Rules and Policies
January 13, 2021

1. Adoption of December policy meeting minutes
2. Rule Review Update
   a. Rules for initial review
   b. Rules at CSI
   c. Comments received on weight-loss rules
   d. Adoption of CME rules
3. Legislative Update
   a. Summary of lame duck (see attached memos on SB 310, HB 263 and HB 442)
   b. Legislative outreach initiatives
Dr. Soin called the meeting to order at 9:01 a.m.

Minutes Review

Dr. Bechtel moved to approve the draft minutes of the November 10, 2020 meeting of the Policy Committee. Mr. Giacalone seconded the motion. The motion carried.

Rule Review Update

Ms. Anderson stated that there will be fewer rules to be reviewed in 2021, but the group will include rules that are used by the Board often. Among the rules scheduled for review in 2021 are the sexual misconduct rules, the delegation rules, and the rules on prescribing controlled substances for self and family. The 2021 rule review schedule is included in the meeting materials.

Ms. Anderson stated that the Board is scheduled to adopt new rules at today’s Board meeting. The continuing medical education (CME) rules, including the mandatory one hour of education on the duty-to-report, has been through the required hearings and will be ready for adoption by the Board at its January 2021 meeting.

Rules with the Common Sense Initiative

Temporary Military Licensure

Ms. Anderson stated that the Board is scheduled to adopt rules this afternoon regarding military licensure. The Common Sense Initiative (CSI) required changes to proposed Rule 4731-36-04 to
reference the Board’s processes as described in proposed Rule 4731-36-03. CSI also requested that language be added to explain that licensure fees would be waived. Ms. Anderson noted that statute requires the fee to be waived, and this is why the explanation was not initially included in the proposed Rule. The explanation of the waived licensure fees has been added to the proposed Rule as Paragraph H.

In response to a question from Dr. Bechtel, Ms. Anderson stated that although licensure fees will be waived, the applicant will still be responsible for paying for the background check as required by statute. Ms. Montgomery asked that measures be taken to ensure that the Board does not end up absorbing the costs of the background checks. Ms. Anderson stated that she will work with Mr. Turek to make sure the instructions for the applicants is clear on that point.

Dr. Bechtel moved to recommend approval of the proposed amendments to Rule 4731-36-04, to be filed with the Joint Committee on Agency Rule Review. Dr. Johnson seconded the motion. The motion carried.

**Light-Based Medical Devices**

Ms. Anderson stated that many comments were received on the proposed light-based medical devices rule and have been included in the Committee materials packet. The rules have been discussed with the Physician Assistant Policy Committee as well. Ms. Anderson stated that the physician assistant statutes, especially 4730.21, Ohio Revised Code, already specify how a supervising physician and a physician assistant should work together with respect to the competence of the physician assistant to utilize light-based medical devices, the type of supervision to be given by the supervising physician, and the number of physician assistants that may be supervised at one time. These statutory provisions are slightly different from what has been proposed in this rule.

Ms. Anderson has drafted changes to the rule to address these concerns and to treat physician assistants differently in accordance with statute. For registered nurses, licensed practical nurses, and in some cases cosmetic therapists, the rule would establish a number of procedures to be viewed, require on-site supervision, and limit the physician to supervising up to two individuals.

Because these changes are significant, Ms. Anderson wished to consult with the Physician Assistant Policy Committee and ensure their concerns are being addressed, as well as the Board of Nursing since the rule would affect some of their licensees. Ms. Anderson also asked for the Committee’s input on the definitional concerns that were raised in the public comments.

Ms. Montgomery asked for clarification of whether the rule applies to vascular lasers, which was one of the questions in the public comments. Dr. Bechtel stated that the rule specifically discusses what types of skin lesions are considered vascular in nature and therefore amenable to treatment. Dr. Bechtel stated that the energy of vascular lasers is absorbed by the hemoglobin in the blood, which dissipates energy and causes blood vessels to branch down. Dr. Bechtel was satisfied with the rule’s description of what skin lesions are considered vascular. Dr. Bechtel was also comfortable with defining vascular lasers as light-based medical devices. Ms. Anderson thanked Dr. Bechtel for clarifying that issue.

Dr. Bechtel continued that the rule is focused on patient safety. Dr. Bechtel stated that vascular lasers are probably the safest of all the lasers and have a lower risk of scarring, and that is why the vascular laser was chosen for expansion into the scope of practice of nurses and cosmetic therapists. The rule also includes rigorous educational requirements, including eight hours of classroom education. The
practitioners are required to observe 15 cases and then perform 20 cases under direct supervision of a physician. Also, physicians cannot supervise more than two individuals at one time. In response to two articles on laser safety sent by the Cleveland Clinic, Dr. Bechtel stated that one article was on ablative lasers, which are not expanded by this rule because of the greater risk of scarring. The other article was published outside the United States. Dr. Bechtel reiterated that he is comfortable that the guardrails and educational requirements in the rule will promote patient safety.

Dr. Schottenstein asked if the Board of Nursing has statutes that governs their licensees’ authorization for supervision that could potentially allow them more leeway than this proposed rule would. Ms. Anderson replied that she did not believe that was the case, but she would like to get input from the Board of Nursing.

Regarding the scope of cosmetic therapists, Mr. Giacalone asked Dr. Bechtel to comment on what makes hair removal and tattoo removal different from vascular treatment. Dr. Bechtel responded that cosmetic therapists can perform laser hair removal and those who already do so can continue under this rule. However, the rule would require cosmetic therapists who are beginning to practice laser hair removal to undergo extensive educational instruction. Dr. Bechtel stated that removal of tattoos is very complicated and requires a laser to be specifically chosen based on the tattoo pigment. Tattoo removal also has a much higher incidence of scarring. While allowing cosmetic therapists to use laser for tattoo removal may be something the Board could consider in the future, it is not included in the current proposed rule due to the challenging process and potential risks.

Dr. Bechtel moved to circulate the proposed changes to the proposed rule to the Physician Assistant Policy Committee and the Board of Nursing for input. Dr. Johnson seconded the motion. The motion carried.

Weight-Loss Prescribing Rules

Dr. Soin stated that last month the Committee decided to gather additional information on this topic. Since that time, Dr. Soin reached out to key opinion leaders in this field, as well as pharmacists, physicians who treat obesity, and representatives from national obesity associations. Dr. Soin remarked that he received a great deal of valuable information and feedback from these interactions. At the Board’s request, these experts also provided written comments that Dr. Soin found to be excellent and well-written. Dr. Soin stated that it would be helpful to have additional time to review the written comments and provide a more robust update next month.

Dr. Soin observed that there were two general themes in the comments. One theme was the potential opportunity to enhance telemedicine visits for some of the wellness checks that are required by rule. Secondly, the vast majority of comments were on the issue phentermine being labeled as an acute treatment and whether there are any opportunities for chronic use. Dr. Soin stated the more information will be gathered for review next month.

Hearing Rules

Ms. Anderson stated that though minor changes to the hearing rules have already been approved by the Board, the Hearing Examiners have requested that the rule be amended so they would have the ability to hold virtual hearings via video conference upon motion from a party or from the Hearing Examiner, even when the current emergency is over. Ms. Montgomery was in favor of this change because of the added flexibility it could provide to licensees and the potential to increase the number of hearings held.
Ms. Montgomery moved to refile the hearing rule with the proposed change. Dr. Bechtel seconded the motion. The motion carried.

