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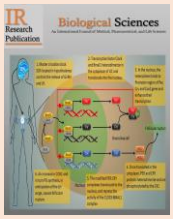

Pharmacotherapy of obesity weight loss maintenance and risk reduction

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ABSTRACT

Obesity, a global health crisis, necessitates multifaceted interventions. This abstract provides a concise overview of obesity pharmacotherapy, covering its context, objectives, significance, and preliminary findings. With obesity's rising prevalence, diverse approaches are crucial. Pharmacotherapy complements lifestyle changes and surgical options. This study aims to succinctly present the current landscape of obesity pharmacotherapy, emphasizing its potential and challenges. Obesity-related ailments, like diabetes and cardiovascular diseases, impose a substantial burden on healthcare systems. Pharmacotherapy aids weight management, catering to severe obesity and unresponsive cases. Various drugs targeting appetite regulation, nutrient absorption, and energy expenditure have emerged. Medications such as orlistat, phentermine/topiramate, and bupropion/naltrexone exhibit moderate effectiveness. However, side effects and sustained treatment requirements pose difficulties.

Introduction

Evidence on both older and new anti-obesity drugs is that these drugs are safe, and many non-bariatric physicians believe them to be inherently dangerous,perhaps more dangerous than the obesity for which they are prescribed, at least unless the patients are egregiously overweight. One reason for this is that weight management drugs, in general, and anorectics, in particular, have had a history of unexpected adverse effect [1]. Although there is little evidence in the medical literature that the dangers enumerated in the product labeling for older drugs have actually occurred, nor is there much documentation of long-term safety and efficacy for older weight management drugs. As a result, an unproven conjecture based on chemical structural similarities to amphetamines regarding the sympathomimetic amine drugs phentermine, diethylpropion, and Phendimetrazine persists, and the potential benefits of effective obesity pharmacotherapy will greatly restrict the use of these drugs [1]. In 2008, The American Society of Bariatric Physicians (ASBP) conducted a national survey examining how bariatric physicians use pharmacotherapy for obesity treatment [2]. The survey revealed a discrepancy between how bariatric medicine physicians actually prescribed pharmacological agents for treating obesity and published treatment guidelines. The obesity treatment guidelines of the National Heart, Lung, and Blood Institute (NHLBI) for the diagnosis and

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treatment of obesity was issued in September 1998 [3]. The expert committee, in formulating the NHLBI guidelines, decided that diagnosis and treatment decisions should be predicted entirely based on body mass index (BMI) or waist circumference (WC) thresholds. This decision was controversial because it was based on opinion and not evidence and because it restricted treatment, especially obesity pharmacotherapy. Some clinicians opposed the decision when the NHLBI guidelines were adopted and published [4]. A consortium of the American Heart Association, the obesity society, and the American College of Cardiology recently received the NHLBI guidelines, and the revision did not change reliance on BMI and WC for diagnosis. More recently, several other obesity treatment guidance documents have emerged that focus on making pharmacotherapy treatment decisions on complication-eccentric rather than BMI-centric decisions [5, 6]. The ASBP guidelines have placed emphasis on diagnostic thresholds other than BMI or WC. since its inception [7]. This national society of clinicians practicing obesity treatment developed practice standards and obesity treatment guidelines long before obesity was officially recognized as a disease and long before the use of BMI came into vogue. BMI, originally an epidemiological tool that correlates best with obesity mortality, is known to be an insensitive indicator of abdominal adiposity [8-10] and of the typical comorbidities associated with obesity [11]. In particular, BMI is an insensitive indicator of cardiovascular risk [12,13]. Recently, the ASBP obesity algorithm was introduced that also put more emphasis on static BMI thresholds in making treatment decisions [14], selection of patients for whom controlled substance anorectics medication can be prescribed has become increasingly controversial since the FDA approval of dexfenfluramine in 1996 and the subsequent phentermine/fenfluramine crisis [15]. The ASBP first formalized and published their Anorectic Usage Guidelines in 1990 following the 1985 National Institute of Health (NIH) census conference that first defined obesity by BMI thresholds BMI >27.2 in women or BMI >27.8 in men. The ASBP guidelines emphasize that pharmacotherapy for the chronic progressive illness called obesity, in any individual patient, should be defined as a BMI>30, whereupon the FDA mandated BMI restrictions in clinical trials for anti-obesity drugs and added BMI threshold restrictions to dexfenfluramine as it was approved in 1999 and, at the same time, extended BMI restrictions to older drugs, including phentermine. The ASBP guidance Emphasized that pharmacotherapy for the chronic progressive illness called obesity, in any individual patient, should be defined as a BMI>30 whereupon the FDA mandated BMI restrictions in clinical trials for anti-obesity drugs and added BMI threshold restrictions to dexfenfluramine as it was approved in 1999 and, at the same time, extended BMI restrictions to the older drugs, including phentermine. After 40 years of safe use, the older drugs were suddenly declared unsafe by the government fiat; physicians who prescribed the drugs to patients who did not fit the government-decreed thresholds were precipitously prescribing " off label. In 1998, the NIH published" Clinical Guidelines on the Identifications, Evaluation and Treatment of Overweight and obesity in Adults, The Evidence Report" These guidelines have also been adopted by a variety of medical associations, including the obesity society (formerly North American Association for the study of obesity [16], the American Medical Association [17], the American College of Physicians [18] and numerous other organizations [19]. These associations all define obesity by BMI thresholds and offer guidance to restrict treatment with anti-obesity drugs to patients with BMI >30 or with BMI >27 if the patient has diabetes, hypertension, or hyperlipidemia. Although these treatments were offered only as guides, not intended to override the clinician's judgment, it is the (unfounded) view of many government agencies and state medical boards that the official guidelines are the standard of practice of course. The official FDA label for a given patient when the patient's BMI exceeds the official thresholds, it appears that only the ASBP obesity treatment guidelines recommend that only the ASBP obesity their own judgment in deciding when to initiate pharmacotherapy treatment irrespective of a patient's BMI, for example, a diabetes overweight patient with a BMI <27 may significantly benefit from weight loss induced by an anti-obesity drug. ASBP guidelines acknowledge the use of anti-obesity drugs in other clinical situations where patients may enjoy clinical improvement.

