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RESEARCH ARTICLE

SAFETY OF ANTI-OBESITY AGENTS IN ADULTS NARRATIVE REVIEW

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Key Messages:
Adverse events of anti-obesity agents are variable in clinical involvement and severity, moreover, evidence of safety profile related to anti-obesity agents is not homogenous regarding its strength, as some agents investigated on phase II trials with limited duration of follow up,moreover, safety profile of trails not necessarily consistent with phase III trials results, as phase IV follow up could revealed more significant adverse events

Abstract

Background: Weight management medications are appropriate treatment options for individuals who are overweight or obese and have been unable to achieve weight loss with lifestyle intervention alone. In this narrative review, we aimed to review the adverse effects and safety profile of anti-obesity agents in overweight and obese patients.
Methods: PubMed database was were systematically searched for relevant studies published between January 2012 and July 2022 of randomized controlled trials phase II or III of anti-obesity agents, for adult 18 years old with overweight or obesity without diabetes mellitus or secondary causes of obesity.Studies that met eligibility criteria were extracted and reviewed. 48 studies were screened for eligibility, among them, 18 studies fulfill inclusion criteria and involved in the narrative review.

Introduction:-

Excess body weight is the sixth most important risk factor contributing to the overall burden of non-communicable diseases (NCDs) worldwide. Over the past 30 years, the prevalence ofweight gain has considerably increased in high-, low- and middle-income countries.

According to the latest available estimates and projections, the World Health Organization (WHO) indicated that approximately 1.9 billion adults aged 18 years and over were overweight and 600 million were obese in 2014(1).

In addition, the projection for the next 15 years is not promising**:** if current secular trends continue at the same pace, by 2030 the estimated total numbers of overweight and obese people will be 2.16billion and 1.12 billion, respectively (2), with most residing in low- and middle-income countries.

It is well known that NCDs are the leading causes of death worldwide. Of the 57 million deaths that occurred in 2008, the majority (36 million) were attributed to cardiovascular diseasesdiabetes, cancers and chronic respiratory diseases(1).

Lifestyle intervention is the foundation of weight loss and weight management, but additional treatment modalities are often required to produce adequate weight loss (3,4) .

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Weight management medications are appropriate treatment options for individuals who are overweight or obese and have been unable to achieve weight loss with lifestyle intervention alone. When combined with a reduced-calorie diet and increased physical activity, weight management medications can facilitate achievement and maintenance of clinically meaningful weight loss (that is, weight loss of at least 5%) and lead to corresponding improvements in cardiovascular and metabolic risk factors(5,6).

In this narrative review, we aimed to review the adverse effects and safety profile of anti-obesity agents in overweight and obese patients with no secondary causes of obesity or diabetes mellitus.

Methods:-

PubMed database was were systematically searched for relevant studies published between January 2012 and July 2022.The study selection was in 3stages: in the primary screening stage, an electronic search was conducted using the following terms: (Drug OR medication OR therapy OR pharmacotherapy OR pharmacological therapy OR Anti-Obesity Agents) AND (Obesity) AND (adult) AND (trial) AND (safety OR side effect OR Toxicity)". Article titles and abstracts were then screened. The secondary screening stage involved the assessment of the full-text manuscripts. Finally, in the inclusion stage, studies that met our eligibility criteria were extracted.

Inclusion criteria:

1. Randomized controlled trials phase II or III of anti-obesity agents **.**
2. Adult 18 years old with overweight or obesity without diabetes mellitus or secondary causes of obesity**.**
3. Between January 2012 till July 2022

Results:-

48 studies were screened for eligibility, among them, 18 studies fulfill inclusion criteria and involved in the narrative review.

Review Findings:

Liraglutide:

Liraglutide, a glucagon-like peptide-1 (GLP-1)receptor agonist, is used in the treatment ofobesity because it induces weight loss21-23 andmaintains low-calorie diet–induced weight lossfor at least 1 year,11,24 primarily by means of appetiteinhibition.(7)

In a randomized, head-to-head, placebo-controlled trial that enrolled 195adults with obesity(body-mass index [the weight in kilograms divided by the square of the height inmeters], 32 to 43) who did not have diabetes. After an 8-week low-calorie diet,participants were randomly assigned for 1 year to one of four strategies: a moderateto-vigorous–intensity exercise program plus placebo (exercise group); treatment withliraglutide (3.0 mg per day) plus usual activity (liraglutide group); exercise programplus liraglutide therapy (combination group); or placebo plus usual activity (placebogroup).

The primary end point was the change in body weight (in kilograms) from randomization to week 52.

Adverse events that occurred in at least 10% of all participants, urinary tract infections, upper respiratory tract infection, headache, pyrexia, constipation and palpitations.

Gastrointestinal adverse events**,** decreased appetite, and dizziness were more frequently reported in the groups that received liraglutide (i.e., in the liraglutide group and combination group) than in the other two groups. Cholelithiasis as a serious adverse event and palpitations were reported more frequently in the liraglutide group than in the combination group.

After 1 year, liraglutide treatment alone was associated with an increased resting heart rate; this finding was not observed with the combination strategy.(8)

Sinetrol-XPur:

Sinetrol-XPur is extracted by physicalmethods in a concentrated foam using particular varieties of orange, grapefruit, and guarana.(9-12)

The potential mechanisms of Sinetrol-XPur against obesity may be based on antioxidation, (10)antiinflammation,(10)and lowering blood triglyceride (TG), and cholesterol contents.(12)

A study investigated the effect of Sinetrol-XPur on weight and body fat reduction in overweight or obese Korean participants. Among 100 overweight or obese participants enrolled in a 12-week randomized, double-blinded, controlled study, 86 participants completed the trial. Participants took either two Sinetrol-XPur tablets (450 mg per tablet) or two placebo tablets once a day.

