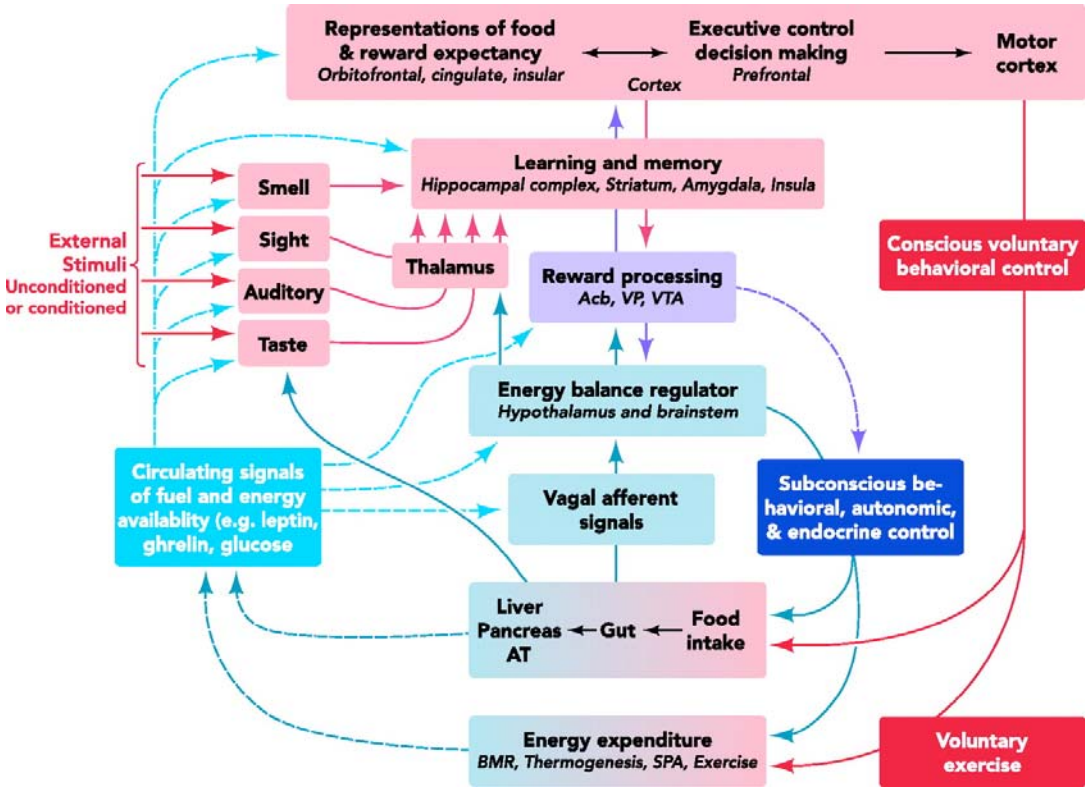


Figure 4: Major systems and pathways responsible for the neural integration of internal and external information in the control of appetite and energy expenditure with permission from ref. [5] Berthoud HR. Blue areas and pathways are mainly involved in metabolic and energy balance regulation. Red areas and pathways are mainly involved in communication with the external world through cognitive and emotional processes such as learning and memory, reward, mood, stress, choice decision making.

All received diet and exercise counseling. After 1 year treatment atleast 5% weight loss was achieved by 47. 2%, 40. 7% and 25% in the Ln twice daily, once daily and placebo respectively. More than 10% weight loss was achieved by 22. 6%of those receiving Ln twice daily, 17. 4% for Ln once daily and 9. 7% for placebo. The BLOOM study evaluated 3182 patients for upto 2years with similar results [69]. The BLOOM-DM study evaluated the safety and efficacy of Ln In 604 patients (BMI-27-45Kg/m2) with diabetes mellitus (DM)on metformin or sulfonylureas or both but not insulin/exenatide/pramlintide and a glycosylated haemoglobin of 7-10% were randomly assigned in 3 groups i. e., Ln10mg bd (n=253), Ln10mgod (n=95) or placebo (n=257) with a follow up for 1 year. along with 600 kcal/day diet and 30 min exercise. The study found that 37. 5% of patients on Ln 10mg bd44. 7% on Ln 10mg od and 16. 1% on placebolost atleast 5%. Approximately half the patients in treatment arm achieved a glycosylated Hb A1c levels <7% almost twice the rate of placebo.

