Phentermine

A Systematic Review for Plastic and Reconstructive Surgeons

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Purpose: Phentermine is the most prescribed antiobesity drug in America, with 2.43 million prescriptions written in 2011. Case reports suggest there are anesthetic risks, such as refractory hypotension, involved with its perioperative use. Despite these risks and the frequency of phentermine use among plastic surgery patients, there are no published guidelines for the perioperative management of phentermine use in the plastic surgery literature. To address this patient safety issue, we performed a systematic review and provide management recommendations.

Methods: A systematic review of the pharmacology of phentermine and the anesthetic risks involved with its perioperative use was undertaken using the search engines PubMed/MEDLINE, EMBASE, and Scopus.

Results: A total of 251 citations were reviewed, yielding 4 articles that discussed perioperative phentermine use and complications with anesthesia. One was a review article, 2 were case reports, and 1 was a letter. Complications included hypotension, hypertension, hypoglycemia, hyperthermia, bradycardia, cardiac depression, and acute pulmonary edema.

Conclusions: The relationship between phentermine and anesthesia, if any, is unclear. Hypotension on induction of general anesthesia is the most reported complication of perioperative phentermine use. Specifically, phentermine-induced hypotension may be unresponsive to vasopressors that rely on catecholamine release, such as ephedrine. Therefore, the decision to perform surgery, especially elective surgery, in a patient taking phentermine should be made with caution. Because of the half-life of phentermine, we recommend discontinuing phentermine for at least 4 days prior to surgery. This differs from the classic 2-week discontinuation period recommended for "fen-phen." The patient should be made aware of the increased risk of surgery, and a skilled anesthesiologist should monitor intraoperative blood pressure and body temperature for signs of autonomic derailment.

Key Words: Adipex, anesthesia, patient safety, pharmacology, phentermine

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Obesity is a chronic medical problem that requires a multidisciplinary approach including lifestyle modifications, bariatric surgery, and pharmacotherapy.[1] As obesity becomes increasingly epidemic and its ill effects are increasingly recognized, we anticipate that the rate of antiobesity medication use will increase. Phentermine (Adipex-P, Lomaira) is a sympathomimetic amine that is classically prescribed for weight loss. Historically, it was used in combination with fenfluramine and was colloquially referred to as "fen-phen." This combination drug was withdrawn from the US marketplace in 1997 because of several deaths from plexogenic pulmonary hypertension, perioperative hypotension, and sudden cardiac death.[2–10] The morbidity and mortality of the combination drug were largely attributed to fenfluramine. As a single agent, phentermine has remained on the market under the brand name Adipex-P.[11–15]

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Overall, 2.43 million patients were prescribed phentermine in 2011, but there are no data regarding the prevalence of phentermine use among plastic surgery patients.[16] In 2011, 1.6 million people presented for cosmetic surgery.[17] Anecdotally, we know that a sizeable subset of these cosmetic surgery patients uses phentermine. Because case reports suggest that phentermine and general anesthesia may result in hypotension resistant to vasopressors that act through catecholamine release, such as ephedrine,[7,18] the perioperative management of phentermine is an important patient safety issue.[7,16,18]

However, a search of the plastic surgery literature revealed zero publications regarding the perioperative safety of phentermine. Given the paucity of data surrounding this plastic surgical patient safety issue, we performed a systematic review of the history of phentermine, its pharmacology, and the anesthetic risks involved with its use. From, this, we provide recommendations on the management of these patients.

Inclusion Criteria for Review

A systematic review of available English-language literature was conducted using the search engines PubMed/MEDLINE, Google Scholar, EMBASE, and the Cochrane Database of Systematic Reviews to identify citations related to perioperative phentermine use and anesthetic agents. The literature search was conducted using the following term combinations: "phentermine" OR "fenfluramine/phentermine" OR "fen-phen" OR "phen-fen" AND "anesthesia" OR "anaesthesia" "anesthetic" OR "anesthetics" OR "anaesthetic" or "anaesthetics." Studies were screened for relevance based on their titles and abstracts. Articles were included if they reported a complication of perioperative phentermine use and anesthesia. Articles satisfying inclusion criteria were reviewed.