The safety evaluation was performed on blood parameters and vital signs. Compared to baseline, the hepatotoxicity markers, such as ALT, AST, gamma-glutamic transpeptidase (c-GTP), showed a significant reduction in the intervention group. No significant differences were observed between the two groups for safety parameters.No moderate or severe side effects were observed during the intervention study. (13)

Efpeglenatide:
Efpeglenatide one of glucagon-like peptide-1 receptor agonists (GLP-1RAs) that can reduce body weight by promoting satiety and reducing food intake, through peripheral and potentially through direct actions on the central nervous system (CNS). (14-16)

In phase II, randomized, placebo-controlled, double-blind trial, participants with a body mass index (BMI) ≥30 kg/m2 or ≥27 kg/m2 with comorbidity were randomized 1:1:1:1:1 to efpeglenatide (4 mg once weekly, 6 mg once weekly**,** 6mg once every 2 wk, or 8 mg once every 2 wk; n = 237) or placebo (n = 60) in combination with a hypocaloric diet.

The primary endpoint was body weight change from baseline after 20 weeks of treatment.

The most frequently reported adverse events were GI AEs, which occurred in 64.4% to 83.1% of participants in the efpeglenatide groups, and in 46.7% of participants in the placebo group. Nausea was the most common GI adverse event in participants treated with efpeglenatide.

In participants receiving efpeglenatide, most adverse events leading to discontinuation were GI disorders**;** none of these GI adverse events were classified as serious adverse events.

Overall, 10 serious adverse events were reported in six participants receiving efpeglenatide; of these, eight led to treatment discontinuation in four participants and were as follows: severe dehydration and severe acute renal failure (one participant; 6 mg once weekly), severe abdominal pain, moderate nausea and severe vomiting (one participant; 6 mg once weekly), moderate cholecystitis with moderate cholelithiasis (one participant; 8 mg once every 2 wk), and severe worsening of diverticulitis (one participant; 8 mg once every 2 wk). Two other participants experienced serious adverse events that did not lead to discontinuation**;** these were prostate cancer (one participant; 4 mg once weekly) and erysipelas (one participant; 6 mg once weekly). Only severe dehydration and severe acute renal failure were considered definitely related to the study drug. No serious adverse events were reported in the placebo group**.**

No cases of cardiovascular adverse events, acute pancreatitis, thyroid cancer or cerebrovascular adverse events were reported.

Symptomatic hypoglycemia was reported in one participant each in the efpeglenatide 6 mg once-weekly (two events) and efpeglenatide 8 mg once-every-2-wk groups (one event).
No severe symptomatic hypoglycemia events were reported.(17)

IQP-AE-103:
IQP-AE-103 is a combination of dehydrated powder of okra (Abelmoschus esculentus (L.) Moench) pods and inulin**,** a heterogeneous mixture of fructose polymers extracted from chicory roots.

Due to this physicochemical property, okra pods can potentially induce satiety and fullness and help to control the calorie intake(18,19). Additionally, okra pods contain dietary fiberand proteins (19), which may play a role in fat binding, thus decreasing absorption of dietary fat and consequently leading to body weight reduction (20).

The study was performed to determine the efficacy and tolerability/safety of IQP-AE-103 on body weight reduction in overweight to moderately obese adults, in which a double-blind, randomized, placebo-controlled trial involved one hundred and eight subjects (BMI between 25 and 35 kg/m2) that were randomly assigned to either the low-dose or the high-dose IQP-AE-103 group, or the placebo group. Following a 2-week run-in period, subjects received two capsules of investigational product after three daily main meals for 12 weeks.

No clinically significant changes in vital signs, safety laboratory parameters and urine analysis were observed in the study in either of the intervention groups or the placebo group at week 12.

A total of 12 adverse events were reported during the course of the study (6 in high-dose IQPAE- 103group, 4 in low-dose IQP-AE-103 group, and 2 in the placebo group), which included upper respiratory tract infections, symptoms of common cold, urinary tract infection, dental root inflammation, or lumbago(21).

Lorcaserin:

Lorcaserin, a selective serotonin receptor (5-hydroxytryptamine receptor 2C, 5-HT2C) agonist, achieving weight loss by increasing satiety and decreasing food intake (22,23).

In a double-blind, randomized controlled trial, 171 obese adults were assigned to receivelorcaserin at a dose of 10 mg, or placebo, twice a day for 24 weeks. Diet and exercise counselling were givento all patients through the treatment period. Primary outcomes were proportion of patients achievingat least 5% and 10% reduction in body weight and mean change in body weight.

A higher proportion of patients taking lorcaserin (58.82%) experienced AE than did those in the placebo group (51.76%). The most common AE with greater incidence in the lorcaserin groupwas dizziness. Although nausea, headache, back pain, upper respiratory tract infection, and cough were more common (>5%) in thelorcaserin group, there was no statistical difference compared withthe placebo group(24).

Coadministration of Lorcaserin and Phentermine:

Lorcaserin is a selective serotonin (5-HT) 2C receptor agonist approved for weight management in patients with a BMI ≥30kg/ m2, or ≥27kg/m2 with ≥1weight-related comorbidity, as an adjunct to a reduced-calorie diet and increased physical activity (25).

Phentermine, indicated for short-term obesity management, is a sympathomimetic amine thought to suppress appetite through norepinephrine release in the hypothalamus (26,27).

In clinical studies, coadministration of serotonergic and noradrenergic drugs has led to additive weight loss (28). However, phentermine may be associated with increased serotonergic activity (29,30). Lorcaserin is a serotonergic agent; therefore, coadministration with phentermine could theoretically result in serotonergic events, adversely impacting safety.