Why use Pharmacotherapy

Is Pharmacotherapy at all so controversial? There have been numerous clinical trials in the past if all the weight management drugs, and these trials have been reviewed in several extensive meta-analysis, of all which agree that pharmacotherapy is an effective addition to obesity treatment [20-24]. Several studies have shown that patients in weight loss programs who are placed on a weight management drug lose more weight than those on the same program without the drug, in both short-term and long-term trials. In a study by Warden et al. [25], patients administered sibutramine lost 12% of their original weight at 52 weeks, whereas those on the same program with no drug lost 6%.In a clinical study, patients on phentermine and a low-carbohydrate ketogenic diet lost significantly more than untreated patients over 2 years (P= o.o144) [26]. Haddock et.al. [27] reported that, compared to published long-term studies, both 52-week weight loss and patient retention were better when. phentermine was combined with caloric restriction

in a private practice setting. Bariatric physicians who use pharmacotherapy generally agree with the assertions of Haddock et al. that the rate of patient retention was higher in patients placed on weight management medication than in those without modification. Obesity is a chronic illness; the longer the patient stays in therapy, the higher the likelihood of both short-term weight loss and long-term successful weight maintenance. Pharmacotherapy can also produce beneficial effects other than weight loss and metabolic improvements produced by weight loss. There is a evidence that quality of life (QOL) improves with weight loss 28 and evidence that suggests that pharmacotherapy by producing greater weight loss, enhances QOL improvement [29].

When should Pharmacotherapy be Initiated?

The current dogma stipulates that pharmacotherapy is only " indicated" after obesity is diagnosed and that the diagnosis of obesity requires a patient with a BMI >30 or in the case of a patient with obesity. comorbidities, body mass index >27. These indications are explicitly stated on the label of each FDA-approved medicine for obesity. This is indeed a dogma for the reality that the chronic illness currently categorized as obesity is a dynamic pathophysiological process that begins as the patient starts to store excess fat. The earliest pathological change was the infiltration of expanding adipose tissue with inflammatory cells. These macrophages and T cells initiate the release of inflammatory and pro-inflammatory molecules that, in turn, initiate pathological changes in other organs and tissues throughout the body., including the central nervous system (CNS). The disease pathology begins early, but the diagnosis is delayed until the late stage of chronic progressive disease. This pattern was restricted during irreparable damage. Once the drug is indicated," the disease is incurable.

Medications

Phentermine

Phentermine has been the most widely prescribed anti-obesity drug since the FDA first approved it for marketing 55 years ago. Drugs enduring popularity with physicians and patients are a testament to their effectiveness and safety. Surveys in 2008 and 2012 revealed that 97% of the responding bariatric physicians used pharmacotherapy to treat obesity and that 98% of them used phentermine as their first choice as an anti-obesity drug. Phentermine is a substituted phenethylamine derived from B-phenethylamines. Phenethylamines are a naturally occurring monoamine alkaloid found in mammals and many other organisms, such as chocolates, legumes, nuts, seeds, and all varieties of animal protein. The B- Oh any let hula mine skeleton is also the framework for the neurotransmitter's epinephrine, norepinephrine, dopamine, and many other natural and synthetic compounds, such as phentermine albuterol and other bronchodilators, decongestants, antidepressants such as bupropion, and drugs used in children and adults for attention deficit, such as methylphenidate, atomoxetine, lisdexamfetamine, and amphetamine.

The principal central nervous system atomic site of action and whether and how molecular action influences eating behavior, food intake, and ultimately body weight in humans are unknown. A recent FDA review of a New Drug Application for an orally disintegrating form of phentermine 30 stated," weight loss seems to occur due to a combination of anorectic (decreased food consumption), thermogenic (increased metabolic activity) and drug induced increased physical activity". The references cited for this statement are from studies on rodents [31, 33] There are no reports of investigations into the mechanism of action in humans. Phentermine is available in two forms. Phentermine hydrochloride HCl and Phentermine base were attached to an ion-exchange resin. Generic Phentermine in the United States is Phentermine HCl and is available as 37.5mg tablets and as capsule containing 15,30 or 37.5mg. Phentermine resin is available in Australia, Costa Rica, The Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Malaysia, New Zealand, Panama, Singapore, and South Africa. The molecular weights of the two formulations differ, Phentermine HCL,185.7and Phentermine base,149.3. Because of this difference, a 30 mg dose of phentermine base is equivalent to 37.5 mg of Phentermine HCL. Phentermine has several distinct therapeutic effects in clinical use. The first and most obvious symptom is appetite suppression. The other effects are subtler at first but become increasingly obvious with long-term continuation. These effects include improvements in a variety of harmful eating behaviors and detrimental eating cognition, improvement in eating behavior and cognition as determined by the Eating Behavior Questionnaire(EBQ) a 10 question psychometric scale of eating cognition and behaviors, persists in phentermine-treated patients even after the patient has been taking phentermine for years [34, 35] example include measurable improvements in stress and emotional eating, improvement in eating control, less tendency for rapid, out of control eating,control over grazing, diminution of craving,and better ability to adhere to an eating plan; Many Patients, but not all,will notice that their perceived strength diminishes with time. This is true of the effect on appetite compared to other effects. Typically, if the drug is discontinued, as the labeling

advice, hunger, and all prior harmful cognition and eating behavior reappear, leading to weight gain, even though the patient struggles to continue to diet when they complain that the drug has become less effective in controlling their hunger and eating, consideration should be given to an increase in dose rather than to discontinue the drug treatment. The dose was increased using a method known as the dose-to-effect titration.