Role of Other Monotherapies Like Tesofensine(Ts)

Ts is an presynapticinhibitor of noradrenaline, dopamine and serotonin reuptake and also stimulates cholinergic system indirectly. It is a sympathomimetic of the family of sibutramine initially investigated during the treatment for parkinsonism and alzheimers disease. Although in phase 2 study with a double blind placebo controlled randomized trial study showed that proportion of patients achieving >=5kg (4. 9% was 59%, 87%, and 91% for 0. 25, 0. 5, and 1mg groups, respectively, compared with 29% of controls the heart rate was significantly elevated along with significant increase in BP and highest frequency of mood changes [70]. Hence Neurosearch initiated phase 3 trials with. 5 and. 25 mg doses only endorsed by FDA and EMA. Atrial of 6000 patients is planned [71].

Role of Pramlintide (Symlin)

Pramlintide (Pram), a synthetic soluble analog of the pancreatic hormone amylin was originally used for DM (type1&2) as an adjunctive to mealtime has been approved by FDA as an antihyperglycemic agent. It has been associated with reduced appetite, food intake and increased satiety, through delayed gastrointestinal motility and currently is under investigation for obesity treatment [72, 73]. In a 16week dose escalation RCT Pram 240µg given in a s/c injection caused a 3. 7% mean weight lossas compared to placebo (p<0. 001

and >=5% weight loss was achieved in 31% of patients (p<0. 001) [74]. Weight loss was regained in placebo group in obese patients participating in a 4 month RCT of Pram at doses of 120, 240, 360μgfollowed by a single blind extension to 1 year but maintained or continues in all but the Pram 120μg twice daily arm was demonstrated. The most common side effect was nausea.

Pram Combination-Pram has been combined with recombinant methyl human recombinant methyl human leptin **(metreleptin**). an adipocyte derived hormone involved in longterm signaling of adiposity and energy intake [75]. In early trial this combination of an amylin and a leptin agonist has demonstrated greater weight loss than either drug alone [75, 76]. **Pram/Metreleptin** at 20 weeks caused a weight loss of 12. 7%+-0. 9% (mean+SD) as compared to 8. 4%+0. 9%for Pram alone (p<0. 001%)and 8. 2%+1. 3%for metreleptin (p<0. 01%) [75]. Pram is also being evaluated with phen and exenatide besides was with the banned drug sibutramine.

Glucagon like Peptide-1-Liraglutide, Exenatide-Anorexic GLP-1 are gut hormones that increase secretion of insulin in pancreatic β-cells. GLP-I analogues such as exenatide and liraglutide are approved for the treatment of type 2 DM. Phase IIItrials with liraglutide have demonstrated beneficial weight loss in obese patients. These agents have double mechanisms of action1) on gastrointestinal tract and 2) on braini. e. to increase the secretion of leptin leading to suppression of appetite, energy intake and a delay in gastric emptying. Long term effect is the decrease in HbA1clevel and systolic BP [77, 78] A RCT of 20 weeks of liraglutide (1. 2, 1. 8mg, 2. 4mg, 3mg) as compared to orlistat (120mg) treatment in 564 nondiabetic obese patients demonstrated mean weight loss of 4. 8kg. 5. 5kg, 6. 3kg, 7, 2kg respectively. as compared to 2. 8kg with orlistat (p=0. 003for1. 2mg, (p<0. 0001 for 1, 8-3mg liraglutide [79]. Higher doses liraglutide (2. 4mg and 3mg) demonstrated 80g> mean weight loss than orlistat. The most common side effects were nausea and vomiting but these were not significantly different to the placebo group. Patients treated with liraglutide also showed a significant decrease in BP and prevalence of preDM (84-96%).

Lixisenatide(Lyxyna)-GLP-1 receptor agonist approved for marketing by EMA in Feb 2013 and has been evaluated in clinical study program called GetGoal. Lixisenatide activates the GLP-I receptor and thereby exercises the range of phsiological effects generated by GLP-1, which consist of increased insulin secretion, inhibition of glucagon secretion and decreased GIT motility alongside the promotion of satiety. Lixisenatide demonstrated significant reduction in glycated hemoglobin (HbA1c)and fasting and post prandial plasma glucose compared to placebo in the Get Goal Study. The effect on glycaemia was evident with both monotherapy and insulin and oral antidiabetic agent combination. Furthermore, a general trend towards reduced bodyweight was reported. In head to head trials, lixisenatide demonstrated a superior effect with respect to reduction in postprandial plasma glucose and had a tendency towards fewer side effects than exenatide and liraglutide. However, lixisenatide seemed to be less or at best equivalent to exenatide and liraglutide in reducing HbA1c, fasting plasma glucose, and body weight. The combination of basal insulin, having a lowering effect on fasting plasma glucose, and lixisenatide curtailing the postprandial glucose excursions, makes sense from a clinical point of view. Therefore lixisenatide is undergoing clinical development as a combination product with insulin glargin (Lantus). At present the main place in therapy for Lixisenatide seems to be in combination with basal insulin with large multicenter trials deciding its future (reviewed in ref. [80]).