This was a 12-week, randomized, double-blind, pilot safety study of N5238 nondiabetic patients with obesity or overweight with ≥ 1comorbidity randomized to lorcaserin 10 mg twice daily (BID; LOR BID) alone or with phentermine 15 mg once daily (QD; LOR BID1PHEN QD) or 15 mg twice daily (LOR BID1PHEN BID).

The nine common potentially serotonergic adverse events included in the primary end point were dry mouth, headache, dizziness, fatigue, insomnia, nausea, diarrhea, vomiting, and anxiety.

During the study, 94 patients (N=235) reported at least one of these adverse events: 29 (37.2%) in the LOR BID group, 33 (42.3%) in the LOR BID1PHEN QD group, and 32 (40.5%) in

Adverse events with the highest absolute frequency reported in at least one of the groups and at ≥ 5%were headache, fatigue, insomnia, dry mouth, diarrhea, cough, constipation, dizziness, and nausea.

Discontinuation due to adverse events was seen in 5.1%of LOR BID, 2.6% of LOR BID1PHEN QD, and 11.4% of LOR BID1PHEN BID patients.

The only adverse events that led to study drug discontinuation in more than one patient within a dose group were headache (LOR BID, n52; LOR BID1PHEN BID, n52) and dizziness (LOR BID1PHEN BID, n52).

Three serious adverse events occurred during the study: one case of atrial fibrillation (LOR BID1PHEN BID); one patellofemoral arthritis and one appendicitis (both LOR BID1PHEN QD). The investigator considered the serious adverse event of atrial fibrillation in the LOR BID1PHEN BID group to be related to treatment with both study drugs. No deaths occurred during the study(31).

Coadministration of Canagliflozin and Phentermine:

Canagliflozin (CANA), a sodium–glucose cotransporter 2 (SGLT2) inhibitor for the treatment of adults with type 2 diabetes, lowers the renal threshold for glucose reabsorption (RTG), thereby increasing urinary glucose excretion (UGE) and resulting in amild osmotic diuresis and a net caloric loss (32,33).

Phentermine (PHEN), a sympathomimetic amine anorectic that stimulates satiety centers in the brain via upregulation of dopamine, noradrenaline, and serotonin, is indicated for short-term weight management (34).

By increasing satiety,the mechanism of PHEN may complement that of CANA, and coadministration may prevent potential increased caloric intake associated with SGLT2 inhibition, resulting in additional weight loss.

This 26-week, phase 2a, randomized, double-blind, PBO-controlled, multicenter, parallel-group study enrolled individuals who were obese or overweight without type 2 diabetes (N = 335, aged 18–65 years, BMI ≥30 to <50 kg/m2 or BMI ≥27 to <50 kg/m2 with hypertension and/or dyslipidemia). Participants were randomized (1:1:1:1)to receive PBO, CANA 300 mg, PHEN 15 mg, or coadministration of CANA 300 mg and PHEN 15 mg (CANA/PHEN) orally once daily.

The overall incidence of adverse events was 57.3, 59.5 ,54.1 ,and 66.3% with PBO, CANA, PHEN, and CANA/PHEN, respectively.

A higher incidence of AEs leading to discontinuation was observed with CANA (10.7%) versus PBO, PHEN, and CANA/PHEN (6.1, 5.9, and 3.6%, respectively).

The higher incidence of discontinuation due to AEs with CANA was mainly driven by fatigue in two participants, fungal infections (fungal UTI in one participant and genital mycotic infection in two female participants), and headache in two participants.

Three participants discontinued due to AEs with CANA/PHEN: one each due to restlessness and influenza, genital mycotic infection (female), and increased HbA1c.

One serious AE of epistaxis was reported in the CANA/PHEN group that was not considered to be related to study drug and did not lead to discontinuation.

No deaths occurred in any group. No treatment-emergent fractures, male genital mycotic infections, renal- or photosensitivity-related AEs, or AEs of diabetic ketoacidosis or related events were reported in any group.

The incidence of female genital mycotic infections was 10.3 and 7.2% with CANA and CANA/PHEN, respectively, compared with no events with PBO and PHEN; most events were generally mild or moderate in intensity, with one severe event with CANA.

The incidence of UTIs was low overall, with a numerically higher incidence with CANA/PHEN and CANA versus PHEN and PBO (2.4, 4.8 ,1.2 ,and 0%, respectively). All UTIs were mild or moderate, with no reports of upper UTIs.

The incidence of osmotic diuresis–related AEs was 0, 2.4, 3.5, and 9.6%with PBO, CANA, PHEN, and CANA/PHEN, respectively. One participant(1.2%) in the CANA group and one participant (1.2%) in the PHEN group experienced a volume depletion–related AE; none were reported with CANA/PHEN or PBO.

No cognitive disorders, psychomotor disorders, or drug abuse/withdrawal related AEs were observed in any group.

The incidence of psychiatric disorder–related AEs (e.g., agitation**,** anxiety, insomnia) was low and generally similar across groups (4.9, 2.4, 2.4**,** and 4.8% with PBO, CANA, PHEN, and CANA/PHEN, respectively).

The incidence of pooled AEs of palpitations**,** tachycardia, increased heart rate, and irregular heart rate was higher with CANA/PHEN (3.6%) versus PBO, CANA**,** and PHEN (1.2, 1.2, and 0%, respectively)**;** none were serious or led to study drug discontinuation).

PHEN may increase BP and pulse rate and is contraindicated in individuals with a history of cardiovascular disease (35).

Cathine:
The pharmacological action of cathine includes central (anorexia, increased alertness, increased sensory stimulation, hyperthermia) as well as peripheral effects (increased respiration and heart rate**,** rise of blood pressure, constipation, urine retention) (36).