The long-term effects of phentermine (and in fact all other anti-obesity drugs) have long been ignored, but they are clearly the basis for better success with long-term maintenance when Phentermine is included in a maintenance regimen. One long-term effect observed in a significant number of patients is a reduction in carbohydrate cravings. Such craving typically disappear quickly with early stages of a weight management programs, especially of the caloric restriction component also restricts carbohydrate intake vary low carbohydrate craving disappear promptly on such diets when no weight management medication are used, and it is to tell whether Phentermine helps inhibitor laying craving after the first 3 days on such diet. Patients with carbohydrate intake greater than 20 g daily without phentermine will sometimes still complain of carbohydrate cravings, and it is these patients that the addition of phentermine will sometimes produce diminution of craving if, later in the course of weight loss or during maintenance, carbohydrates. cravings become problematic, the addition of phentermine or an upward adjustment of pH enter mine dose may alleviate cravings, and the addition of hydroxy tryptophan combined with carbidopa to phentermine. Duration of Action Phentermine HCL and Phentermine base are both long acting, with a biological half-life of about 24 hours.

Clinical effectiveness

Phentermine is still the most effective anti-obesity agent. A recent study on long-term phentermine use found that 3% of patients had equal weight loss. to or greater than 10 of the initial baseline weight at one year.

Contraindication

Contraindications to prescribing phentermine include pregnancy, nursing infants, and previous severe allergic reactions to phentermine. Although pregnancy is a contraindication, phentermine and other anorectics have been widely used to prevent excessive weight gain during pregnancy from 1959 to 1979, without any adverse effects on either the gestation or the fetus. After the FDA introduced pharmaceutical pregnancy categories in 1979 and gave Phentermine a category X rating obstetrician stopped prescribing phentermine during pregnancy. However, there is no known teratogenic effect of phentermine. Patients can be advised to continue taking it while trying to become pregnant, and then discontinue it once pregnancy is diagnosed. Nursing mothers should not have phentermine prescribed since the drug may find its way into the breast milk, producing an anorectic effect in the infant. Administration of phentermine to someone who has had a prior severe allergic reaction may induce anaphylaxis.

Ages

Although Phentermine labeling states that the drug should not be used in patients aged 16 years and under, it has been used in children as young as age 3 without ill effects [36, 37]. Typically, guidelines for treating obesity in children and adolescents either omit mentioning the sympathomimetic amine anorectics or condemn their use [38]. The 2008 ASBP survey revealed that 56% of protecting bariatric physicians prescribed anorectics for adolescents. Some caution is advisable here, since pediatricians seem to be uniformly opposed to using older anorectics.It is indeed congruous that the same pediatrician who willingly uses schedule II amphetamine to treat attention deficit hyperactivity disorder (ADHA) in their patients refuses to consider less dangerous schedule IV substances such as phentermine and diethylpropion for treating obesity. It is indeed in congruous that the very same Pediatrician who will willingly use schedule II amphetamine to treat attention deficit hyperactivity disorder (ADHA) in their patients refuse to consider for less dangerous schedule IV substances such as Phentermine and diethylpropion for treating obesity. Informed Consent should be obtained from the parents before prescribing Phentermine for an adolescent, and the parent should be forwarded that the patient's pediatrician would likely be opposed to the use of Phentermine. There is no upper age limit for phentermine. There is no upper age limit for Phentermine.

Dose

The normal starting dose of Phentermine HCL for adults is 15 to 18 .75 mg (half of a 37.5 mg tablet) once or twice daily with the second dose before 3 pm. if a second dose is required. Although the drug has a biological half-life of 18 to 24 h and once-daily dosing should be efficacious, some patients benefit from twice-daily dosing. Phentermine has stimulant effects. Typically, they are mild and fade quickly. In patients who have a history of overreaction to stimulants or panic anxiety, a lower starting dose of 15 mg may be advisable. An even lower starting dose could be achieved by breaking the 37.5 mg

tablet into quarters to achieve a dose of approximately 9 mg 8 mg tablets, available before the Phen-fen crisis in 1997, are no longer manufactured, and the starting dose for younger adolescents should be either approximately 9 or 15 mg/day, and one early study reported that patients administered phentermine on an alternating months schedule had the same weight loss as patients given Phentermine continuously [39]. This practice is not recommended because it interrupts weight loss, sometimes with significant weight gain during the off months. Patient taken off Phentermine often begin to gain in the first month, become discouraged and disillusion with their treatment, and are thus lost to follow-up.

Dose Ranging

Although some early clinical trials used dose-to-effect titration of Phentermine doses [40]. There are only a few modern papers reporting phentermine doses exceeding 37.5 mg/day for treating obesity. There are no modern, double-blind, randomized, placebo-controlled prospective phentermine dose-ranging clinical trials in the medical literature. There are, however, several reports suggesting that dose-to-effect titration has been in use for phentermine for many years. Haddock et al. in their study state," in case of excessive hunger, the initial starting dosage was doubled for Phentermine HCL " Their starting dose was either 30 or 37.5 mg/day; so, some patients were started on either 60 or 75 mg/day.