Cannabinoid-1 Receptor antagonists (Rimonabant and Tranabant)-The endocannabinoid (EC) system plays an important role in regulation of energy metabolism, foodintake and gastrointestinal (GI) motility. The stimulation of CB1 Receptors in the EC system is believed to affect central and peripheral actions on lipid actions and glucose metabolism in adipose tissue and help to regulate food intake, energy balance and GI motility [81]. Also Crespo *et al.* showed that cannabinoid and orexin-A systems share a common mechanism in food intake and indicate that the hypothalamic orexigenic circuits are involved in the cannabinoid CB1 receptor antagonism mediated reduction of appetite [82]. Rimonabant was the first CB1 receptor antagonist identified for obesity (reviewed in Leite CE 2009) [83]. Although extensive Rimonabant In Obesity (RIO) program comprised of four randomised, double blind, placebo controlled phase 3 clinical trialsrecruiting over 6000 overweight or obese patients whose weight at start was on average 94-104kg [84-87]. Each of the four studies in rimonabant showed significant reduction in body weight and waist circumference over a period of 1 to 2 year period. Rimonabant also improved cardiometabolic risk factors, including triglycerides, blood pressure, insulin resistance, C reactive proteinlevel, and high density

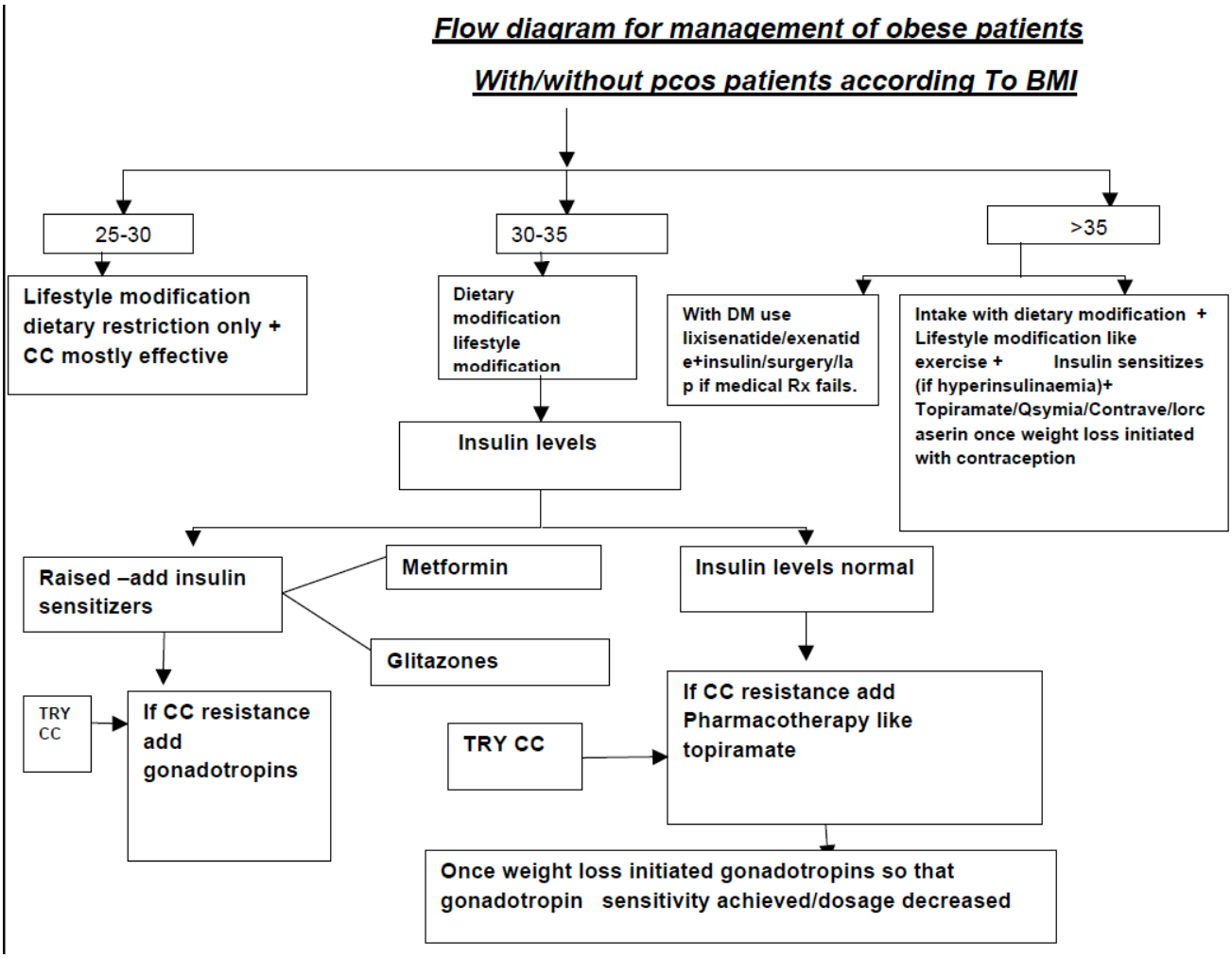
lipoprotein cholesterol level concentration in both nondiabetic and overweight, obese patients with type 2 DM. However as later reports showed use of rimonabant was associated with anxiety, depression, suicidal ideation, the incidence of psychiatric side effects in 26% of participants as compared to 14% in placebo group lead to refusal of authorization by USFDA to rimonabant. Although it was marketed in 18 EU member states in November 2008 the EMA subsequently withdrew authorization for rimonabant from Europe. Despite that Van Gaal believed that by proper selection of patients and lower dosage these psychiatric side effects can be prevented. Similarly the alteration of GI motility [88] is considered as important by others who still believe in use of lower doses of rimonabant with its multiple mechanisms of action and in obese diabetics [89]. Tanabant, a second CB1 antagonist has also been assessed in 52 week trials and showed 4kg placebo adjusted significant weight reduction [90] but psychiatric sideffects have led to withdrawl and other development of pfizer CB1 otonabant, and Bristol-Myers Squibb compound SLV-319 has also been stopped.