Overweight and obese patients (n = 241, mean BMI 34.6 ± 3.4 kg/m²) were randomly allocated to one of three doses of cathine (16 mg, 32 mg, 53.3 mg) or placebo in addition to a multimodal lifestyle intervention program in a multicenter, double-blind, controlled, dose-finding study for 24 weeks. Primary outcome was weight loss.

During the clinical trial, a total of 243 adverse events were documented. No suspected unexpected serious adverse reactions were reported. Eight of the adverse events were serious, but without any causal relationship to the study medication.

60 adverse events were classified as non-serious ADRs. These reactions included, amongst others, cardiovascular events (e.g., tachycardia, increase in blood pressure) as well as events related to the central nervous system (e.g., restlessness, sleep disorder, depression).

The number of ADRs increased in proportion to the cathine dosage the patients received. Notably, high dose cathine group reported cardiovascular related events as following:
5 palpitation, 2 chest pain, 3 hypertension, 1 ischemia and 1 ECG QT prolongation(37).

Green Tea:
The main components of green tea include catechins, such as Epigallocatechin gallate (EGCG), epigallocatechin, Epicatechin gallate and epicatechin, which have been shown to be beneficial to human health [10]. Among the above catechins, EGCG is the most abundant green tea catechin and is considered the most bioactive component for reducing body weight, which it accomplishes by decreasing adipocyte differentiation and proliferation during lipogenesis (38).

A randomized, double-blind trial was conducted. A total of 115 women with central obesity were screened. 102 of them with a body mass index (BMI) ≥ 27kg/m2 and a waist circumference (WC) ≥ 80cm were eligible for the study**.**

These women were randomly assigned to either a high-dose green tea group or placebo group. The total treatment time was 12 weeks. The main outcome measures were anthropometric measurements, lipid profiles, and obesity related hormone peptides including leptin, adiponectin, ghrelin, and insulin.

No subjects withdrew from the study because of discomfort or adverse events associated with the treatment. There were no major adverse events noted during this trial(39).

Beloranib:
Methionine aminopeptidase 2 (MetAP2) inhibition reduces fat biosynthesis and stimulates fat oxidation and lipolysis(40).

MetAP2 inhibitors are a novel class of drugs that produce striking weight loss in animal and clinical studies [9–11]. Beloranib is a selective and potent MetAP2 inhibitor that significantly reduces food intake, body weight, fat content and adipocyte size in obese rodent models [9].

This phase II, double-blind, randomized study investigated the effects of Beloranib suspension (0.6, 1.2 and 2.4 mg) or placebo, administered subcutaneously, for 12 weeks in 147 participants (primarily white women) with obesity. No diet or exercise advice was administered.

There were no deaths or serious adverse events considered by the investigators to be related to the study drug.

There were no clinically significant changes in laboratory findings**,** ECG measurements or vital signs. Semen analysis and sex hormones (follicle-stimulating hormone, luteinizing hormone**,** testosterone, sex hormone-binding globulin and inhibin B**)**were assessed in male participants during the study and at 3months after the study, and no differences were observed in patients who received Beloranib treatment**.**

A total of 24 (16%) participants withdrew early from the study because of adverse events. The rate of study withdrawal because of adverse events was highest in the 2.4mg Beloranib group (17/35 participants).

There were nine sleep-related adverse events (mostly insomnia) that led to withdrawal from the study. These were associated with higher doses of Beloranib**:** 1.2mg Beloranib (1/37 participants) and 2.4mg Beloranib (8/35 participants).

Injection site-related adverse events were mostly mild and occurred at a similar incidence rate among all the Beloranib and placebo groups. Sleep-related and gastrointestinal adverse events were more frequent with the 2.4mg dose of Beloranib than placebo. Adverse events were generally mild to moderate in severity and transient in nature.

There was a decrease in mean systolic blood pressure in all Beloranib groups as measured by ABPM, and the reduction was statistically significant in the group that received the highest dose of Beloranib (2.4 mg)(41).

Lorcaserin:
Lorcaserin is a novel selective serotonin 2C (5-HT2C) receptor agonist in clinical development for weight management**.**

The 5-HT2C receptor in the hypothalamus modulates food intake by activating the proopiomelanocortin system of neurons that induces hypophagia(42).

A randomized, placebo-controlled, double-blind, parallel arm trial involved 4008 patients, aged 18–65 yr, with a body mass index between 30 and 45 kg/m2 or between 27 and 29.9 kg/m2 with an obesity-related comorbid condition.

Patients were randomly assigned in a 2:1:2 ratio to receive lorcaserin 10 mg twice daily (BID), lorcaserin 10 mg once daily (QD), or placebo. All patients received diet and exercisecounseling.

A higher proportion of patients taking lorcaserin BID (82.6%)or lorcaserin QD (81.5%) experienced AE than did those in the placebo group (75.3%).

The ordered primary endpoints were proportion of patients achieving at least 5% reduction in body weight, mean change in body weight, and proportion of patients achieving at least 10% reduction in body weight at 1 yr. Serial echocardiograms monitored heart valve function.

The most common AE that occurred more frequently in both lorcaserin groups were headache, upper respiratory infection**,** nausea, dizziness, and fatigue.

Investigators considered six serious AE to be possibly related to the study drug; three occurred in the placebo group (syncope**,** ventricular tachycardia, and anaphylactic reaction), and three occurred in the lorcaserin BID group (syncope, moderate depression, and acute anxiety attack).

The overall incidence of depression and depressed mood was low, and the sum was not higher in the lorcaserin groups than in the placebo group.

No lorcaserin-associated changes in clinical laboratory parameters or electrocardiogram parameters were identified(43).