Combination and Drug Interactions

Although some online chemical databases [41] list a variety of drug interactions, the listing is for drug interactions or known contraindications to combining phentermine with any other drug. Although the FDA label warns of combining phentermine with monoamine oxidase inhibitors because of the possibility of hypertensive crisis, there is no published evidence that such an event has ever occurred, even though obesity itself is a risk factor for hypertensive crisis [42]. Phentermine has insignificant effects on 5-hydroxy tryptophan and serotonin metabolism [43] and can be safely used in patients taking selective serotonin inhibitors antidepressants.

Diethylpropion

Diethylpropion is a safe and effective weight management drug that is widely used. The ASBP medication surveys in 2008 and 2012 revealed that 64% and 63% of bariatric physicians used it for an average of 15% and 18% of their patients, respectively. Diethylpropion is another sympathomimetic amine derived from B-Phenethylamines, and its molecular structure is similar to that of amphetamines. The FDA has long presumed that all sympathomimetic amines, including diethylpropion, have adverse effects similar to, if not identical to, amphetamine. Thus, the product labeling for diethylpropion includes the same conjecture. Its mechanism of action was similar to that of phentermine. Diethylpropion has therapeutic effects similar to those of phentermine, and patients on diethylpropion initially notice appetite suppression. Later, they noticed improvements in eating behaviors with a short half-life and less potent stimulation effects, and diethylpropion has been used safely and with good effectiveness in adults [45], the elderly [46], and in the past, in children [47].

Duration of action

Diethylpropion has a biological half-life of 4–6 hours. The clinical duration of action was approximately 4 h. Plasma- levels obtained with the 75 mg time-released diethylpropion formulation administered once daily indicated a more gradual release than the immediate-release formulation (three 25 mg tablets given in a single dose); after administration of a single dose of one 75 mg controlled-release tablet or diethylpropion hydrochloride solution (75 mg dose) in a crossover study using normal human subjects, the amount of parent compound and its active metabolites recovered in the urine within 48 hours for the two dosage forms were not statically different (http//attenuate-drug/clinical pharmacology.htm). Diethylpropion is a useful weight-management agent. Because of its shorter duration of action, it can be administered later in the day when the patient has trouble with evening hunger cravings or loss of control of eating behavior. Patients in whom phentermine causes insomnia are candidates for diethylpropion. Some patients can tolerate a low dose of phentermine in the morning and may benefit from a morning dose of phentermine and afternoon dose of diethylpropion.

Contraindications

Contraindications of diethylpropion are similar to those of Phentermine: Pregnancy, nursing an infant, and prior allergic reactions to diethylpropion. The drug was frequently prescribed for the prevention of excessive weight gain during pregnancy, with no known problems for 20 years after diethylpropion was approved in 1959 until 1979, when the FDA Pharmaceutical pregnancy categories were introduced. Since there have been no human clinical trials of diethylpropion during pregnancy, the drug was assigned a category, and the majority of obstetricians stopped prescribing the drug.

Ages

Diethylpropion labelling indicated that the drug is not used in children under the age of 16 years. The situation is analogous to the situation with Phentermine, Pediatrician who once used diethylpropion for children, but then stopped for reasons unrelated to the diethylpropion itself. There were no upper age limits.

Dose

The drug is available as 25 mg immediate-release tablets and 75 mg controlled-release tablets. The recommended dose was 75 mg daily. Some patients do well with 25 or 50 mg daily. 30% of the bariatric physicians responding to the 2008 ASBP survey indicated that they sometimes used higher doses of 100 to150 mg daily.

Adverse side effects

Diethylpropion has adverse effects that are similar to those of phentermine. In general, adverse effects due to diethylpropion are less frequent and have lower intensity, and the FDA presumes that the adverse effects of diethylpropion are identical to those of amphetamine and methamphetamine. Diethylpropion labelling includes all the same theoretical objections listed in Phentermine Labelling.

Combinations

Although various databases list drug interactions with diethylpropion, interactions with amphetamines have not been observed with diethylpropion. Diethylpropion is very safe and may be used in patients taking other drugs, including other weight management drugs.

Phendimetrazine

Although Phendimetrazine has been available since its approval in 1959, there are only a few reports of its use in peer reviewed literature [48, 49].

Clinical usefulness

Fifty-six % of bariatric physicians have found Phendimetrazine to be a useful drug: those who use it do so in 18% of their patients. Phendimetrazine is another sympathomimetic amine derived from B - Phenethylamines, and its molecular structure is similar to that of amphetamine. The FDA has long presumed that all sympathomimetic, Including Phendimetrazine, have effects and adverse effects similar to, if not identical to, those of amphetamines. Its mechanism of action is thought to be similar to that of phentermine. Phendimetrazine has a therapeutic effect that is similar to that of phentermine. Patients on Phendimetrazine first noticed suppression of appetite, and then later noticed improvements in eating behavior.

Contraindications

These are the same as those of phentermine.

Mechanism of action

In the body, Phendimetrazine is converted to phenmetrazine, the active metabolite of phenmetrazine, which is a sympathomimetic with anorectic properties.

Dose

The typical dose was 35 mg three times daily. The maximum dose listed in the package labeling and PDR was 70 mg three times daily.

Dosage Ranging

Some patients tolerate a dose that is higher than the typical dose. The 2008 ASBP survey found that only 51% of bariatric physicians prescribed Phendimetrazine at the recommended daily dose of 105 mg of the reminder,16% prescribed 140 mg/day, 5% prescribed 175 mg/day, 26% prescribed 210 mg/day, and 1% prescribed 280 and 315 mg as their higher dose. The beneficial effects, adverse effects, and potential or relative contraindications are similar to those of phentermine. Phendimetrazine can be used in combination with the same drug as is Phentermine.