Consult Agreement Rules

Ms. Anderson stated that the Board of Pharmacy is required by statute to submit any proposed changes to its consult agreement rules to the Medical Board for input. The Board has had an opportunity to review the Board of Pharmacy’s proposed changes and Ms. Anderson has been notified of some minor typographical errors. Likewise, the Medical Board is required by statute to submit any potential changes to its consult agreement rules to the Board of Pharmacy for their input.

Dr. Johnson moved to communicate to the Board of Pharmacy the Board’s comments on the Board of Pharmacy’s proposed consult agreement rules. Dr. Johnson further moved to approve submission of the Medical Board’s proposed consult agreement rules to the Board of Pharmacy for consultation as required in Section 4729.39(E)(2), ORC. Dr. Bechtel seconded the motion. The motion carried.

Legislative Update

**Senate Bill 246, Occupational Licensing Reciprocity:** Ms. Wonski stated that the legislative staff has worked with the bill’s sponsor and the committee chair to address concerns for retaining the Board’s ability to make determinations on whether an applicant has adequately met Ohio’s qualifications for licensure. Last week, the Senate committee adopted the Board’s requested changes. These amendments allow greater flexibility for all licensing boards in making determinations on applicants’ fitness to practice. Ms. Wonski thanked Mr. Smith, who was instrumental in both drafting and negotiating the amendments.

Ms. Montgomery asked if there has been discussion on allowing the Board to consider applicants’ offenses beyond the five-year limit for cases of violence or sexually-related offenses. Ms. Wonski replied that the fitness-to-practice language allows the Board more flexibility to consider older offenses if they resulted in action on the applicant’s license in another state. Mr. Smith commented that Ms. Wonski is working diligently on House Bill 263 to request a longer look-back period on convictions.

**House Bill 263, Occupational Licensing:** Ms. Wonski stated that this legislation would require the Board to provide a comprehensive list of criminal offenses that would prevent a person from becoming licensed in Ohio. The legislative staff has worked with several other health care boards, as well as the bill sponsor and committee chair, to develop solutions to the boards’ issues. The Senate Transportation, Commerce, and Workforce Committee had a third hearing on this bill last week. The Board submitted testimony expressing its concerns with the language and offered suggested changes. The bill is scheduled for its fifth hearing today.

**Senate Bill 364, Interstate Medical Licensure Compact:** Ms. Wonski stated that this bill would require Ohio to join the Interstate Medical Licensure Compact. This legislation has not moved recently, but the staff continues to monitor it closely. Ms. Wonski did not expect the bill to move during this General Assembly, but this language may be seen again early next year.

**House Bill 492, Physician Assistants:** Ms. Wonski stated that this bill would expand the ability of physician assistants to perform procedural sedation for the purpose of rapid intubation.
stated that several stakeholders have expressed opposition to the bill. The bill has not moved much through the legislative process, but the staff is monitoring it closely.

**Senate Bill 236, Radiation Control and Radiation Technology Professionals:** Ms. Wonski stated that this legislation would authorize the State Director of Health, when adopting rules for Ohio’s radiation control program, to deviate from the suggested state regulations for control of radiation if doing so is warranted and does not pose a health, environmental, or safety risk. The staff is watching this legislation because an amendment was added that would grant anesthesiologist assistants the ability to order or direct others to administer drugs under a supervision agreement. The Ohio State Medical Association and the Ohio Society of Anesthesiologists have expressed a neutral position on the amendment.

**Senate Bill 305, Telemedicine:** Ms. Wonski stated that this bill would require insurers to provide coverage for telehealth services during a state of emergency. If the bill begins to move, the Committee will be updated at the next meeting.

**House Bill 388, Out-of-Network Care (Surprise Billing):** Ms. Montgomery asked Ms. Wonski for her evaluation of this bill’s progress and flexibility. Ms. Wonski stated that under this legislation, hospitals would be required to notify patients if a test or other service is out of the patient’s insurance network, inform the patient if there is way to obtain that service in-network, and provide the cost of any such services if they are not emergency in nature. The bill has had its third hearing in the Senate, so it is possible that it may pass in this legislative session. This bill has the support of the Ohio Department of Insurance.

**Federal Legislation:** Dr. Schottenstein asked if the Board has the ability to provide input on federal legislation. Ms. Wonski stated that the four pieces of federal legislation that is listed in the legislative tracker are not expected to move this year. If there is federal legislation that could potentially move and the Board feels strongly about, the legislative staff can weigh in with Ohio’s congressional representatives and senators to make the Board’s position known.

**Pharmacy Board Updates**

There were no Pharmacy Board updates at this time.

**Adjourn**

**Dr. Bechtel moved to adjourn the meeting. Dr. Johnson seconded the motion.** All Committee members voted aye. The motion carried.

The meeting adjourned at 9:43 a.m.

bt
MEMORANDUM

TO: Mark Bechtel, M.D., President
    Members, State Medical Board of Ohio

FROM: Kimberly C. Anderson, Chief Legal Counsel

RE: Rule Review Update

DATE: December 29, 2021

Attached are the updated rule schedule and rule spreadsheet. Please let me know if you have any questions.

Action Requested: No action requested
# Legal Dept. Rules Schedule

**As of December 29, 2020**

## To January Board Meeting for Adoption

- 4731-10 CME rules
- JCARR jurisdiction ends 1/3/2021

## RULES AT CSI

### Comment Deadline 5/27/20

- 4731-18 – Light Based Medical Device Rules

### Comment Deadline 10/19/20

- 4731-11-02
- 4731-11-03
- 4731-11-04
- 4731-11-04.1
- 4731-11-07
- 4731-11-11

### Comment Deadline 11/6/20

- 4731 Chapter 13 – 36 rules

### Comment Deadline 11/23/20

- 4759-4-04
- 4759-4-08
- 4759-6-02

## RULES SENT FOR INITIAL CIRCULATION

### Comment Deadline – September 25, 2020

- 4731-6-14

## RULES AT JCARR

### Ready to be filed with JCARR

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### Rules for review in 2021

- 4731-1-12-Examination-Due 11.30.21
- 4731-1-16-Massage Therapy Curriculum-Due 11.30.21
- 4731-11-08-Utilizing controlled substances for self and family members-Due 8.17.21
- 4731-14-01-Pronouncement of Death-Due 6.30.21
- 4731-23-01-Delegation of Medical Tasks-Definitions-Due 11.30.21
- 4731-23-02-Delegation of Medical Tasks-Due 11.30.21
- 4731-23-03-Delegation of Medical Tasks-Prohibitions-Due 8.17.21
- 4731-23-04-Violations-Due 8.17.21
- 4731-26-01-Sexual Misconduct Definitions-Due 6.30.21
- 4731-26-02-Prohibitions-Due 6.14.21
- 4731-26-03-Violations; Miscellaneous-Due 6.30.21
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MEMORANDUM

TO: Mark Bechtel, M.D., President
Members, State Medical Board of Ohio

FROM: Kimberly C. Anderson, Chief Legal Counsel

RE: Comments Received regarding Weight Loss Rules, 4731-11-04 and 4731-11-04.1, OAC

DATE: December 30, 2020

Rules 4731-11-04 and 4731-11-04.1 are currently pending at CSI. One comment was received, from Jennifer Hayhurst at OSMA, requesting that the Board consult with experts in obesity medicine to obtain comments regarding the proposed rules. The Policy Committee agreed to consult with experts and Dr. Soin convened a meeting on November 23, 2020. All interested parties were invited to make a presentation and to provide written comments regarding the rules.