IQP-GC-101:
IQP-GC-101, a patented herbal blend that contains the standardized extracts of Garcinia cambogia (Malabar tamarind), Camellia sinensis (green tea), unroasted Coffea arabica (green coffee), and Lagerstroemia speciosa (Banaba) in a specific ratio, is hypothesized to reduce body weight by inhibition of de novo fatty acid synthesis(44) and stimulation of metabolic rate and thermogenesis (45).

A randomized**,** placebo-controlled, double-blind, parallel group study conducted over 14 weeks (including a 2-week run-in phase) aimed to investigate the efficacy and safety of IQP-GC-101 in reducing body weight and body fat mass in overweight Caucasian adults. Subjects took three IQP-GC-101 or placebo tablets, twice a day, 30 min before main meals. All subjects also adhered to a 500 kcal/day energy deficit diet with 30% of energy from fat.

Ninety-one overweight and mildly obese subjects (46 in the IQP-GC-101 group, 45 in the placebo group) completed the study.

No serious adverse events (AEs) were reported. Nine AEs were reported by subjects from the IQP-GC-101 group, and four AEs were from the placebo group**;** there was no significant difference in the frequency of AEs reported between the two groups.

All of the AEs were rated as ‘mild’ or ‘moderate’ in severity by the investigators and were considered unrelated to the consumption of the study products.

In IQP-GC-101 group, 83 participants were reported infection of upper respiratory tract, 74 participants were reported bronchitis and 36 one were reported cystitis(46).

Diethylpropion, Fenproporex, Mazindol, Sibutramine and Fluoxetine:
Diethylpropion (DEP):
DEP acts on the central nervous system (CNS); this drug increases the release of noradrenaline in the synaptic cleft of the hypothalamic neurons, thus stimulating noradrenergic receptors and inhibiting hunger(47-49).

Fenproporex (FEN):
FEN also acts on the CNS as an appetite-suppressingdrug by increasing catecholamine action(50,51).

Mazindol (MZD):
MZD is a nonamphetaminic**,** tricyclic derivative that blocks the reuptake of norepinephrine in the presynaptic neurons and reduces food intake by suppressing neurons in the lateral hypothalamus(51-53).

Sibutramine (SIB):
SIB is the newest of these drugs; it acts as a reuptake inhibitor of serotonin and noradrenaline in the CNS(54,55).

Fluoxetine (FXT):
FXT is indicated for the treatment of depression and bulimia nervosa**,** with no formal indication for the treatment of obesity.21 However, it is sometimes employed off-label by physicians to promote weight loss due to an acute effect via selective inhibition of serotonin reuptake in the presynaptic neurons(56,57).

A prospective, randomized, placebo (PCB)-controlled study conducted at a single academic institution enrolled a total of 174 obese premenopausal women. To compare the efficacy and safety of diethylpropion (DEP), fenproporex (FEN), mazindol (MZD), fluoxetine (FXT) and sibutramine (SIB) in promoting weight loss.

Participants randomly received DEP 75mg (n=28), FEN 25mg (n=29), MZD 2mg (n=29), SIB 15mg (n=30), FXT 20mg (n=29) or PCB (n=29) daily over 52 weeks. Diet and physical activity were encouraged.

The primary endpoints were changes in body weight and the proportion of women who achieved at least 5% weight loss by week 52 in the intent-to-treat population.

At week 4, dry mouth was the most prevalent adverse event (79 cases, 45.1%), and there was no difference in its frequency among the experimental and placebo groups. The second most common adverse event was constipation (36 cases, 20.6%), which was more frequent in the DEP, SIB and MZD users compared with the PCB users.

Twenty-three patients (13.2%) reported anxiety, which was more prevalent in the DEP group compared with PCB, whereas irritability was more frequent with DEP and FEN in relation to PCB. All the other reported adverse events did not differ in frequency in women treated with medication compared with women treated with PCB. No serious adverse events were noted during the study period.

At week 52, the heart rate increasedsignificantly in women treated with SIB compared with PCB(58).

Litramine IQP G-002AS:
Litramine IQP G-002AS is a natural fiber complex derived from Opuntia ficus-indica, enriched with additional soluble fiber from Acacia spp. IQP G-002AS is standardized for its lipophilic activity and has been shown to reduce the dietary fat absorption through GI fat binding. The lipophilic IQP G-002AS binds to dietary fat, forming fa-fiber complexes, which are not absorbed by the intestine and, hence, are eliminated (59).

One hundred twenty-five overweight and obese adults participated in double-blind, randomized**,** placebo-controlled study, Subjects were advised on physical activity, and received nutritional counseling, including hypocaloric diet plans (30% energy from fat and 500 kcal deficit/day). After a 2-week placebo run-in phase, subjects were randomized to receive either 3 g/day of IQP G-002AS (IQ) or a placebo. The primary endpoint was change in body weight from baseline; secondary endpoints included additional obesity measures and safety parameters.

The study comprised of a 2-week placebo run-in phase and a 12**-** week treatment phase.

There were no significant changes between baseline and 12 weeks in mean heart rate and mean blood pressure. Also, no clinically relevant changes in any blood parameters were noted in the two treatment groups(60).

Semaglutide:
Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that is approved, at doses up to 1 mg administered subcutaneously once weekly, for the treatment of type 2 diabetes in adults and for reducing the risk of cardiovascular events in persons with type 2 diabetes and cardiovascular disease(61).Semaglutide induced weight loss in persons with type 2 diabetes and in adults with obesity who were participants in a phase 2 trial(62-64).

In a double-blind trial, 1961 adults were enrolled with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%.