We identified 251 citations in the literature search. After eliminating duplicate articles and screening titles, abstracts, and full texts, 4 articles were included in the review (Fig. 1). Of these 4 articles, 1 was a review article, 2 were case reports, and 1 was a letter (Table 1).[7,16,18,19] Analyzing the articles served 2 aims with respect to more comprehensively characterizing phentermine. First, they contributed to a historical and pharmacological profile of the drug. Second, they contributed to a risk profile of the drug by identifying several complications associated with its perioperative use, including hypotension, hypertension, hypoglycemia, hyperthermia, bradycardia, cardiac depression, and acute pulmonary edema.

History

Phentermine and fenfluramine were first introduced to the market in 1959 and 1973, respectively, as standalone weight-loss medications indicated for short-term use.[20,21] Both drugs were associated with adverse effects such as dry mouth, palpitations, diarrhea, and sedation.[22] In 1979, the 2 drugs were combined in a double-blind, randomized controlled trial, which showed that fen-phen, compared with either standalone drug regimen, had similar efficacy but fewer adverse effects.[23] Fen-phen quickly became a popular weight-loss adjunct. Peak drug mentions for phentermine and fenfluramine were 5.0 and 3.8 million in 1996, compared with 1.0 and 0.1 million in 1994, respectively.[24] However, in 1996, 24 cases of fen-phen–related cardiac valvular disease were reported in the *New England Journal of Medicine*.[2,25] In May 1997, the *Boston Herald* published a front-page article on the death of a 30-year-old woman who

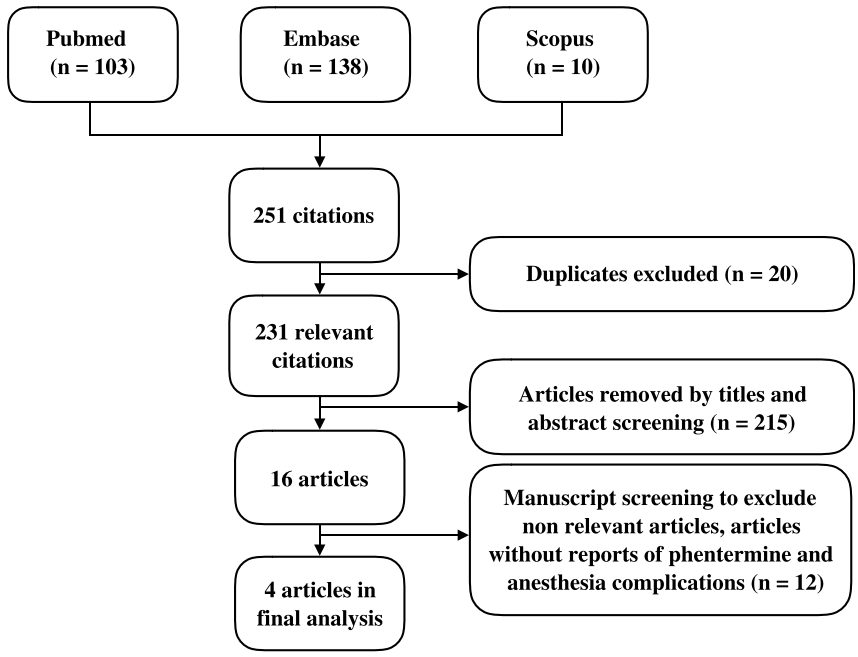

FIGURE 1. Flowchart of included studies.

developed heart problems after taking fen-phen for 1 month.[26] Fenfluramine and its derivative, dexfenfluramine, were voluntarily taken off the market the following year.