Role of **Quercetin**-Quercetin is a flavonol from Minosa phelica leaves. The docking of Quercetin with CB1 receptors showed binding energy of -6. 56Kcal/mol with 4 hydrogen bond in comparison to the drug rimonabant. Since rimonabant has been removed from the market this drug may offer antiobesity effects without the sideeffects of conventional CB1 antagonists. Hence this CB1 adaptogen needs to be studied further with a need for an effective drug with no potential or possible psychiatric or teratogenic sideeefects [91].

Role of Surgical Treatment for Obesity

Because in type2 DM obese patients the outcomes had been so impressive, International Diabetes Federation has recently recommended consideration of bariatric surgery as an accepted treatment options in patients with a BMI of 30-35kg/m2 when DM can't be

Table 1:



adequately controlled by traditional medical managements [92]. The mechanism suggested for weight loss is change in gastric microbiota [93]. In 2011 the FDA extended the approval of LAP-BAND adjustable gastric banding systems to be used for patients who had not lost weight succesfully with nonsurgical methods and had a BMI of 30-34kg/m2with existing condition related to their obesity although previous approval was limited to a BMI >=35kg/m2 with a comorbidity or 40kg/m2 without.

In 2012 Mingrove *et al.* [94] compared weight loss surgery to conventional intensive medical treatment for type 2 DM. They compared 2 surgical procedures roux-en-Y-gastric bass (RYGB) and biliary pancreatic diversion with conventional medical treatment of type 2 DM in a severely obese population. At 2 years diabetes remission as defined as a fasting glucose level of 100mg/dl or Hb A1c levels of <6. 5% had occurred in no patients in the medical therapy group vs 75% of gastric bypass group and 95% of the bilio pancreatic diversion group (p<0. 001) With a greater improvement in Hb A1c in both surgical groups the authors concluded that weight loss with surgical treatment may be more effective than conventional medical therapy for controlling hyperglycemia in severely obese diabetic patients.

In another study Schauer *et al.* compared the efficacy of medical therapy alone with medical therapy +RYGB or sleeve gastrectomy alone in obese persons with uncontrolled DM [95]. This study also showed that surgery with medical therapy caused much better glycemic control in contrast to medical therapy alone. Preoperative BMI did not predict control after the surgical procedures on all studies. The risks associated with surgery along with complications and recurrence with RYGB and the lack of any approved drug has resulted in more and more development of newer endoscopic procedures [96-99].

CONCLUSIONS

Since obesity has grown to epidemic proportions, nearly half of reproductive age women are overweight or obese, with unfavourable ovarian stimulation protocols, higher gonadotropin consumption, lower number of follicles selected. Also because of risk, success rates and economic aspects of infertility treatment in many countries insurance companies refuse to sponsor obese patents for IVF treatment [100]. When writing the article in the last decade wasvery optimistic that the next decade would bring rimonabant as the magic drug for the management of severely obese but besides the psychiatric side effects for which it got banned the recent discovery that endocannabinoids play an important role in human reproduction takes it away from the armamentarium of drugs required for the treatment of obesity in patients who desire conception [101]. Although whatever newer drugs are available are not safe atleast one can use them with contraception to lose body weight before patients can again be taken up for IVF or other treatment (Table **1**).

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