Attached you will find written materials provided by the following individuals:

1. Ethan Lazarus, M.D., Clinical Nutrition Center, Greenwood Village, CO;
2. Barto Burguera, M.D., Ph.D., Marcio Griebeler, M.D., Diana Isaacs, PharmD, W. Scott Butsch, M.D., Cleveland Clinic
3. Bruce Barker, M.D., Ohio Health, Delaware, OH
4. Elizabeth W. Adamson, Executive Director, Ohio Association of Physician Assistants
5. Chris Gallagher, Obesity Action Coalition
6. Ted Kyle, RPh, MBA, ConscienHealth, Pittsburgh, PA
7. Angela Kay Fitch, M.D., MGH Weight Center, Boston, MA

I have also attached the proposed rules, 4731-11-04 and 4731-11-04.1, OAC.

Recommended Action: Review the comments and advise as to next steps.
November 20th, 2020

Dear Honorable Members of the State Medical Board of Ohio:

Thank you so much for the opportunity to testify on your upcoming proposed rule OAC 4731-11-04 (weight loss) that is currently pending with the State of Ohio’s Common Sense Initiative (CSI). I am sorry that I am not able to testify in-person or by phone, but I would like to provide some additional commentary as you consider this rule.

As written, I am concerned that this rule will HURT more people than it will help. Let me try to explain.

People with obesity are already highly stigmatized for their disease. Yet, this disease is serious. This is now being exacerbated by COVID-19. People with obesity are 3-6x more likely to die or require a ventilator.

The explanation that this rule has served Ohioans well for many years and therefore should be reaffirmed is short-sighted, and doesn’t take into account changes with regards to our understanding of obesity as a disease (recognized by the American Medical Association in 2013). It is not consistent with the way in which obesity care is delivered in the rest of America. This policy would be like telling people with depression to simply “Think happy thoughts.” Treating depression this way is unlikely to help people, and very likely to cause harm vs. offering patients the current standards of care with regards to depression pharmacotherapy. Obesity treatment is no different.

This rule is in direct conflict with an evidence-based guideline published by the Endocrine Society in 2014 stating that long-term phentermine prescribing is appropriate (Endocrine society pharmacotherapy 2014 guideline, pp 357-358, attached).

This rule is in direct conflict with the position statement of the Obesity Medicine Association, a group of over 3,000 physicians, Nurse Practitioners and Physician Assistants (attached).

This rule is not consistent with American Medical Association policy calling on the AMA to “Work with state and specialty societies to identify states in which physicians are restricted from providing the current standard of care with regards to obesity treatment” and to “work with interested state medical societies and other interested stakeholders to remove out-of-date restrictions at the state and federal levels prohibiting healthcare providers from
providing the current standard of care to patients affected by obesity.” I have spoken with the AMA Council on Legislation and they would be happy to assist you with this policy.

I understand your concerns that Phentermine is a controlled substance; however, decades of experience have shown it to be well tolerated and have very low potential for addiction (Hendricks article attached).

Another study of 13,972 adults treated with phentermine was published in 2019 showed “Greater weight loss without increased risk of incident CVD or death in patients using phentermine monotherapy for longer than 3 months... This study supports the effectiveness and safety of longer-term phentermine use for low-risk individuals.” (Lewis et al, attached).

Long-term phentermine and topiramate have been shown to safely improve weight loss and reduce the failure rate after gastric bypass surgery (attached).

Continuing on your current path of not allowing physicians to practice medicine which is the standard of care in the rest of the country leaves millions of vulnerable Ohioans living with obesity at risk for serious complications of obesity ranging from medical (diabetes, hypertension, heart disease, COVID-19 complications, cancer) to functional impairments (inability to walk comfortably, back, pain, joint pain) to mental health (decreased quality of life, increased depression) and even financial loss (wage bias and job bias against those living with obesity, being forced to pay for expensive brand-name anti-obesity medications when inexpensive generics are readily available, as in study above).

Your policy would allow the on-label prescribing of Phentermine at 15 mg/d if it is part of the brand-name drug Qsymia, but not allow its generic counterparts to be used at exactly the same dosage of phentermine. Because Qsymia is expensive and not on most formularies, this is in effect telling your population that they must use a brand name drug but will not allow the same components to be used, at much lower cost, with no reasonable explanation given.

Now is the time to trust your physicians to practice good medicine. Allow your physicians to treat their patients. Stop singling out obesity as this is simply an extension of decades old weight bias. You are not instructing your physicians how to treat diabetes, depression or hypertension. Don't tell your physicians how to treat obesity. Finally, today, you have a chance to adopt the same policies as the rest of the country. It is time for Ohio to emerge from the 1980’s and accept the current standards of care for obesity.

I urge you to retire the entire statement around weight management, or if you find yourselves unable to commit to that, to at least remove the language singling out phentermine.
Thank you for your consideration.

Sincerely,

[Signature]

Ethan Lazarus, MD

Obesity Medicine Physician since 2004
Board Certified: American Board of Family Medicine
Diplomate: American Board of Obesity Medicine
Obesity Medicine Association President-Elect
The Obesity Society - Member
American Medical Association - Delegate
Objective: To formulate clinical practice guidelines for the pharmacological management of obesity.

Participants: An Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer. This guideline was co-sponsored by the European Society of Endocrinology and The Obesity Society.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, the European Society of Endocrinology, and The Obesity Society reviewed and commented on preliminary drafts of these guidelines. Two systematic reviews were conducted to summarize some of the supporting evidence.

Conclusions: Weight loss is a pathway to health improvement for patients with obesity-associated risk factors and comorbidities. Medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone. Many medications commonly prescribed for diabetes, depression, and other chronic diseases have weight effects, either to promote weight gain or produce weight loss. Knowledgeable prescribing of medications, choosing whenever possible those with favorable weight profiles, can aid in the prevention and management of obesity and thus improve health. (J Clin Endocrinol Metab 100: 342–362, 2015)

Summary of Recommendations

1.0 Care of the patient who is overweight or obese

1.1 We recommend that diet, exercise, and behavioral modification be included in all obesity management approaches for body mass index (BMI) ≥ 25 kg/m² and that other tools such as pharmacotherapy (BMI ≥ 27 kg/m² with comorbidity or BMI over 30 kg/m²) and bariatric surgery (BMI ≥ 35 kg/m² with comorbidity or BMI over 40 kg/m²) be used as adjuncts to behavioral modification.