Phentermine, which was on the market for 20 years as a standalone weight-loss medication prior to its incorporation into the fen-phen combination, had no reported adverse effects. It remained on the market. Its use dramatically decreased after fen-phen was withdrawn but began to regain popularity in 2004.[27]

As one of the earlier types of pharmacotherapy for obesity, phentermine was approved only for short-term use, usually interpreted as 12 weeks.[28] For decades, phentermine was the only antiobesity medication available for prescription. Starting in 2012, several medications were newly approved for long-term treatment of obesity: lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide.[29] Phentermine/topiramate (Qsymia) produced a greater weight loss than either component drug as monotherapy, with a mean 9.2% to 14.4% weight loss from baseline over a 24- to 56-week period.[29–33] However, the disadvantages to phentermine/topiramate include a cumbersome dose titration, neuropsychiatric effects, and teratogenicity. In addition, these new therapies are expensive. Because of its accessibility and affordability, phentermine remains the most prescribed prescription antiobesity drug in America.[29]

Pharmacology

Phentermine is a centrally acting sympathomimetic that is structurally related to amphetamines.[16,28,34,35] Phentermine is typically dosed at 15 or 37.5 mg daily, 1 to 2 hours before or after breakfast.[36] It is US Food and Drug Administration approved for short-term use as an adjunct to exercise, behavioral modification, and caloric restriction in patients who have a body mass index of 30 kg/m^2 or greater or 27 kg/m^2 or greater and other metabolic risk factors such as diabetes, hyperlipidemia, and controlled hypertension.[36,37]

The longest phentermine clinical trial lasted 36 weeks and showed that patients taking phentermine lost, on average, 27 lb compared with 10.5 lb in the placebo group.[12] A meta-analysis of randomized clinical trials revealed patients taking phentermine lost on average 3.6 kg compared with patients taking placebo, with an effect size of 0.685.[38] Although indicated for only 3 months of use, it is commonly used off-label for longer in order to maintain a desired weight.[27,39–44] Tolerance unresponsive to increasing dosage can occur within 6 to 12 weeks.[45]

The half-life is approximately 20 hours, and the medication is primarily excreted in urine as an unchanged drug.[46] Within 4 days of discontinuing the medication, plasma levels should fall to less than 5%. Fenfluramine is rapidly metabolized into the active metabolite,

TABLE 1. Study Characteristics

Reference	Medication	Anesthesia	Complication	Other Risk Factors	Level of Evidence
Jeffers,[7] 1996	Fen-phen	General	Persistent hypotension, hypoglycemia, hyperthermia		Review
Stephens and Katz,[16] 2005	Phentermine	General	Hypertension	Diabetes mellitus type 2, hypertension, hyperlipidemia	Case report
Rich et al,[18] 1998	Fen-phen	Regional with sedation	Hypotension and bradycardia	Concurrent fluoxetine use	Case report
Giese,[19] 1998	Fen-phen		Cardiac depression and acute pulmonary edema		Letter

norfenfluramine, both of which have a half-life of 20 hours and are excreted in the urine.[47]

Phentermine's mechanism of action is similar to that of other anorexants and involves the hypothalamic release of norepinephrine to suppress appetite.[35,36,48] It also acts as a weak, reversible monoamine oxidase (MAO) and serotonin reuptake inhibitor.[16,48,49] Although the dopaminergic and serotonergic effects are deemed clinically insignificant, patients are still advised not to take phentermine within 14 days of taking MAO inhibitors or concurrently with serotonin reuptake inhibitors.[50,51] Plasma serotonin is primarily degraded in the lung by the MAO-A isoenzyme.[52] Monoamine oxidase A inhibition by phentermine coupled with other serotonergic medications, such as fenfluramine, is theorized to cause toxic levels of serotonin, leading to carcinoid syndrome-like valvular disease and pulmonary hypertension.[15,53–60]

Phentermine is contraindicated in patients with uncontrolled hypertension; further, it should be used with caution in those with medication controlled hypertension, as it may diminish the effects of antihypertensive agents.[61] Blood pressure monitoring for the first few weeks of use is recommended.[15] Additional adverse effects are similar to those of other sympathomimetics and include palpitations, tachycardia, central nervous system stimulation, and gastrointestinal effects.[14,62] Administering this medication in the evening can increase the risk of insomnia.[36]