Similar percentages of participants in the semaglutide and placebo groups reported adverse events (89.7% and 86.4%, respectively), Gastrointestinal disorders (typically nausea, diarrhea**,** vomiting, and constipation) were the most frequently reported events and occurred in more participants receiving semaglutide than those receiving placebo (74.2% vs. 47.9%). Most gastrointestinal events were mild-to-moderate in severity**,** were transient, and resolved without permanent discontinuation of the regimen.

Serious adverse events were reported in 9.8% and 6.4% of semaglutide and placebo participants**,** respectively.

The incidence of serious gastrointestinal disorders (1.4% of participants in the semaglutide group and 0% in the placebo group) and hepatobiliary disorders (1.3% with semaglutide and 0.2% with placebo).

More participants in the semaglutide group than in the placebo group (7.0% vs. 3.1%) discontinued treatment owing to adverse events (mainly gastrointestinal events).

One death was reported in each group, with neither considered by the independent external event adjudication committee to be related to receipt of semaglutide or placebo.

Gallbladder-related disorders (mostly cholelithiasis) were reported in 2.6% and 1.2% of participants in the semaglutide and placebo groups**,** respectively. Mild acute pancreatitis (according to the Atlanta classification18) was reported in three participants in the semaglutide group (one participant had a history of acute pancreatitis**,** and the other two participants had both gallstones and pancreatitis); all recovered during the trial period.

There was no difference between groups in the incidence of benign and malignant neoplasms(65).

Liraglutide:

Liraglutide, a glucagon-like peptide 1 (GLP-1)analogue, increases the postprandial insulin levelin a glucose-dependent manner, reduces glucagonsecretion, delays gastric emptying, and inducesweight loss through reductions in appetite andenergy intake(66,67).

In a randomized, double-blind trial, which consisted of a 56-week treatmentperiod and a 26-week follow-up period, investigators enrolled adolescents (12 to <18 yearsof age) with obesity and a poor response to lifestyle therapy alone.

Participantswere randomly assigned (1:1) to receive either liraglutide (3.0 mg) or placebo subcutaneouslyonce daily, in addition to lifestyle therapy. The primary end point wasthe change from baseline in the body-mass index.

Overall, the percentage of participants who reported adverse events during the treatment period (from week 0 to week 56) was similar in the liraglutide group and the placebo group (111 participants [88.8%] and 107 participants[84.9%]**,** respectively)

Most adverse events weremild or moderate in severity and were deemedby the individual site investigator as unlikely tobe related to the trial treatment.

Gastrointestinalevents — including nausea, vomiting, and diarrhea— were the events most frequently reportedwith liraglutide; these events were more commonwith liraglutide than with placebo (occurring in81 participants [64.8%] vs. 46 participants[36.5%].

Adverseevents that led to discontinuation of thetrial treatment occurred in 13 participants in theliraglutide group and none in the placebo group, in 10 participants, discontinuationwas due to gastrointestinal events.

Serious adverse events were reported by 3 participantsreceiving liraglutide (three events) and5 participants receiving placebo (six events) duringthe 56-week treatment period.

During the 26-week follow-up period,additional serious adverse events occurredin 1 participant who had received liraglutide (oneevent) and 4 participants who had received placebo(five events).

Events related to psychiatric disorders occurredin 13 participants (10.4%) in the liraglutidegroup and in 18 participants (14.3%) in theplacebo group during the treatment period.

1 participant in the liraglutide groupcommitted suicide approximately 340 days afterthe initiation of treatment, and 2 participants(1 per treatment group) reported a suicide attemptduring the 26-week follow-up period. The site investigators and sponsor deemed these three events as unlikely to be related to the trial treatment.

One participant in the placebo group hadacute cholecystitis and cholelithiasis during thetreatment period. One participant in the liraglutidegroup had a single episode of pancreatitiswhich was moderate in severity, and recoveredwithout treatment. More hypoglycemic episodesoccurred with liraglutide than with placebo (26 vs.18). No

instance of hypoglycemia in either groupwas deemed severe according to the AmericanDiabetes Association–International Society forPediatric and Adolescent Diabetes classifications(68).

Tirzepatide:
Tirzepatide is a once-weekly subcutaneousinjectable peptide (approved by the Food andDrug Administration [FDA] for type 2 diabetes)engineered from the native GIP sequence, withagonist activity at both the GIP and GLP-1 receptors(69).

Preclinical data demonstrated that theaffinity of tirzepatide for GIP receptors wasequal to the affinity of native GIP for GIP receptors,whereas tirzepatide bound GLP-1 receptorswith affinity approximately five times weakerthan native GLP-1 bound GLP-1 receptors(69).

GIPactivation appeared to act synergistically withGLP-1 receptor activation to allow greater weightreduction in mice than that achieved with GLP-1receptor monoagonism(69).

In a phase 3 double-blind, randomized, controlled trial, theinvestigators assigned 2539adults with a body-mass index (BMI; the weight in kilograms divided by the squareof the height in meters) of 30 or more, or 27 or more and at least one weight-relatedcomplication, excluding diabetes, in a 1:1:1:1 ratio to receive once-weekly,subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, includinga 20-week dose-escalation period. Coprimary end points were the percentagechange in weight from baseline and a weight reduction of 5% or more.

Overall, 78.9 to 81.8% of participants treatedwith tirzepatide reported at least one adverseevent that emerged during the treatment period,as compared with 72.0% of participants in theplacebo group.

The most frequentlyreported adverse events were gastrointestinal(nausea, diarrhea, and constipation). These adverseevents occurred in more participants in thetirzepatide groups than in the placebo group,were transient and mild to moderate in severity.

Serious adverse events were reported by 160participants (6.3%) overall. Similar percentagesof participants in the tirzepatide and placebogroups reported serious adverse events.