Abbreviations: ACE, angiotensin-converting enzyme; AED, antiepileptic drug; ARB, angiotensin receptor blocker; BID, twice a day; BMI, body mass index; BP, blood pressure; CCK, cholecystokinin; CI, confidence interval; DPP-4, dipeptidyl peptidase IV; ER, extended release; GLP-1, glucagon-like peptide-1; H1, histamine; HbA1c, glycated hemoglobin; POMC, proopiomelanocortin; PYY, peptide YY; QD, every day; RCT, randomized controlled trial; SC, subcutaneous; SGLT, sodium-glucose-linked transporter; SSRI, selective serotonin reuptake inhibitor; T2DM, type 2 diabetes; TID, three times a day.
to reduce food intake and increase physical activity when this is possible. Drugs may amplify adherence to behavior change and may improve physical functioning such that increased physical activity is easier in those who cannot exercise initially. Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications. (1)

1.2 In order to promote long-term weight maintenance, we suggest the use of approved1 weight loss medication (over no pharmacological therapy) to ameliorate comorbidities and amplify adherence to behavior changes, which may improve physical functioning and allow for greater physical activity in individuals with a BMI ≥ 30 kg/m² or in individuals with a BMI of ≥ 27 kg/m² and at least one associated comorbid medical condition such as hypertension, dyslipidemia, type 2 diabetes (T2DM), and obstructive sleep apnea. (2)

1.3 In patients with uncontrolled hypertension or a history of heart disease, we recommend against using the sympathomimetic agents phentermine and diethylpropion. (1)

1.4 We suggest assessment of efficacy and safety at least monthly for the first 3 months, then at least every 3 months in all patients prescribed weight loss medications. (2)

1.5 If a patient’s response to a weight loss medication is deemed effective (weight loss ≥ 5% of body weight at 3 mo) and safe, we recommend that the medication be continued. If deemed ineffective (weight loss < 5% at 3 mo) or if there are safety or tolerability issues at any time, we recommend that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered. (1)

1.6 If medication for chronic obesity management is prescribed as adjunctive therapy to comprehensive lifestyle intervention, we suggest initiating therapy with dose escalation based on efficacy and tolerability to the recommended dose and not exceeding the upper approved dose boundaries. (2)

1.7 In patients with T2DM who are overweight or obese, we suggest the use of antidiabetic medications that have additional actions to promote weight loss (such as glucagon-like peptide-1 [GLP-1] analogs or sodium-glucose-linked transporter-2 [SGLT-2] inhibitors), in addition to the first-line agent for T2DM and obesity, metformin. (2)

1.8 In patients with cardiovascular disease who seek pharmacological treatment for weight loss, we suggest using medications that are not sympathomimetics such as lorcaserin and/or orlistat. (2)

2.0 Drugs that cause weight gain and some alternatives

2.1 We recommend weight-losing and weight-neutral medications as first- and second-line agents in the management of a patient with T2DM who is overweight or obese. Clinicians should discuss possible weight effects of glucose-lowering medications with patients and consider the use of antihyperglycemic medications that are weight neutral or promote weight loss. (1)

2.2 In obese patients with T2DM requiring insulin therapy, we suggest adding at least one of the following: metformin, pramlintide, or GLP-1 agonists to mitigate associated weight gain due to insulin. The first-line insulin for this type of patient should be basal insulin. This is preferable to using either insulin alone or insulin with sulfonylurea. We also suggest that the insulin therapy strategy be considered a preferential trial of basal insulin prior to premixed insulins or combination insulin therapy. (2)

2.3 We recommend angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers rather than β-adrenergic blockers as first-line therapy for hypertension in patients with T2DM who are obese. (1)

2.4 When antidepressant therapy is indicated, we recommend a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the antidepressant to make an informed decision about drug choice. Other factors that need to be taken into consideration include the expected length of treatment. (1)

2.5 We recommend using weight-neutral antipsychotic alternatives when clinically indicated, rather than those that cause weight gain, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the alternative treatments to make an informed decision about drug choice. (1)

2.6 We recommend considering weight gain potential in choosing an antiepileptic drug (AED) for any given patient, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the drugs to make an informed decision about drug choice. (1)

2.7 In women with a BMI > 27 kg/m² with comorbidities or BMI > 30 kg/m² seeking contraception, we suggest oral contraceptives over injectable medications due to
weight gain with injectables, provided that women are well-informed about the risks and benefits (ie, oral contraceptives are not contraindicated). (2)

2.8 We suggest monitoring the weight and waist circumference of patients on antiretroviral therapy due to unavoidable weight gain, weight redistribution, and associated cardiovascular risk. (2)

2.9 We suggest the use of nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs when possible in patients with chronic inflammatory disease like rheumatoid arthritis because corticosteroids commonly produce weight gain. (2)

2.10 We suggest the use of antihistamines with less central nervous system activity (less sedation) to limit weight gain. (2)

3.0 Off-label use of drugs approved for other indications for chronic obesity management

3.1 We suggest against the off-label use of medications approved for other disease states for the sole purpose of producing weight loss. A trial of such therapy can be attempted in the context of research and by healthcare providers with expertise in weight management dealing with a well-informed patient. (Ungraded Best Practice Recommendation)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the pharmacological management of obesity a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that 1 denotes very low quality evidence; 2, low quality; 3, moderate quality; and 4, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that panelists considered in making the recommendation; in some instances, there are remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the CGS before the members are approved by the Society’s Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflicts of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

A systematic review was commissioned by the Endocrine Society to quantify weight gain and weight loss associated with a discrete list of drugs chosen a priori by this guideline Task Force (3). The systematic review compared a list of 54 commonly used drugs chosen a priori by the Task Force (drugs suspected of having weight implications) that were compared to placebo in randomized controlled trials. For trials to be included, the length of treatment had to be ≥ 30 days. The outcome of interest for the review was weight change (expressed in absolute and rel-
atic terms). The Task Force also used evidence derived from existing systematic reviews, randomized trials, and observational studies on the management of medications for other conditions that may result in weight gain. Economic analyses and cost effectiveness studies were not reviewed or considered as a basis for the recommendations. Drugs associated with weight gain and suggested alternatives are presented in Supplemental Table 1.

In several of the recommendations, we used evidence derived from randomized clinical trials about the benefits of shared decision making in terms of improving patients’ knowledge, reducing decisional conflict and regret, and enhancing the likelihood of patients making decisions consistent with their own values (4). Although there is abundant evidence for the value of shared decision making across several clinical scenarios, specific evidence for obesity management is scant. This highlights a limitation of the existing literature and poses a challenge for implementing a specific strategy for shared decision making in managing obesity.

Medical management of the disease of obesity

The Task Force agrees with the opinion of prominent medical societies that current scientific evidence supports the view that obesity is a disease (5).

Weight loss produces many benefits including risk factor improvement, prevention of disease, and improvements in feeling and function. Greater weight loss produces greater benefits, but modest (5 to 10%) weight loss, such as that produced by lifestyle modifications and medications, has been shown to produce significant improvements in many conditions (5, 6).

Medications used for the management of conditions other than obesity can contribute to or exacerbate weight gain in susceptible individuals. Many of these conditions are also associated with obesity. Healthcare providers can help patients prevent or attenuate weight gain by appropriately prescribing medications that would promote weight loss or minimize weight gain when treating these conditions. Healthcare providers can help selected patients successfully lose weight by appropriately prescribing weight loss medications or in some cases surgical intervention as an adjunct to lifestyle change.