Anesthetic Risks

Our literature search has revealed that phentermine has many perioperative implications. When used alone, phentermine is associated with hypotension upon induction of general anesthesia. This hypotension is hypothesized to be due to catecholamine depletion and subsequent autonomic dysfunction upon induction of general anesthesia.[63] Because of this putative mechanism, phentermine-induced hypotension is unresponsive to vasopressors that stimulate tissue catecholamine release. Direct sympathetic agonists, such as phenylephrine, should be used instead.[7,46,64] One case report found that the same association can occur on induction of sedation-analgesia when phentermine is used with fluoxetine.[7,18] The second case report identified in our literature search described a case of perioperative hypertensive crises similar to an unidentified pheochromocytoma linked to phentermine use, indicating that the effects of phentermine on anesthesia can be highly labile and unpredictable.[16] Both case reports highlight the variable risk of perioperative phentermine use and anesthetics. No reports of death due to phentermine and anesthesia were found.

A second safety consideration of perioperative phentermine use is body temperature homeostasis. Phentermine, along with other sympathomimetic amines, increases endogenous heat production but inhibits dissipation of the heat by peripheral vasoconstriction.[65] Patients should be regularly monitored for increasing body temperature throughout the procedure.

Interactions between anesthetics and other illicit sympathomimetic drugs have also been reported. Users of methamphetamines who undergo surgery tend to have heart rate and blood pressure stability issues because of cerebral vascular damage, left ventricular hypertrophy, cardiac fibrosis, and decreased cardiac compliance.[66] Anesthetic considerations for 3,4-methylenedioxymethamphetamine users include fluid and electrolyte monitoring, blood pressure lability, tachycardia, and hyperthermia.[66] Cocaine users have higher risks of intraoperative hemodynamic instability, myocardial ischemia, and cerebrovascular stroke.[67–72] In addition, higher concentrations of anesthetics may be required for users of cocaine and amphetamines, which could complicate existing cardiac arrhythmias, which are common adverse effects of sympathomimetic drug use.[73] As phentermine's mechanism of action is closely related to these illicit drugs, similar complications could occur with perioperative phentermine use.

Lastly, there were no reports of interactions between phentermine and tumescent local anesthetic found.

Recommendations

Plastic surgeons treat many patients taking antiobesity medications.[74] Although approved by the US Food and Drug Administration nearly 60 years ago, phentermine has been linked to multiple adverse events associated with anesthesia in the literature.[7,16,18,19,55] The relationship between phentermine and anesthesia, if any, has not been clearly elucidated. Of note, blood pressure lability seems to be the greatest danger related to perioperative phentermine use. Therefore, the decision to perform surgery in a patient taking phentermine should be made with caution.

Our recommendation is to ask patients specifically about their phentermine (Adipex-P) use. If a patient discloses current or previous use, this critical information must be passed along to the anesthesia team, and the patient must be educated of the increased risk of anesthesia. Few plastic surgeon Web sites advise patients to preoperatively discontinue their phentermine use; those that do so recommend discontinuing the medication 2 weeks prior to surgery.[75,76] This recommendation, however, is based on fen-phen combination drug, rather than monotherapeutic phentermine.

Because of the half-life of phentermine, we recommend discontinuing phentermine for at least 4 days prior to surgery. In addition, patients should be diligently screened for elevated blood pressure to help identify those for whom phentermine use is inappropriate. Medications should be reviewed for possible interactions with phentermine that potentiate serotoninergic or dopaminergic effects.

Intraoperatively, anesthesiologists should closely monitor blood pressure and body temperature for signs of autonomic derailment. Phentermine-induced hypotension that occurs upon induction of general anesthesia may be resistant to vasopressors that increase catecholamine release, such as ephedrine.[7] Instead, direct-acting vasopressors should be used.

Until the newer antiobesity medications become more affordable and accessible, phentermine will remain popular among consumers. Cosmetic surgery patients may be more likely to be on phentermine or other antiobesity medications. However, there are no current data on the prevalence of phentermine use in plastic surgery patients. Plastic surgeons should be aware of the risks of perioperative phentermine use and proper management of intraoperative autonomic dysregulation. Given the paucity of data regarding phentermine use in plastic surgery patients, this patient safety issue should be more closely studied, and further studies on the rate of phentermine use and frequency of nonreporting use are needed.

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