Phentermine. Still Good After 50 Years

By Michael Anchors, MD, PhD

Phentermine, the most prescribed appetite suppressant in the world for a long time, first came on the market in 1959.(1) Few medicines have been as successful for such a long time. Phentermine is well-known, safe and trusted, or should be; however the drug's use has declined strangely and tragically. Phentermine can save lives from the obesity epidemic. However, few United States doctors know the truth about it and it is no longer approved in Europe and Canada. This article is an effort to redress the situation.

There are three possible reasons for the decline in phentermine use. 1) Better drugs might have supplanted it, 2) new dangers might have been uncovered, 3) phentermine has been defamed, and medical scholarship is now too degraded to expose the error.(2,3) I will examine each possibility.

Discussion

Are Better Weight-loss Pills Available?

No. In fact, among FDA approved medicines, none has shown greater efficacy than phentermine.(4) I will discuss other medicines in order of their frequency of current use.

- Sibutramine (Meridia) is approved for use in a dose up to 15 mg, because at higher doses it raises blood pressure. However, a 15mg dose is not very effective for weight loss.
- The use of orlistat (Xenical and Alli) only blocks fat-calories and its use is limited by the side effect of diarrhea. Americans have been gaining weight mostly due to sugar, so Xenical seems off-point. Acarbose (Precose) blocks the absorption of sugar, but is not used for weight-management since the effective dose causes so much flatulence.
- Phendimetrazine (Bontril) is converted by the liver to the active form phenmetrazine, which was linked to primary pulmonary hypertension (PPH) in a case-control study.(5) Wyeth-Ayerst Pharmaceuticals discontinued sales of its Plegine brand of phendimetrazine, but Bontril soldiers on. I was consulted about a case of PPH associated with Bontril. I am not sure if Bontril causes PPH, but someone should investigate this.
- Diethylpropion (Tenuate) is more expensive and less effective than phentermine, with fewer initial side-effects. It is useful in patients worried about, or prone to side effects. Alternatively, the initial side-effects of phentermine can be reduced by the simple tactic of starting at the half-dose level for a week or two before taking the whole tablet.
- Methylamphetamine (Desoxyn) carries a black box warning stating that it is addictive.

Dangerous Side Effects of Phentermine

The second possible reason for the declining use of phentermine is the discovery of new, dangerous side-effects. Four effects have been claimed, however none of them are true: 1) phentermine is addictive, 2) phentermine raises blood pressure, 3) phentermine damages heart valves, and 4) phentermine is a monoamine oxidase (MAO) inhibitor and causes serotonin syndrome. A fifth issue is that some doctors believe phentermine is approved for only a few weeks' use, or it is ineffective after that time. This is also untrue.(9,10)

1) Phentermine is Addictive

I have not found phentermine to be addictive in my practice over 13 years, concerning 5,000 patients. Neither are there case reports or published studies of phentermine's addiction; however most physicians interviewed believe that it is addictive. There is no black box warning on phentermine, only a note that it is *chemically related* to addictive drugs which does not imply that phentermine itself is addictive. Doctors are confused about this. Phentermine, sibutramine and dexedrine are all phenethylamines. The word "Amphetamine" is shortened from Alpha-Methyl-beta-**PHE**ne**T**hyl**AMINE**.

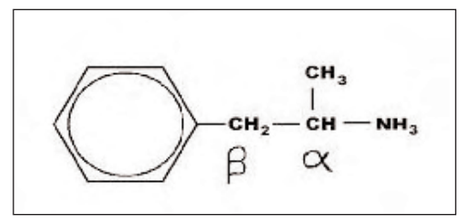

Figure 1: Dexedrine, the prototype amphetamine.

CLINICAL

The principal effect of dexedrine is the release of norepinephrine (NE) from NE-containing neurons.(6) At clinical doses, dexedrine also releases dopamine. The propensity to cause addiction is thought to be related to increasing dopamine dosage.

"Addiction" means 'overuse with loss of control, anti-social behavior, increasing dose, and withdrawal symptoms upon discontinuation.' Increasing drug dosage or withdrawal symptoms alone in the setting of responsible use, are insufficient to trigger the term "addiction." Beyond doubt, dexedrine is addictive in addiction-prone people.

Derivatives of dexedrine, such as methylamphetamine (Desoxyn) or MDMA (Ecstacy) with methyl groups on the N atom, release serotonin as well as NE at clinical doses, creating the potential for serotonin syndrome (see below). Phentermine adds a methyl group to the alpha carbon of dexedrine.