This guideline will target how providers can use medications as an adjunct to lifestyle change therapy to promote weight loss and maintenance. It will also address how prescribers can prevent or attenuate weight gain when prescribing for diabetes, depression, and chronic diseases often associated with obesity. The evidence review addresses medications with a weight loss indication, as well as those medications that affect weight when prescribed for a nonobesity indication, ie, that have been associated with significant weight gain and increase in risk of comorbidities or with weight loss.

Clinical encounter with the patient who is overweight or obese

There are a number of steps a clinician should take in the clinical encounter.

- Annual and symptom-based screening for major chronic conditions associated with obesity in all adult patients with a BMI of 30 kg/m² or above. These include T2DM, cardiovascular disease, hypertension, hyperlipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, osteoarthritis, and major depression.
- Timely adherence to national cancer screening guidelines with the understanding that individuals who are obese are at increased risk for many malignancies (7).
- Identification of contributing factors, including family history, sleep disorders, disordered eating, genetics, and environmental or socioeconomic causes.
- Identification of and appropriate screening for secondary causes of obesity (Table 1). These need not be automatically screened for unless the history and/or physical examination suggests the diagnosis or suspicion of the diagnosis.
- Adherence to the AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (8), which was updated in 2013 and includes recommendations for assessment and treatment with diet and exercise, as well as bariatric surgery for appropriate candidates.
- Identification of medications that contribute to weight gain. Prescribe drugs that are weight neutral or that promote weight loss when possible.
- Formulation of a treatment plan based on diet, exercise, and behavior modifications as above.

Rationale for pharmacological treatment of obesity

The challenge of weight reduction

If permanent weight loss could be achieved exclusively with behavioral reductions in food intake and increases in energy expenditure, medications for obesity would not be needed. Weight loss is difficult for most patients, and the patient’s desire to restrict food and energy intake is counteracted by adaptive biological responses to weight loss (9–12). The fall in energy expenditure (out of proportion to reduction in body mass) and increase in appetite that are observed after weight loss are associated with changes in a range of hormones (12–14). Some of these changes represent adaptive responses to weight loss and result in al-
Clinical, this means that the individual must reduce energy intake or increase energy expenditure indefinitely as long as the reduced weight is maintained. The primary determinant of resting energy expenditure appears to persist indefinitely as long as the reduced weight is maintained. These medications primarily secreted in response to glucose and promote insulin release from the pancreas as well as satiety. Ghrelin is produced in the stomach, and it is unique among gut hormones in that it is orexigenic and levels increase with time since the last meal. These hormones signal areas in the hindbrain and arcuate nucleus, as do insulin and leptin. Leptin is secreted from adipose tissue, and circulating levels are proportional to fat mass. It is an anorectic hormone, which exerts its effects by inhibiting neuropeptide Y/Agouti-related peptide neurons and activating pro-opiomelanocortin (POMC)/cocaine amphetamine-related transcript neurons in the arcuate nucleus, resulting in decreased food intake and increased energy expenditure, although the increase in energy expenditure has been disputed in leptin-deficient humans treated with leptin (15).

Obesity in humans is almost universally associated with high leptin levels and failure to respond to exogenous leptin; thus, leptin analogs have not been found to be useful so far in the treatment of obesity. In humans, many other cues such as reward and emotional factors play a role in food intake aside from hunger, and another pathway is responsible for reward-associated feeding behavior. Increased hunger and decreased satiety after weight loss are associated with an increase in the 24-hour profile of circulating levels of the orexigenic hormone ghrelin and reductions in the levels of the anorexigenic hormones PYY, CCK, leptin, and insulin. These changes in appetite-related hormones appear to persist for at least 1 year after weight reduction and may remain altered indefinitely in a manner that promotes increased energy intake and ultimately weight regain (14, 16–23).

Mechanisms of action of pharmacological agents

With the exception of orlistat, medications indicated for obesity target appetite mechanisms. The medications available for obesity treatment work primarily in the arcuate nucleus to stimulate the POMC neurons, which promote satiety. Some of the medications discussed in Section 1.0 are serotoninergic, dopaminergic, or norepinephrine-ergic, and others are more likely to affect satiety and reduce total energy intake by blocking the appetite-regulating systems that occur as a patient moves from being obese to being closer to a healthy weight. These latter changes underlie many of the health benefits of weight loss.

Table 1. Causes of Obesity

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<td>β blockers</td>
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*Controversial whether hypothyroidism causes obesity or exacerbates obesity.

b Depression associated with overeating or binging.

No approved weight loss medication appears to promote long-term thermogenesis. These medications promote weight loss through effects on appetite, increasing satiety, and decreasing hunger, perhaps by aiding in resisting food cues or by reducing caloric absorption (14).

As discussed above, weight loss is usually associated with a reduction in total energy expenditure that is out of proportion to changes in lean body mass; the primary determinant of resting energy expenditure appears to persist indefinitely as long as the reduced weight is maintained. Clinically, this means that the individual must reduce energy intake or increase energy expenditure indefinitely to sustain weight loss.

Neuroendocrine dysregulation of energy intake and energy expenditure in obesity

Signals to appetite and controlling centers within the central nervous system and in particular the hypothalamus and the brainstem come from the gut, adipose tissue, liver, and pancreas (Figure 1). Distention of the gastrointestinal tract is communicated to the brain. In the process of food intake, gut hormones are secreted that signal satiety in the hindgut primarily; these include most notably peptide YY (PYY; secreted in ileum and colon) and cholecystokinin (CCK; in duodenum), but also gastric inhibitory polypeptide (K cells in duodenum and jejunum) and GLP-1 (L cells in ileum), which are primarily secreted in response to glucose and promote insulin release from the pancreas as well as satiety. Ghrelin is produced in the stomach, and it is unique among gut hormones in that it is orexigenic and levels increase with time since the last meal. These hormones signal areas in the hindbrain and arcuate nucleus, as do insulin and leptin. Leptin is secreted from adipose tissue, and circulating levels are proportional to fat mass. It is an anorectic hormone, which exerts its effects by inhibiting neuropeptide Y/Agouti-related peptide neurons and activating pro-opiomelanocortin (POMC)/cocaine amphetamine-related transcript neurons in the arcuate nucleus, resulting in decreased food intake and increased energy expenditure, although the increase in energy expenditure has been disputed in leptin-deficient humans treated with leptin (15).
releasing agents/reuptake inhibitors (Figure 2) (24). Phentermine is primarily a noradrenergic and possibly dopaminergic sympathomimetic amine. Lorcaserin is a serotonin agent specifically stimulating the serotonin type 2c receptor (25). The combination of phentermine and topiramate, which is a neurostabilizer and antiseizure medication, seems to be additive (26); however, it is unclear how topiramate enhances appetite suppression. Buproprion is a dopamine and norepinephrine reuptake inhibitor (27), which stimulates POMC neurons. In combination with naltrexone, buproprion enhances efficacy due to the release of feedback inhibition of POMC neurons that naltrexone potentiates. GLP-1 agonists also affect the POMC neurons and cause satiety (18). Orlistat blocks absorption of 25 to 30% of fat calories and is not appreciably absorbed systemically (28, 29). Another class of medications is associated with weight loss without an effect on appetite. This class is the SGLT-2 inhibitors for T2DM, which promote weight loss by preventing the reabsorption of glucose as well as water in the renal tubules (30).