Overall, approximately 21% of serious adverseevents were considered to be related tocoronavirusdisease 2019 (Covid-19), which affectedparticipants in all treatment groups.

Eleven deaths were reported: 4 (0.6%) in the5-mg tirzepatide group, 2 (0.3%) in the 10-mggroup, 1 (0.2%) in the 15-mg group, and 4(0.6%) in the placebo group.

There were four reported cases of adjudication-confirmed pancreatitis, evenly distributedacross treatment groups, including the placebogroup (Table 4). None were adjudicated as severe.

No cases of medullary thyroid cancer werereported. The reported incidence of cholelithiasiswas similar among the tirzepatide and placebogroups. Cholecystitis and acute cholecystitis werereported more frequently in the tirzepatidegroups than in the placebo group, although theincidences were low (≤0.6%)(70).

Discussion:-

Adverse events of anti-obesity agents are variable in clinical involvement and severity, moreover, evidence of safety profile related to anti-obesity agents is nothomogenous regarding its strength, as some agents investigated on phase II trials with limited duration of follow up, moreover, safety profile of trails not necessarily consistent with phase III trials results, as phase IV follow up could revealed more significant adverse events.

Regarding the safety profile of some anti-obesity agents such as sinetrol-XPur, IQP-AE-103,Green tea and litramine, it is unclear due to small sample size, short duration of follow up and underreporting of side effects, based on such limitations it is difficult to discuss its safety profile, more reassuring results in need upon phase III trial(13,21,39,60).

Notably, cathine safety profile can predispose cardiovascular events (tachycardia, hypertension, ischemia and QT interval prolongation). Moreover, Patients with pre exciting cardiovascular or disease electrolytes disturbances are potentially at risk of decompensation of their heart status if they exposed to cathine as anti-obesityagents,however, more accurate results with longer follow up are required(37).

Beloranib safety profile is concerning for patients with pre-exciting sleeping or psychiatric disorder as can participate insomnia, more importantly, its usage in old age, depleted volume status or patient on antihypertensive medications is potentially risky, because it can decrease systolic blood pressure and disturb hemodynamic stability(41).

Triggering of upper respiratory tract infections or bronchitis considered risk factors for exacerbation of chronic lung diseases, as IQP-GC-101 can induce such sort of infections, its use potentially risky on patients with chronic lung diseases, more over IQP-GC-101 can induce cystitis, probably more subjected to such concern are patients with diabetes or females. however, due to short duration of follow up and underreporting of side effects, more results in need upon phase III trial(46).

Exposure to efpeglenatide can result in severe dehydration and nephrotoxicity, especially such concerns are increased with patients at risk, mainly patients with volume depletion or renal disease. Moreover, patients on oral anti diabetic agent potentially at risk of hypoglycemia upon coadministration of efpeglenatide(17).

Despite acute kidney injury is not reported as adverse effect of liraglutide as anti-obesity agent that investigated in randomized controlled trial (trial 4) , however , acute interstitial nephritis and acute tubular necrosis which sometimes require dialysis, has been reported(71).

Risk factors to develop acute kidney injury upon exposure to liraglutide are volume contraction(72), Coadministration of medications known to result in kidney injury during episodes of dehydration (e.g., drugs that inhibit the renin-angiotensin system(72) or preexisting kidney impairment.

Gallbladder disease and biliary tract disease, including cholelithiasis, cholecystitis, and cholangitis have been reported with glucagon-like peptide-1 (GLP-1) receptor agonists, some have required hospitalization or cholecystectomy(73,74,75).

Resolution of biliary stones following discontinuation has been documented(76)It dose- and time-related(77); not fully understood. Animal studies and in vitro data have demonstrated that glucagon-like peptide 1 enhances the proliferation and functional activity of cholangiocytes, which may result in gallbladder diseases(78,79).

Some authors have postulated a change in bile acid production and secretion, suppressed secretion of cholecystokinin, decreased gallbladder emptying, prolonged gallbladder refilling, weight loss, or potentially a combination of these factors(80).

Risk factors to develop gallbladder disease upon exposure to liraglutide are higher doses(81), Longer duration of treatment (e.g., >26 weeks)(81) or patients who experience above-average weight loss with liraglutide treatment(82).

GI effects are the most common adverse reactions associated with glucagon-like peptide 1 receptor agonists, mainly diarrhea, nausea, and vomiting (83,84).

Constipation, dyspepsia, and abdominal pain may also occur. GI effects tend to decrease over time (85).

GI adverse effects are dose-related; however, the exact mechanism is not fully understood. May be a result of delayed gastric emptying or activation of centers involved in appetite regulation, satiety, and nausea (72).

Risk factors to develop GI symptoms upon exposure to liraglutide are dose; generally greater with higher doses and or rapid titration (86).

Using liraglutide or tirzepatidecan increased resting heart rate, it has been observed in placebo-controlled trials; monitoring is recommended. When used for chronic weight management, the manufacturer recommends discontinuation in patients who experience a sustained increase in resting heart rate**.**

Moreover, suicidal behavior, with one case of attempted suicide, has been reported in patients treated for obesity by liraglutide; monitor for new or worsening depression, suicidal thoughts or behavior, or unusual changes in mood or behavior(86).

The FDA has requested that the manufacturer of lorcaserin voluntarily withdraw the weight-loss drug from the US market because a safety clinical trial shows an increased occurrence of cancer,The FDA is taking this action because it believes that the risks of lorcaserin outweigh its benefits based on its completed review of results from a randomized clinical trial assessing safety.

Reviewed data from the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) clinical trial. It was a randomized, double-blind, placebo-controlled, multicenter, parallel group trial conducted between January 2014 and June 2018, the median follow-up time was 3 years and 3 months.