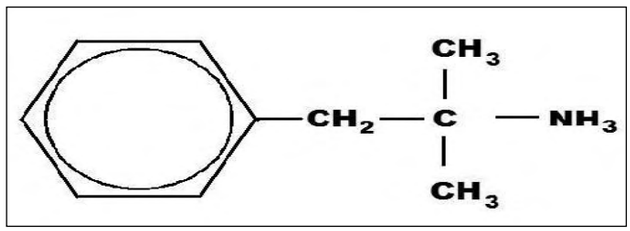

Figure 2. Phentermine differs from dexedrine by a single methyl group.

This small difference makes a big difference. At doses up to 30 mg phentermine does not release dopamine, explaining its lack of addictive potential.(5) Phentermine has no methyl groups on the N atom either, so it does not release serotonin to clinical levels.

By the way, sibutramine, like phentermine, is also a phenethylamine (but not actually an "amphetamine"). I have drawn the structure to display the "amphetamine backbone." No one has claimed that sibutramine is addictive.

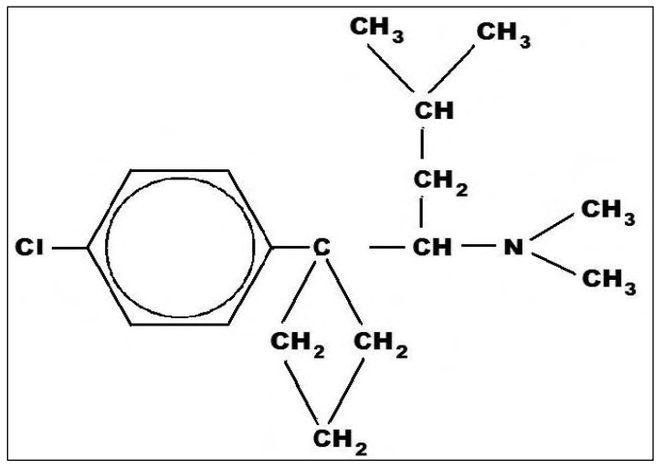

Figure 3. The "amphetamine backbone" inside sibutramine.

Sibutramine has methyl atoms on the N atom giving it serotonin potential. Indeed, the producers of sibutramine hoped this characteristic would enhance its anorectic effect, just as the addition of certain Serotonin Selective Reuptake Inhibitor (SSRI) drugs to phentermine extends its effect.(7,8) They wanted "phen-pro" in a single pill. Unfortunately for them, the SSRI effect of sibutramine is manifested only at doses over 15 mg where it raises blood pressure.

2) Blood pressure

Phentermine raises blood pressure a little during the first or second week, especially when, unwisely, started at a dose of 30 mg. After that, with rapid weight loss, blood pressure returns to baseline or decreases. There is little effect on blood pressure when phentermine is started at the half-dose level or when it is combined with a beta-blocker.

It is written in many places that phentermine raises blood pressure and many experts (without experience) say so; but in the primary research literature, blood pressure was always unchanged.(11)

Phentermine does not bind to alpha-receptors directly; at clinical doses it only engenders the release of NE from neurons.(6) The release is greatest the first time the patient ever takes phentermine. Afterwards, neurons become partially depleted of NE and the tendency to produce side-effects or the main anorectic effect diminishes. That is why phentermine must be stopped a week or two before elective surgery involving general or regional anesthesia. If phentermine is used, instead, up to the moment of surgery and the patient kept NPO, blood pressure may fall when anesthesia is induced. Pressors to restore blood pressure may not work in that situation since the patient is catecholamine-depleted. This danger could be avoided by giving ample IV saline before surgery, but the anesthesiologist must know to do that beforehand.

3) Heart valves

Around 1992, Michael Weintraub discovered that when fenfluramine was added to phentermine, the anorectic action was increased and extended.(12) This is the so-called "phen-fen" combination. In 1997, Mayo Clinic reported 24 cases of heart valve disease (cardiac valvulopathy) in patients on phen-fen.(13) There were three cases of valve disease with patients on fenfluramine alone, but no cases in patients on phentermine alone, even though more people had taken phentermine. The editors at *New England Journal of Medicine* (NEJM) should have requested modification of the title "The Association of Valvular Heart Disease with Fenfluramine-phentermine," but at the time the journal had an explicit anti-diet pill bias.(14,15) They let the faulty title pass through. They similarly winked at Lucien Abenhaim's title "Appetite suppressant drugs and the risk of primary pulmonary hypertension" in 1996.(5) Only fenfluramine was significantly implicated in that study, so the inclusive moniker "appetite suppressant drugs" was inappropriate.

The NEJM's poor editorial performance confused everyone and the British Medical Association, followed by Europe and

Canada, banned both phentermine and fenfluramine. The state of Florida banned the "combination of phentermine with any other medicine for the purpose of weight loss."