1.0 Care of the patient who is overweight or obese

1.1 We recommend that diet, exercise, and behavioral modification be included in all overweight and obesity management approaches for BMI ≥ 25 kg/m² and that other tools such as pharmacotherapy (BMI ≥ 27 kg/m² with comorbidity or BMI over 30 kg/m²) and bariatric surgery (BMI ≥ 35 kg/m² with comorbidity or BMI over
40 kg/m²) be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when this is possible. Drugs may amplify adherence to behavior change and may improve physical functioning such that increased physical activity is easier in those who cannot exercise initially. Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications. (1|QQQQ) (Table 2 and Supplemental Table 1)

**Evidence and relevant values**

Weight loss medications reinforce behavioral strategies to create negative energy balance. Most weight loss medications affect appetite and, as a result, promote adherence

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**Table 2. Advantages and Disadvantages Associated with Weight Loss Medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Inexpensive ($)</td>
<td>Side effect profile</td>
</tr>
<tr>
<td></td>
<td>Greater weight loss</td>
<td>No long-term data</td>
</tr>
<tr>
<td>Topiramate/phentermine</td>
<td>Robust weight loss</td>
<td>Expensive ($$$)</td>
</tr>
<tr>
<td></td>
<td>Long-term data</td>
<td>Teratogen</td>
</tr>
<tr>
<td>Lorcarserin</td>
<td>Side effect profile</td>
<td>Expensive ($$$)</td>
</tr>
<tr>
<td></td>
<td>Long-term data</td>
<td></td>
</tr>
<tr>
<td>Orlistat, prescription</td>
<td>Nonsystemic</td>
<td>Less weight loss</td>
</tr>
<tr>
<td>Orlistat, over-the-counter</td>
<td>Long term data</td>
<td>Side effect profile</td>
</tr>
<tr>
<td></td>
<td>Inexpensive ($)</td>
<td>Less weight loss</td>
</tr>
<tr>
<td>Natrexone/bupropion</td>
<td>Greater weight loss</td>
<td>Side effect profile</td>
</tr>
<tr>
<td></td>
<td>Food addiction</td>
<td>Side effect profile</td>
</tr>
<tr>
<td></td>
<td>Long-term data</td>
<td>Mid-level price range ($)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Side effect profile</td>
<td>Expensive ($$$)</td>
</tr>
<tr>
<td></td>
<td>Long-term data</td>
<td>Injectable</td>
</tr>
</tbody>
</table>

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*a* Less weight loss = 2–3%; greater weight loss = >3–5%; robust weight loss = >5%.

*b* Long term is 1–2 years.
to the diet. The medication that blocks fat absorption reinforces avoidance of high-fat (energy-dense) foods, in addition to promoting malabsorption of fat calories. Medications act to amplify the effect of the behavioral changes to consume fewer calories. They do not “work on their own.” To get maximal efficacy, obesity drugs should be used as adjuncts to lifestyle change therapy, and in some cases weight loss is limited without lifestyle change. Whatever baseline behavioral treatment is given, the effect of the drug will be static (33, 34). Just as increasing the dose of medication increases weight loss, increasing the intensity of behavioral modification increases weight loss (33). Patients should be made aware that lifestyle changes are needed when using a weight loss medication and that the addition of a weight loss medication to a lifestyle program will likely result in greater weight loss (6, 35–38).

In making this recommendation, the Task Force acknowledges the variation in the strength of evidence for the different lifestyle interventions and pharmacological interventions for obesity. However, the strong recommendation for reserving pharmacological interventions as an adjunct therapy also depends on values and preferences, with an emphasis on avoiding the side effects, burden, and cost of medications while promoting a healthier lifestyle that has benefit beyond weight loss.

1.2 In order to promote long-term weight maintenance, we suggest the use of approved (see Footnote 1) weight loss medications (over no pharmacological therapy) to ameliorate comorbidities and amplify adherence to behavior changes, which may improve physical functioning and allow for greater physical activity in individuals with a BMI $\geq 30$ kg/m$^2$ or in individuals with a BMI of $\geq 27$ kg/m$^2$ and at least one associated comorbid medical condition such as hypertension, dyslipidemia, T2DM, and obstructive sleep apnea. (2| modulation)

### Evidence

Caloric restriction through diet and behavior modification has been shown to produce modest but effective weight loss for controlling comorbid medical problems such as diabetes, hypertension, and obstructive sleep apnea (39, 40) (Table 3). Moreover, the adjunctive use of weight loss medication can produce even greater weight loss and cardiometabolic improvements (36, 37, 41–45). Although all of these medications and others have been shown to be effective as adjunctive treatment, none have been shown to be effective on their own. The systematic reviews conducted to support the 2013 AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults (8) evaluated the observational literature about the association of various BMI cutoffs and the incidence of death and cardiovascular disease. That guideline adopted the arbitrary BMI cutpoints of $\geq 30$ kg/m$^2$ and $\geq 27$ kg/m$^2$ with medical related comorbidity that had been determined by the U.S. Food and Drug Administration (FDA) and listed on the package inserts of FDA-approved obesity medications. Our Task Force adopted these cutpoints, realizing that they are arbitrary and only low-quality evidence supports associations determined by these cutpoints. Nevertheless, we had to use cutpoints to provide patients and clinicians with specific implementable and practical recommendations.

The only medication available in the European Union for chronic obesity management is orlistat. We encourage additional scrutiny of medications available in the United States by the European Medicines Agency (EMA) and the

### Table 3. Comorbid Conditions in Obesity and Evidence for Amelioration With Weight Reduction

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Improvement After Weight Loss</th>
<th>First Author, Year (Ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1DM</td>
<td>Yes</td>
<td>Cohen, 2012 (132); Mingrone, 2012 (133)$^a$; Schauer, 2012 (134); Buchwald, 2009 (135)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)</td>
</tr>
<tr>
<td>Dyslipidemia and metabolic syndrome</td>
<td>Yes</td>
<td>Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Yes</td>
<td>Wannamethee, 2005 (139)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Variable outcomes</td>
<td>Andersen, 1991 (140); Huang, 2005 (141); Palmer, 1990 (142); Ueno, 1997 (143)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Yes</td>
<td>Christensen, 2007 (144); Fransen, 2004 (145); Huang, 2000 (146); Messier, 2004 (147); van Gool, 2005 (148)</td>
</tr>
<tr>
<td>Cancer</td>
<td>Insufficient evidence</td>
<td>Adams, 2009 (149); Sjöström, 2009 (150)</td>
</tr>
</tbody>
</table>

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

$^a$ This study showed that weight gain within the normal-weight BMI category (ie, increase from 23 to 25 kg/m$^2$) increased risk of T1DM 4-fold.
funding of additional long-term clinical trials in the European Union and elsewhere to study the safety and efficacy of these medications, with the goal of providing access to medications for chronic obesity management to patients in need across the world.

1.3 In patients with uncontrolled hypertension or a history of heart disease, we recommend against using sympathomimetic agents phentermine and diethylpropion. (1[116]116) (Table 4)

Evidence
The product labels for medications approved for chronic weight management (46–49) include contraindications and cautions based on clinical data submission on > 1500 individuals treated with each medication before approval. These contraindications are detailed in Table 4. Prescribers should be familiar with these product labels in order to avoid contraindications and to judiciously choose patients based on product cautions.