Orlistat

Clinical usefulness

Orlistat has not proven to be very useful in clinical practice because few patients tolerate gastrointestinal side effects. Although 44% of medical bariatric specialists prescribe Orlistat, these physicians only use it in 6% to 8% of their patients. Orlistat is a very safe, but only modestly effective, weight loss drug. It is an intestinal lipase inhibitor that prevents the absorption of some of the fat a patient consumes for a few hours taking the drug. Its effectiveness is limited by its unpopularity, with the majority of patients finding it useful for its maintenance. It is available as a prescription 120mg capsule marketed as Xenical and also as an over the counter 60mg capsule (Alli) Dosage: Either 60mg capsule or 120mg three times daily.

Adverse reactions and side effects

The most common side effects of orlistat are abdominal discomfort, oily stools, oily diarrhea, and increased flatus.

Management of adverse reactions and side effects.

Severe adverse reactions are virtually unheard of, but gastrointestinal side effects are very common. Most patients learn to sketch the drug if they plan to eat a full meal. The adverse effects of orlistat can be reduced by reducing the amount of fat ingested during meals.

Phentermine/Topiramate

The FDA first approved topiramate in 1996 for the treatment of refractory epilepsy. At that time, since most epilepsy drugs in use induced weight gain or obesity, observation of weight loss among epilepsy patients treated with topiramate quickly led to weight loss trials in humans [50, 53] that demonstrated both significant weight loss and successful weight loss maintenance. These reports, together with others, indicate the effective use of topiramate in the treatment of binge eating disorders [54, 55, 56], leading to trials combining Topiramate with Phentermine. The FDA approved the combination of Phentermine with Topiramate (Qsymia) in 2012, Approval was controversial, The FDA had asked the sponsoring company, vivas, Inc (Mountain view CA), to provide additional safety data. Despite the controversy, the 2012 ASBP Prescribing Practice Survey, performed a few months before FDA approval, revealed that 61% of the bariatric Physicians were already using Phentermine Combined with generic Topiramate for some of their Patients and that 43% indicated they would prescribe Osmia were it to be approved.

Duration of Action

Twenty-four hours

Clinical usefulness

The various Osmia trials proved that the combination is an effective anti-obesity medicine,47% of patients on a high daily dose lost 10% or more of their baseline weight at 1 year, weight loss at 1 year averaged 12.8% of baseline weight, and 11.4% at 2 years.

Contraindication

Women taking topiramate during the first trimester of pregnancy have an increased risk of developing craniofacial defects, primarily cleft palates. Topiramate is found in the milk of nursing mothers, and because its effect on newborns is unknown, topiramate is not recommended during breastfeeding. Acute closed-angle glaucoma syndrome is a rare condition. Idiosyncratic reactions to topiramate. Although this usually responds to prompt treatment, it is probably best to avoid topiramate in patients with established angle-closure glaucoma unless the patient's ophthalmologist agrees and monitors eye pressure frequently.

Ages

The use of Qsymia in patients under the age of 18 years has not been evaluated and includes adolescents and children without problems peculiar to the ages; therefore, physicians and patients can draw their own conclusions. Since only 7% of the patients in the clinical trials were aged ≥ 65 years, the FDA recommends caution in patients in this age group, even though no. Differences in efficacy and safety were also observed. Both Phentermine and Topiramate have been used individually in this age group.

Dose

As a part of the FDA-mandated Risk Evaluation and Mitigation strategy program, Qsymia is available only through Pharmacies certified as trained in Qsymia dispensing by the FDA, the drug comes in capsules of four strengths Phentermine strengths are expressed as Phentermine base. The equivalent phentermine dose expressed as Phentermine HCl was approximately 4,7,9.3,14 and 18.75 mg. Topiramate is an extended-release form of topiramate, with a peak plasma level at 9 h. The resin form of phentermine has a half-life of 24 hours. Patient who has been on the usual dose (7.5 mg Phentermine/ 46 mg Topiramate) for 12 weeks and lost 3% or less of initial body weight, the dose escalated to 11.25 mg/69 mg for 14 days and then increased to a high dose (15 mg/92 mg), and adverse side effects (common side effects are multiple and are primarily due to the topiramate components. These side effects include paresthesias, headache, dizziness, dysgeusia, insomnia, constipation, and dry mouth. Less frequent side effects include short-term memory loss, dyslexia, nausea, and depression. Acute angle closure glaucoma can occur but is very rare and is thought to be an idiosyncratic reaction to the embedded sulfur atom in the molecule. In practice, the combination Phentermine/topiramate is not well tolerated long-term by patients; more than one-half of a patient discontinue the combination because of side effects mainly due to the Topiramate [57].

Lorcaserin

Locaserin (Belviq) is a selective serotonin 2C receptor agonist with minimal activity at other serotonin receptors, Including the 2B Heart Valve receptors. After it was established that fenfluramine acts as a serotonin 2 B receptor agonist in heart valvulopathy [58]. Vivi's initiated search for specific serotonin 2C receptors was initiated. After establishing that lorcaserin was a potent 2C receptor agonist but did not activate 2 B receptors, a clinical development process was initiated. During the ensuing clinical trials, the FDA required that multiple echocardiograms be obtained on the subject; at one year, 2.2 % of placebo-treated patients developed. Cardiac Valvulopathy whereas 2.3% of lorcaserin-treated subjects did so. The differences were not statistically significant. The valve changes were predominantly mitral and aortic regurgitation of the sort observed in the aging population. No changes in pulmonary artery pressure were noted in 59 47% of Locaserin-treated subjects in the clinical trials that achieved a 5% weight loss at 1 year, and 22.5% achieved a 10% or greater loss. Weight loss at 1 year averaged 6%, but placebo-adjusted weight loss was approximately 4%. The FDA is requiring Arena Pharmaceuticals (San Diego California) to conduct a post-marketing 5 -year long-term cardiovascular outcomes trial (NCT02019264)Many Physicians are already prescribing a combination of Belviq and Phentermine(NCT 01987427).