We now know that reported cases of anorectic-associated valvulopathy were due to norfenfluramine, the major metabolite of fenfluramine, and had nothing to do with phentermine. Norfenfluramine binds to HT2B receptors, including those on heart valves.(16) There have been no reported instances of valvulopathy with phentermine.(17)

I worry about discussing these issues since clinicians may believe that the mere existence of discussion implies uncertainty. "Where there's smoke, there's fire." In the United States, where there's smoke, too often there are only lawyers and press agents. However, that which keeps life simple for the doctor can make life dangerous for the patient. Doctors should not be diverted from using good medicines by legal fog and journalistic sensationalism. We lost ephedra and Vioxx that way.

4) Serotonin Syndrome

Since phentermine at clinical doses has no effect on serotonin levels, you might wonder why anyone would think it could cause serotonin syndrome. Serotonin syndrome is a rare, acute, serious syndrome in patients on high-dose or multiple serotonergic medications characterized by agitation, confusion, hyperreflexia, diarrhea, sweating and fever.(18) The connection with phentermine is that Richard Wurtman, who brought dexfenfluramine to the US, published that phentermine is a monoamine oxidase (MAO) inhibitor.(19) If this were true, phentermine might raise serum serotonin. To obtain these results in patients on prescribed doses, Wurtman used higher concentrations of phentermine in the test tube than those in vivo.

The true test of his idea would have been the following: (1) Are concentrations of serum serotonin in patients on phentermine higher than normal? and (2) Are there case reports of serotonin syndrome in patients on phentermine? In fact, serum serotonin levels in patients on phentermine are unchanged,(20) and there have been no case reports of serotonin syndrome in patients on *prescribed* doses of phentermine.(17,21)

While that should be the end of the story, two case reports must be considered. First, the 1996 report(22) of a 22 year-old woman who took phentermine alone for an unstated period of time to lose weight. She did well, and after stopping phentermine months later started on fluoxetine (Prozac) for depression for three months. Eight days after stopping fluoxetine, she took a single 30 mg capsule of phentermine. Within hours she felt "jittery; everything's in fast motion." She noted that her thoughts were "going too fast. . . .They keep skipping back and forth. . . . I don't have time to finish my sentences." She had no other signs or symptoms of serotonin syndrome. Specifically there was no fever, tachycardia, diaphoresis or diarrhea. After receiving Valium, her symptoms subsided quickly. This was clearly a case of stimulant side-effects, not serotonin syndrome. Phentermine should never be started at 30 mg, but at a lower dose.

More interesting is the recent case of a 24 year-old normal weight female who took an online diet pill sold to her as phentermine 37.5 mg, without a prescription.(23) After several days of restlessness, nausea and insomnia, she was found unresponsive in bed and taken to a tertiary care hospital.

- The drug's identity and purity was not analyzed. Using a test kit not detecting phentermine, the urine drug screen was positive for amphetamines. The authors themselves admit "drug abuse cannot be ruled out."
- Although serotonin syndrome was considered in the differential from the beginning, serum phentermine, and serum or platelet serotonin, were not measured.
- Only after the unconscious patient received haloperidol 10 mg, did she develop muscle jerks and rigidity, consistent with neuroleptic malignant syndrome (NMS).

The initial creatinine kinase level was 17,000, consistent with a preceding seizure. Indeed, the patient had a witnessed seizure in the rehab center. She developed tachycardia and fever only after being in the hospital several days. In addition to haloperidol, the patient received phenytoin, diazepam, cyprohetadine and antibiotics. She was intubated and placed in a pentobarbital coma for two days. All told, this poor woman was in the hospital for 23 days.

The authors provided a table to help distinguish NMS from serotonin syndrome.

According to the table the patient had NMS not serotonin syndrome, however it is difficult to know what she had after taking so many medicines, and the fact that so many tests went unreported. It would be a mistake to allow medical scholarship of this order to deprive us of phentermine.

	NMS	Serotonin Syndrome
Onset	Insidious, days to weeks	Acute (minutes to hours)
Resolution	Slow, often > 1 week	Improvement or resolution often with 24 hours
Psychiatric	Altered mental status, stupor, somnolence, mutism	Altered mental status, agitation, hypomania, hyperactivity, restlessness, somnolence (less common)

Table 1: Signs and symptoms of NMS vs Serotonin Syndrome

5) Many doctors believe Phentermine is not indicated for use beyond a few weeks.

The original FDA indication was for "a few weeks" and never changed. This advice was because the studies on which approval was based generally lasted between 4 and 20 weeks. No company sought to amend the indication and it was not in their financial interest to do so. The FDA expressly recognizes that economic factors as much as medical considerations determine which indications are sought by companies.