For the sympathomimetic agents phentermine and diethylpropion, regulatory approval was given based on a smaller clinical profile and without a cardiovascular outcomes study. There is thus a lack of evidence on safety for these products across broad populations. In making a strong recommendation, the panel placed a high value on avoiding harm and a lower value on potential short-term weight loss.

Implementation remarks
Because phentermine and diethylpropion are associated with elevations in mean blood pressure (BP) and pulse rate in treated populations, we do not advocate their prescription in patients with a history of cardiovascular disease, and we suggest caution and careful monitoring in patients with hypertension history. Thus, caution is advised in prescribing these agents in patients with hypertension, history of cardiac arrhythmia, or seizures. A serotonin receptor agonist such as lorcaserin would be a better choice in a patient with these conditions.

Another example is the patient with obesity and depression on a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). In these patients, lorcaserin would not be the best choice due to the potential for serotonin syndrome. A better choice would be phentermine/topiramate or phentermine alone. Orlistat is likely to be safe in all instances due to its mechanism of action. Other cautionary instances are outlined in Table 4.

1.4 We suggest assessment of efficacy and safety at least monthly for the first 3 months, then at least every 3 months in all patients prescribed weight loss medications. (2[116]116)

Evidence
Diet, behavior modification, and, if appropriate, pharmacotherapy have been shown to be safe and effective in producing modest but effective weight loss and amelioration of comorbid medical problems. To promote maximum effectiveness, frequent assessments are indicated to assess effectiveness of the treatment, ensure accountability, and monitor safety and efficacy of the weight loss medications. The more accountable patients are to weight loss programs, the better the outcomes that are expected. Moreover, any adverse side effects of the weight loss medications can be detected early and rectified (8). The AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults reviewed randomized clinical trials on weight loss interventions and determined that the best weight loss outcomes occur with frequent face-to-face visits (16 visits per year on average) (8, 38).

1.5 If a patient’s response to a weight loss medication is deemed effective (weight loss ≥ 5% of body weight at 3 mo) and safe, we recommend that the medication be continued. If deemed ineffective (weight loss < 5% at 3 mo) or if there are safety or tolerability issues at any time, we recommend that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered. (1[116]116)

Evidence
Weight loss medications do not change the underlying physiology of weight regulation in any permanent way. Trials of weight loss medication that have used a crossover design have demonstrated that the weight loss effects of these medications are only sustained as long as they are taken and these same benefits occur on introducing the medication in patients previously treated with lifestyle alone. Historically, patients and providers thought that weight loss medications could be used to produce an initial weight loss that could subsequently be sustained by behavioral means. The available evidence does not support this view. Much as antihypertensive medications lower BP to a new steady state with BP rising to baseline levels upon discontinuing medication, weight loss medications promote weight loss to a new steady state with gradual weight gain typically occurring when medications are stopped (50, 51).

1.6 If medication for obesity management is prescribed as adjunctive therapy to comprehensive lifestyle intervention, we suggest initiating therapy with dose escalation based on efficacy and tolerability to the recommended
<table>
<thead>
<tr>
<th>Drug (Generic)</th>
<th>Dosage</th>
<th>Mechanism of Action</th>
<th>Weight Loss Above Diet and Lifestyle Alone, Mean Weight Loss, % or kg; Duration of Clinical Studies</th>
<th>Status</th>
<th>Common Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine resin</td>
<td>AdipexP (37.5 mg), 37.5 mg/d</td>
<td>Norepinephrine-releasing agent</td>
<td>3.6 kg (7.9 lb); 2–24 wk</td>
<td>Approved in 1960s for short-term use (3 mo)</td>
<td>Headache, elevated BP, elevated HR, insomnia, dry mouth, constipation, anxiety</td>
<td>Anxiety disorders (agitated states), history of heart disease, uncontrolled hypertension, seizure, MAO inhibitors, pregnancy and breastfeeding, hyperthyroidism, glaucoma, history of drug abuse, sympathomimetic amines</td>
</tr>
<tr>
<td></td>
<td>Ionamin (30 mg), 30–37.5 mg/d</td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular: palpitation, tachycardia, elevated BP; ischemic events</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Central nervous system: overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gastrointestinal: dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allergic: urticaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Endocrine: impotence, changes in libido</td>
<td></td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Tenuate (75 mg), 75 mg/d</td>
<td>Norepinephrine-releasing agents</td>
<td>3.0 kg (6.6 lb); 6–52 wk</td>
<td>FDA approved in 1960s for short-term use (3 mo)</td>
<td>See phentermine resin</td>
<td>See phentermine resin</td>
</tr>
<tr>
<td>Orlistat, prescription (120 mg)</td>
<td>120 mg TID</td>
<td>Pancreatic and gastric lipase inhibitor</td>
<td>2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y</td>
<td>FDA approved in 1999 for chronic weight management</td>
<td>Decreased absorption of fat-soluble vitamins, steatorrhea, oily spotting, flatulence with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence</td>
<td>Cyclosporine (taken 2 h before or after orlistat dose), chronic malabsorption syndrome, pregnancy and breastfeeding, cholestasis, levotyrosine, warfarin, antiepileptic drugs</td>
</tr>
<tr>
<td>Orlistat, over-the-counter (60 mg)</td>
<td>60–120 mg TID</td>
<td>Pancreatic and gastric lipase inhibitor</td>
<td>2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y</td>
<td>FDA approved in 1999 for chronic weight management</td>
<td>See Orlistat, prescription</td>
<td>See Orlistat, prescription</td>
</tr>
<tr>
<td>Lorcaserin (10 mg)</td>
<td>10 mg BID</td>
<td>5HT2c receptor agonist</td>
<td>3.6 kg (7.9 lb), 3.6%; 1 y</td>
<td>FDA approved in 2012 for chronic weight management</td>
<td>Headache, nausea, dry mouth, dizziness, fatigue, constipation</td>
<td>Pregnancy and breastfeeding</td>
</tr>
<tr>
<td>Phentermine (P)/topiramate (T)</td>
<td>3.75 mg/P/23 mg T ER QD (starting dose)</td>
<td>GABA receptor modulation (T) plus norepinephrine-releasing agent (P)</td>
<td>6.6 kg (14.5 lb) (recommended dose), 6.6%</td>
<td>FDA approved in 2012 for chronic weight management</td>
<td>Insomnia, dry mouth, constipation, paresthesia, dizziness, dysgeusia</td>
<td>Use with caution: SSRI, SNRI/MAOI, St John's wort, triptans, bupropion, dextromethorphan, Pregnancy and breastfeeding, hyperthyroidism, glaucoma, MAO inhibitor, sympathomimetic amines</td>
</tr>
<tr>
<td></td>
<td>7.5 mg/P/46 mg T ER daily (recommended dose)</td>
<td></td>
<td>8.6 kg (18.9 lb) (high dose), 8.6%; 1 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 mg/P/92 mg P/TE R daily (high dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone/ bupropion</td>
<td>32 mg/360 mg 2 tablets QID (high dose)</td>
<td>Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naloxone)</td>
<td>4.8%; 1 y (Ref. 79)</td>
<td>FDA approved in 2014 for chronic weight management</td>
<td>Nausea, constipation, headache, vomiting, dizziness</td>
<td>Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal, MAO inhibitors</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>3.0 mg injectable</td>
<td>GLP-1 agonist</td>
<td>5.8 kg, 1 y (Ref. 30, 31)</td>
<td>FDA approved in 2014 for chronic weight management</td>
<td>Nausea, vomiting, pancreatitis</td>
<td>Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history</td>
</tr>
</tbody>
</table>

Abbreviations: GABA, γ-aminobutyric acid; HR, heart rate; MAO, monoamine oxidase (Ref. 46–49).

a Mean weight loss in excess of placebo as percentage of initial body weight or mean kilogram weight loss over placebo.
For the medications approved for long-term treatment for obesity, the recommended doses are as follows: orlistat, 120 mg three times a day (TID); phentermine/topiramate, 7.5 mg/46 mg every day (QD); lorcaserin, 10 mg twice a day (BID); naltrexone/bupropion, 8 mg/90 mg, 2 tablets BID; and for liraglutide, 3.0 mg SC QD (46–49).