There was a numerical imbalance in the number of patients with malignancies, with one additional cancer observed per 470 patients treated for one year. During the course of the trial, 462 (7.7 percent) patients treated with lorcaserin were diagnosed with 520 primary cancers compared to the placebo group, in which 423 (7.1 percent) patients were diagnosed with 470 cancers. Imbalances in specific cancers including pancreatic, colorectal, and lung contributed to the observed overall imbalance in cancer cases. There was no apparent difference in the incidence of cancer over the initial months of treatment, but the imbalance increased with longer duration on lorcaserin(87).

Despite under reporting of AKI of reviewed trial that investigated canagliflozin , notably , cases of acute kidney injury (AKI) have been reported in patients receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors (specifically canagliflozin and dapagliflozin), including cases that have required hospitalization and dialysis (88).

While canagliflozin may cause reversible kidney-related adverse events (eg, increased serum creatinine, decreased estimated GFR [eGFR]) during the first weeks of therapy, an overall reduction in the risk of AKI and kidney-related serious adverse events was demonstrated in patients who received canagliflozin during the CREDENCE trial (89,90).

As evidence mounts for the positive effects of these agents on long-term kidney outcomes and a possible reduction in the incidence of AKI, clinicians will need to weigh the potential risk of AKI with the overall benefit of these agents (91-97).

Risk factors to develop AKIupon exposure to canagliflozin are preexisting risk factors for AKI (e.g., hypovolemia, chronic kidney insufficiency, heart failure, use of concomitant medications [e.g., diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs])(98).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, including canagliflozin, have been associated with an increased risk of genitourinary fungal infection (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, vulvovaginitis, candida balanitis, balanoposthitis) and, to a lesser extent, urinary tract infections, including severe cases of urinary tract infection with sepsis and pyelonephritis requiring hospitalization (99-101).

These events are generally mild in intensity, respond to treatment, and do not lead to discontinuation (102,103).

Additionally, rare but serious and potentially fatal cases of necrotizing fasciitis (perineum) (ie, Fournier gangrene) have been reported (104,105).

Risk factors to develop genitourinary fungal infection upon exposure to canagliflozin are diabetes and/or uncontrolled hyperglycemia (106,107),older adults, prior history of these types of infections (108),females (108) and uncircumcised males (increased risk for genital infections) (107).

Data regarding the cardiac effects of phentermine alone are limited and conflicting; available evidence suggests that cardiac effects are rare (109).

Phentermine alone may cause increased blood pressure and tachycardia; arrhythmias (including prolonged QT interval on ECG, supraventricular tachycardia, ventricular tachycardia [polymorphic], and ventricular fibrillation); cardiomyopathy (atrial fibrillation-induced); and acute myocardial infarction have been reported in patients with no history of cardiovascular disease (CVD) (110-112).

Phentermine (alone and in combination) has been associated with CNS effects, including delirium, mania, and psychosis (113-117).

Literature has reported insomnia, irritability, and anxiety in 24% to 27% of users (118).

CNS effect of phentermine is dose-related; related to the pharmacologic action; stimulates release of norepinephrine and dopamine (119).

The effect onset is varied; typically occurs within 1 week of initiation (121-123) but may occur several months after initiation (120).

Risk factors to get CNS effects upon exposure to phentermine are high dose (112.5 to 150 mg/day) (115) and or personal or family history of psychiatric disease (113) (120) (116).

No serious adverse events reported due to diethylpropionusage,however, upon reviewing litterateur, its safety profile is concerning,in a scientific statement from the American Heart Association, diethylpropion has been determined to be an agent that may cause direct myocardial toxicity.

Primary pulmonary hypertension has been found to occur with increased frequency in patients receiving some anorexigens, including diethylpropion; use of anorexigens for >3 months has been associated with a 23-fold increase in risk of pulmonary hypertension.

Moreover, the use of some anorexigens, including diethylpropion, has been associated with the development of valvular heart disease. The risk may be increased with extended use, higher than recommended doses, or concomitant use with other anorexigens(121).

The available sympathomimetic drugs which include diethylpropionare only approved by the US Food and Drug Administration (FDA) for the short-term (up to 12 weeks) treatment of obesity because of their potential side effects, potential for abuse, limited duration of use, and regulatory surveillance. They are contraindicated in patients with coronary heart disease, uncontrolled hypertension, hyperthyroidism, or in patients with a history of drug abuse(122).

Also no serious adverse events are reported due to fluoxetine e use as anti-obesity agent in phase II trial , however , reviewing the literature reveal that Anyone considering the use of fluoxetine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years; there was a reduction in risk with antidepressants compared with placebo in adults 65 years and older(123).

Fluoxetine, may increase the risk of bleeding, particularly if used concomitantly with antiplatelets and/or anticoagulants in adult and pediatric patients. Multiple observational studies have found an association with SSRI use and a variety of bleeding complications, ranging from bruise, hematoma, petechia, purpuric disease, and epistaxis to cerebrovascular accident, upper gastrointestinal hemorrhage, intracranial hemorrhage, postpartum hemorrhage, and intraoperative bleeding, although conflicting evidence also exists(124-150).

Gallbladder disease and biliary tract disease, including cholelithiasis and cholecystitis, have been reported with glucagon-like peptide-1 (GLP-1) receptor agonists, including semaglutide and liraglutide (151,152). some have required hospitalization or cholecystectomy (73,74,75).

Reviewing literature revealed that acute kidney injury (AKI), which sometimes requires dialysis, has been reported with semaglutide and other glucagon-like peptide 1 receptor agonists. According to the manufacturer, AKI secondary to semaglutide was seen mostly in patients who had experienced nausea, vomiting, diarrhea, or dehydration(153).

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