The following preamble appears in every copy of the *Physicians Desk Reference*:

> *The FDA has recognized that the FD&C Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for any marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling.*

Doctors have the legal right to prescribe phentermine beyond a few weeks, and should have no additional legal risk from doing so. Does the medicine continue to work for longer periods? The answer is that in many patients, it does. Myself and colleagues confirm, after treating thousands of patients over more than a decade, that phentermine works for longer periods because it reduces hunger. It may or may not reduce weight because not all overeating is driven by hunger.

Patients must still be instructed about diet and comply. If phentermine does not contribute to weight loss after six weeks, or fifty, the physician can stop it just as they would if a blood pressure medicine stopped working. However, it is wrong to cut off the phentermine supply to an overweight patient who is still losing weight merely because of an artificial time-limit of "a few weeks."

Phentermine Has Been Defamed

Since there do not appear to be drugs that are better than phentermine and there is no new evidence of dangers to its use, one is left to assume it is the victim of unsubstantiated fears, rumors and/or myths.

Phentermine: The Basic Facts

1. **Phentermine is available in the following forms:**

- 15 and 30 mg capsules of phentermine base
- capsules of long-acting phentermine resin (Ionamin)
- 37.5 mg scored tables of phentermine hydrochloride.

Note: The 37.5 mg tablets and 30 mg capsules deliver the same phentermine dose, so changing from the capsule to the tablet is not a dosage increase.

2. **The recommended dosage is one pill/capsule every morning with a little food.** A quarter of patients will need to increase to 1.5 pills daily, or one pill twice daily. Before changing the dose the clinician must:

- Warn the patient not to stop the phentermine suddenly from the BID dosage level, because doing so can cause a short, sharp spell of depression. If the patient wishes to go off from BID dosage, reduce to one a day for a full week, then discontinue.
- Document the patient's blood pressure and pulse on the higher dose and be sure the patient does not take other stimulants or much caffeine with the phentermine.

3. **Never prescribe 3 pills daily.**

4. **If a patient has high blood pressure, treat it.** Do not assume phentermine is the sole source of the high blood pressure because it is not - Beta blockers and diuretics are good choices.

5. **The half-life of plain phentermine is 7-8 hours.** The half-life of the resin is 20 hours. The resin should not be used since it causes insomnia and suppresses appetite during the night when most patients aren't eating anyway. Moreover, the resin is expensive and scarce.

6. **The brand name "Fastin" was sold to a diet supplement company.** Bottles of Fastin now contain a non-prescription decongestant, not phentermine. Similarly, "Phentramine" is an over-the-counter diet supplement preying on patients who cannot spell.

7. **Many brands of authentic generic phentermine are available, but some generic capsules sold in commercial pharmacies contain little or no phentermine.** Pharmacists are often unaware of this. Both Adipex-P and generic tablets are always genuine. If you do not specify "tablets only," the pharmacist may fill the prescription with capsules because the profit margin is higher.

Phentermine from online pharmacies is usually fake because it is illegal to sell prescription medicine without a prescription. Recently, two physicians lost their license for selling prescriptions to patients they never saw. It is, however, legal and desirable to monitor patients via email or phone calls after the patient has been seen in an office. Patients must be seen regularly, if not often, and the chart has to make sense.

8. **Phentermine should always be started at the half dose level for a week or two (either the 15 mg capsule, a 30 mg capsule emptying out half, or half the 37.5 mg tablet) before proceeding to the full dose.** Compliance and satisfaction are enormously improved.

9. **Common side effects, which get better with continued use, are dry mouth, nervousness and insomnia.** In my view, the contraindications are:

- Inability or unwillingness to comply with diet instructions
- Hyperthyroidism, untreated or symptomatic
- Tachycardia, untreated or symptomatic
- Myocardial infarction within the last 3 months
- Uncompensated congestive heart failure
- Uncontrolled hypertension
- Sjogren's syndrome

- Sicca syndrome
- Chronic insomnia
- Schizophrenia
- Panic disorder
- Severe bipolar disorder
- Anger management issues
- Substance abuse disorder
- Co-administration of other stimulants or caffeine
- Litigious or argumentative behavior
- Pregnancy/lactation
- Uncontrolled seizure disorder ■

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Michael Anchors MD, PhD, maintains a private practice in Gaithersburg, MD. Although he has been in private practice since 1984, he only recently began practicing bariatrics 100% of the time. Dr. Anchors received his PhD from Harvard Medical School and his MD degree from University of Miami. He has written several books and been published in several medical journals.

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