Duration of Action: Twenty-Four Hours

Clinical usefulness

Whether lorcaserin alone is useful remains unclear. Initial reports on the combination of phentermine/lorcaserin suggest that it is quite effective, perhaps as effective as the combination of phentermine/fenfluramine. Contraindication: The drug was rated as pregnancy category X. Age: The drug has not been tested in adolescents or children. Dose- Ten milligrams twice daily

Adverse side effects

The most common adverse side effects were headache, dizziness, nausea, and diarrhea, and the number of patients who discontinued the drug in clinical trials owing to side effects was low. Potential or theoretical adverse effects: The DEA has decided that the drug is potentially addicting and has deemed it a category IV controlled substance. This development came despite a DEA-requested study." Conducted according to standard abuse-Potential guidelines" evaluating the addiction potential of lorcaserin in Poly drug users, which concluded that " lorcaserin has a very low potential for abuse" The subjective effect of supra therapeutic doses of lorcaserin were, on balance, negative, thereby confirming lorcaserin low risk for abuse" and " The AEs reported in the current study also indicate that supra therapeutic doses of lorcaserin are associated with negative side effects that would mitigate the risk of abuse"60 SSRIs serotonin and norepinephrine reuptake Inhibitor, bupropion, tricycle antidepressants,and monoamine oxidase inhibitors were excluded from the trials.one patient taking dextrose the robin developed serotonin syndrome. It seems prudent to monitor serotonin syndrome in patients on antidepressants. Patients with long-term lorcaserin use experience age-related aortic and mitral valve regurgitation at the same rate as untreated patients. Physicians should closely observe the treated patients for the development of new murmurs. Physicians Prescribing Belviq should familiarize themselves with the approved FDA label for the drug and with the clinical trials data [61-63].

Combination

Early reports on the use of phentermine once daily combined with Belviq have reported good success.

Contrave

Contrave is a combination of bupropion, an antidepressant that is a weak inhibitor of the neuronal reuptake of norepinephrine and dopamine, and naltrexone, a u-opioid receptor antagonist originally approved for the treatment of alcohol and opiate addiction. Bupropion stimulates hypothalamic proopiomelanocortin (POMC) neurons to release alpha-melanocytes-stimulating hormone (alpha-MSH), which is an agonist of melanocortin 4 receptors that initiate a cascade leading to decreased energy intake and increased energy expenditure, resulting in weight loss. As POMC neurons release Alpha-MSH, they also release a U - opioid receptor agonist that induces diminution of alpha-MSH release. Naltrexone blocked this negative feedback, working synergistically with bupropion, thereby amplifying the weight loss effect. Bupropion is a substituted phentermine, but there have been no suggestions for its addiction potential. However, this combination was not classified as a controlled substance.

Duration of Action: 12 hours

Clinical usefulness

49 % of contrave treated subjects in the clinical trials averaged 6% to 8% depending on the trial. The FDA

required Pre-approval, 5 years long-term cardiovascular outcomes trials, but approved the drug in 2014 before the trials were completed, based on favorable preliminary data.

Contraindications

Uncontrolled hypertension, seizure use of other bupropion-containing products- opioids or opioid antagonist use, monoamine oxidase inhibitors use, and pregnancy are contraindications. The drug is also contraindicated in nursing mothers.

Ages: Adults only

The drug combination has not been tested in children and adolescents. Dose: Contrave tab are available at 4mg/90 mg naltrexone/bupropion and 8 mg/ 90 mg naltrexone/bupropion. The recommended daily dose is 32mg naltrexone and 360 mg bupropion. Since nausea effect, patients should be started with one morning 8mg/90mg tablets for the first week and then have gradual dose escalation increasing by one tablet/day each succeeding week until a dose of 32 mg/360mg naltrexone/ bupropion is reached at week 4. If nausea occurs, the dose can be reduced by switching to the 4 mg /90mg tablets or by showing the timing of dose escalation or by using both techniques.

Adverse side effects

Common side effects include nausea, constipation, headache, vomiting, dizziness, Insomnia, dry mouth, and diarrhea. In the clinical trials, 24% of patients on contrave discontinued it because of adverse effects. Uncommon adverse effects: suicidal behavior, activation of mania, seizures, increase in blood pressure and heart rate, allergic reactions, and angle closure glaucoma may occur, but are not common. Both drugs in combination have been widely used; naltrexone first approved in 1984 has been prescribed for more than 1 million patients, and bupropion first approved in 1985 has been prescribed for more than 50 million patients. Physicians prescribing contrave should familiarize themselves with FDA-approved labels and with the clinical trials data [64-66].

Combinations

Presently there are no studies reported combining agents for weight loss. Topiramate: shortly after this sulfa mate substituted monosaccharides was introduced as an anti-epileptic, topiramate was noted to produce weight loss in treated subjects clinical trials demonstrated weight loss comparable to the other anti-obesity drugs, and currently 45% bariatric medicine specialist prescribe Topiramate for weight loss in their patients. Once a very expensive drug is now available as a generic.

Clinical usefulness

Topiramate has been found to be very useful in treating binge eating disorder [67] and in treating drug-induced weight gain produced by antidepressants and some other psychiatric drugs [68]. Topiramate can be used as a single -agent, and since it is not a controlled substance, it can be used as an alternative to the older drugs. Obesity is not considered an indication for topiramate; the drug is not FDA approved for obesity, so its use in obesity is off label. Absolute contraindications: known sensitivity to sulfa mate is an absolute concentration.

Dose

The effective dose for weight management ranges from 25 to 200mg/ day. The typical starting dose for weight management is 25mg at bedtime. If this does not produce the desired effect, the dose can be slowly increased In 25mg increments using dose to effect titration. By increasing the dose once every 2 weeks or at monthly intervals, any annoying side effect can often be avoided, most patients do not need more than 100mg/day in the first year or two of treatment, and some patients with eventually require 200mg/day.

Beneficial effect

Patients with binge eating often experience a diminution in frequency and intensity of binge eating, Patient with iatrogenic drug-induced weight gain either lose weight or stop gaining weight. other patients note a decrease in hunger, eating, or both Patients who have trouble with after-dinner cravings, hunger, or eating behaviors sometimes respond well to topiramate. Adverse side effects: A greater number of patients experience adverse side effects with topiramate monotherapy than do patients on Phentermine monotherapy. As a result, after 6 months of treatment, a greater number of Patients on Topiramate alone have discontinued the drug. Topiramate is a weak carbonic anhydrase inhibitor and can produce symptoms suggestive of Peripheral neuropathy. These symptoms usually disappear if the drug is discontinued. Memory loss for recent events, Psychomotor slowing, difficulty with concentration, depression, Speech or language problems, and dysesthesias are common at doses used for epilepsy and can occur at doses for weight management, but they are less common. Patients sometimes complain of dysgeusia, particularly for carbonated beverages; in some patients, this is actually a beneficial side effect. Patients started on

topiramate should be warned about the eye symptoms of a glaucoma attack. Always discontinue topiramate immediately. If the Patient complains of eye pain or any change in visceral activity. Patients who present with eye symptoms should be immediately referred to an ophthalmologist since untreated secondary angle glaucoma is an ocular emergency that can result in blindness. Neurological reactions can often be alleviated with dose reductions. Combination: Phentermine/Topiramate is an effective scribe either the FDA-approved Combination (Qsymia) or prescribe the two drugs as generics.

Zonisamide

Zonisamide is another antiepileptic drug that can induce weight loss. A clinical trial with zonisamide as monotherapy indicated a respectable weight loss [69-70] and other clinical trials have shown it useful in binge eating [71-72]. Another clinical trial has shown it useful in binge eating [73-74] with good results with a combination of bupropion and Zonisamide [75] and yet another suggests zonisamide is useful in preventing Olanzapine-associated weight gain [76] Probably as a result of these reports.

Liraglutide

Liraglutide is a glucagon-like peptide (GLP-1) receptor agonist that is 97% homologous to native GLP-1. The native hormone is a Postprandially released gut hormone that lowers blood sugar, slows gastric emptying, decreases appetite, improves satiety, and lowers caloric intake. The drug was approved for diabetes in 2010 and has since been used in more than 3 million Patients, many of whom lost weight [77]. An FDA Advisory committee recently recommended approval of the drug at a 3.0 mg/day dose for weight loss, and it is expected that the drug will receive FDA approval.

Other pharmacological agents

Certain drugs are useful as adjuncts in obesity Pharmacotherapy. Generally, those drugs have not proven to be effective in producing weight loss when used alone. Metformin is an agent useful in treating diabetics or patients with insulin resistance. The addition of Metformin in treating diabetes or insulin resistance can prevent or diminish the weight gain attendant to other drugs used in treating these conditions and will occasionally produce modest weight loss More often, there is minimal or no weight loss, met for min offers no benefits to a patient with a normal fasting glucose and insulin levels. Bupropion is a dopamine and norepinephrine reuptake inhibitor. When used as monotherapy, it can produce a modest weight loss that plateaus within a few months 78 Bupropion should be considered when obese Patients are required on antidepressants. The 2008 ASBP Prescribing Practice Survey. indicated that 25% of the bariatric Physicians were using bupropion in 7% of their patient's weight loss is more impressive when naltrexone is combined with bupropion 79 GLP-1 receptor agonists (other than liraglutide), including Exenatide and albiglutide, enhance insulin secretion, suppress glucagon, and slow gastric emptying. Clinical trials in patients with type 2 diabetes have demonstrated weight loss in the range of 1 to 3 kg over 26 to 52 weeks [80-81]. Exenatide (Byetta) is currently in the United States, as is albiglutide as add -on- drug for use in diabetes with poor glucose control and is not intended for monotherapy either for diabetes control or weight loss. Spironolactone will, in some women, inhibit premenstrual chocolate, sugar, and other carbohydrate cravings, Spironolactone at 25mg daily for a few days prior to menses often reduces or eliminates cravings. The combination of hydrochlorothiazide and spironolactone, at 25mg of each, is equally effective and is less expensive 5 - HTP is the immediate precursor of serotonin (5 - hydroxy tryptamine) and has long been known to relieve carbohydrate craving [82]. 5-HTP is converted to serotonin in the brain and activates the leptin-melanocortin an orexigenic signaling Pathway [83] 5- HTP works because it crosses the blood-brain barrier and is then converted to serotonin in the gut, liver, and bloodstream; high oral doses of 5 - HTP are required to produce even small increases in the brain. Serotonin, of 5 HTP is given alone, high doses of up to 900mg/day produce the best results. Many Patients have nausea and other gastrointestinal side effect at such high doses, limiting the effectiveness of 5 HTP alone. A few Patients do well with 150 to 300mg 5 HTP/ day, but for most Patients, low doses are not effective. Carbidopa is a peripheral inhibitor of L- L-aromatic amino acid decarboxylation and inhibits premature decarboxylation of 5 HTP to serotonin before it can cross the blood-brain barrier carbidopa at a 5mg dose; has no other Pharmacological effect L-dopa/carbidopa combinations are used in treating Parkinson disease. The carbidopa inhibits decarboxylation of the L-dopa, increasing its effectiveness. combining carbidopa with 5-HTP increases the effectiveness dramatically 5-HTP / carbidopa in combination has been used extensively in Europe as a treatment for depression, generally a higher dose of 5-HTP than needed for anorectic use [84]. The patient can be started on a dose of 5 mg 5-HTP with 5 mg carbidopa, taken three times daily with meals. If the patient has a good response and no side effects, then the dose may be gradually increased. First to 10mg, then 15mg, and eventually up to 20 or 25mg 5-HTP, always with 5mg carbidopa. Occasional Patients

Table. Agents for weight loss and maintenance

Agent	Mechanism of Action	Examples	Efficacy	Side Effects
Orlistat	Lipase inhibitor; reduces fat absorption	Xenical, Alli	Moderate weight loss	Gastrointestinal issues (oily stools, flatulence)
Phentermine/Topiramate	Appetite suppressant; enhances satiety	Qsymia	Significant weight loss	Insomnia, dizziness, increased heart rate, paresthesia
Bupropion/Naltrexone	Affects reward pathways, reduces food	Contrave	Moderate weight loss	Nausea, headache, constipation, risk of seizures (bupropion)
Liraglutide	GLP-1 receptor agonist; reduces appetite	Saxenda	Significant weight loss	Nausea, vomiting, diarrhea, pancreatitis risk
Lorcaserin	Serotonin receptor agonist; reduces	Belviq	Modest weight loss	Headache, dizziness, nausea, serotonin syndrome risk
Naltrexone/Bupropion	Affects reward pathways, reduces food	Contrave	Moderate weight loss	Nausea, headache, constipation, risk of seizures (bupropion)
Phentermine/Extended-release	Appetite suppressant; enhances satiety	Qsymia	Significant weight loss	Insomnia, dizziness, increased heart rate, paresthesia
Semaglutide	GLP-1 receptor agonist; reduces appetite	Wegovy	Significant weight loss	Nausea, vomiting, diarrhea, pancreatitis risk

benefit from a fourth nighttime dose of 5-HTP can cause gastrointestinal side effects in higher doses. Carbidopa is not used alone therapeutically and has no known side effects. Side effects of carbidopa reported in the medical literature are those of the L-dopa with which the carbidopa is compounded. The only significant adverse side effect is gastric irritation or nausea when the 5-HTP/ carbidopa medication is taken on an empty stomach. Neither serotonin syndrome- nor cardiac valvulopathy has been reported in patients on 5-HTP at any dose level [85]. Thus, 5-HTP/ carbidopa can be thought of as a safe replacement for fenfluramine, and like fenfluramine, it is best when used in combination with Phentermine. Patients treated with 5-HTP /carbidopa alone generally neither experience a significant weight loss nor notice a diminution of sugar or other carbohydrate craving.

Useful combination

Phentermine and 5-HTP/carbidopa are a useful combination with a mechanism of action similar to Phen -fen but with no risk of cardiac Pathology. The 5-HTP tends to modulate the stimulant effect of the Phentermine so that patients tolerate the Phentermine with fewer side effects .weight loss with the combination when both Phentermine and 5-HTP/carbidopa is started in a new Patient is similar to that seen with Phen-fen some Physician prefer to start the Patient on Phentermine and add the 5-HTP/ carbidopa at a later time one report suggest a 16% weight loss at six months with Phentermine and an optimum protein, restricted carbohydrate diet at which point the 5-HTP carbidopa is added resulting in a 17% weight loss at 1 year. Phentermine/Topiramate is the combination used in Virus's new drug Qnexa. Both drugs are currently available as generic and can be prescribed or dispensed by bariatric Physicians. By Prescribing these drugs in combination, the advantages of a fixed dose combination can be avoided, with the possible benefits of producing greater weight loss. The 2008 ASBP survey found that 18% of the physicians who used a combination of anti-obesity drugs used Phentermine/Topiramate. Phentermine/Diethylpropion is a combination useful for patients who benefit from Phentermine but can only tolerate low early morning doses and experience a return of hunger and appetite to the late afternoon or evening. The addition of one or two doses of diethylpropion afternoon may be beneficial. Diethylpropion used in this way seldom provokes insomnia or overstimulation because of its short duration of action. Phentermine/ Fluoxetine, thought to be an effective combination by some 86 Naltrexone found useful by most bariatric specialists. The 2008 ASBP survey found that 3% of Physicians used the combination Phentermine / Fluoxetine. Bupropion/ Zonisamide as a combination has shown some promise. Patients in an initial 12-week trials with this combination reportedly achieved 85% weight loss. Both drugs have been approved, so some bariatric Physicians are using the combination.

Phentermine/Pramlintide as a combination produced 11.3% weight loss at 24 weeks in one study [87-88].

Conclusion

Pharmacotherapy is an integral facet of the multifaceted fight against obesity. While it assists in weight management, its optimal utilization necessitates a careful evaluation of individual characteristics, potential adverse effects, and long-term success. Integrating pharmacological interventions within a comprehensive framework of lifestyle adjustments and medical supervision holds promise for addressing the obesity epidemic and its attendant health challenges. This abstract offers a succinct insight into the pivotal role of pharmacotherapy in tackling obesity's intricate conundrum.

Contribution of authors

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