For orlistat, the drug is available over the counter at a dosage of 60 mg TID. This dosage has been shown to produce greater weight loss than placebo (52). The recommended prescription dosage is 120 mg TID. Given the favorable safety profile and weight loss efficacy of orlistat at 120 mg TID, it is the preferred dose for prescription (47). There is no evidence from clinical trials using dosages higher than 120 mg TID that efficacy is greater at higher dosages, and prescribers should not exceed 120 mg TID. Orlistat, 120 mg TID, has been studied and approved for treatment of adolescents with obesity (58–60).

For phentermine/topiramate extended release (ER), it is necessary to escalate the dose when starting the medication. The clinical trial data support starting at a dosage of 3.75 mg/23 mg QD and maintaining this for at least 2 weeks. If the patient tolerates the medication, an increase to 7.5 mg/46 mg is in order. Because of the more favorable tolerability profile in clinical studies of the 7.5 mg/46 mg dose, further escalation is only recommended for patients who have not lost 3% of their body weight at 12 weeks. In that case, the dose can be increased to 11.25 mg/69 mg, and then to 15 mg/92 mg. The product label recommends a gradual reduction of dose over 3–5 days because of the observation of seizures occurring when topiramate was stopped abruptly in patients with epilepsy (41, 43, 61).

For lorcaserin, the recommended dosage is 10 mg BID. In clinical trials, lorcaserin 10 mg QD produced nearly as much weight loss as 10 mg BID (42, 44, 45).

Naltrexone/bupropion is available in 8mg/90mg combination tablets. One tablet should be started in the morning and in 1 week 1 tablet added before dinner. As tolerated, the dose should be increased to 2 tablets in the morning the 3rd week, and 2 tablets before the evening meal the 4th week to the maximum of 2 tablets twice daily. If side effects such as nausea develop during dose escalation, the dose should not be increased further until tolerated. If a patient has not lost more than 5% of body weight at 12 weeks, naltrexone/bupropion should be discontinued (79, 93).

Liraglutide should be initiated at a dose of 0.6 mg daily by SC injection. The dose can be increased by 0.6 mg per week up to a maximum of 3.0 mg. If side effects such as nausea develop during dose escalation, the dose should not be increased further until tolerated (31).

There are no comparative data of different doses of phentermine and other sympathomimetics used as a single agent. Therefore, the once-daily doses of 30 mg phentermine (37.5 mg as resin) or 75 mg tenuate should not be exceeded.

1.7 In patients with T2DM who are overweight or obese, we suggest the use of antidiabetic medications that have additional actions to promote weight loss (such as GLP-1 analogs or SGLT-2 inhibitors) in addition to the first-line agent for T2DM and obesity, metformin (63). (2)[★★★★]

Evidence

Individuals with obesity and T2DM may have the dual benefit of weight loss and glycemic control while prescribed a regimen including one or more of three currently available drug classes: metformin, the GLP-1 agonists (exenatide, liraglutide), and the new class of SGLT-2 inhibitors. For the goal of clinically significant weight loss, trials comparing GLP-1 agonists and other antihyperglycemic agents have shown weight loss in some subjects in higher ranges between 5.5 and 8 kg (62). Although other agents including metformin and SGLT-2 inhibitors produce more modest weight loss, ie, in the 1– to 3-kg range in most studies, these agents have not been studied in the setting of concomitant behavioral therapy, and the full weight loss potential is therefore not yet known. In summary, because a subset of diabetes patients may have substantial weight loss on certain diabetes agents that also lower blood glucose, most patients with diabetes should try one or more of these before being considered for additional medications designed for the specific goal of weight loss. The most substantial evidence supports a trial of GLP-1 agonists (see recommendation 2.1).

1.8 In patients with cardiovascular disease who seek pharmacological treatment for weight loss, we suggest using medications that are not sympathomimetics, such as lorcaserin and/or orlistat. (2)[★★★★]

Evidence

Because patients with a prior history of cardiovascular disease may be susceptible to sympathetic stimulation, agents without cardiovascular signals (increased BP and pulse) should be used preferentially. For patients with established cardiovascular disease who require medication for weight loss, orlistat and lorcaserin should be used. These drugs have a lower risk of increased BP than phentermine and topiramate ER. Lorcaserin showed a reduc-
tion in pulse and BP greater than placebo in randomized placebo-controlled trials (44).

2.0 Drugs that cause weight gain and some alternatives

A variety of prescription medications have been associated with weight gain. Drug-induced weight gain is a preventable cause of obesity. For all patients, and particularly for patients who have a BMI > 27 kg/m² with comorbidities or BMI > 30 kg/m², the desired level of clinical efficacy for a chosen therapy should be balanced against side effects, including the likelihood of weight gain. In cases where there are no acceptable therapeutic alternatives, the minimal dose required to produce clinical efficacy may prevent drug-induced weight gain. Patients’ initial weight status, the presence of risk factors for cardiovascular disease, diabetes, and other obesity-related health complications, as well as the benefits of pharmacological therapies warrant careful consideration when prescribing a first-line therapy or change in medication.

2.1 We recommend weight-losing and weight-neutral medications as first- and second-line agents in the management of a patient with T2DM who is overweight or obese. (1)

Evidence

The effect of metformin for promoting mild weight loss is likely due to multiple mechanisms (63). However, in animal models, metformin mediates a phenotypic shift away from lipid accretion through AMP-activated Protein Kinase-Nicotinamide phosphoribosyltransferase-Sirtuin 1-mediated changes in metabolism supporting treatment for obesity (64). GLP-1 agonists such as exenatide and liraglutide have also been shown to promote mild weight loss. Pramlintide is an amylin analog that promotes weight loss by increasing satiety and decreasing food intake (65, 66). Dipeptidyl peptidase IV (DPP-4) inhibitors appear to be weight neutral or may lead to minimal weight change. α-Glucosidase inhibitors such as acarbose and miglitol may be weight neutral or lead to a small change in weight (152, 153).

Clinicians should discuss possible weight effects of glucose-lowering medications with patients and consider the use of antihyperglycemic medications that are weight neutral or promote weight loss.

Weight gain is often associated with many diabetes therapies. Patients can gain as much as 10 kg in a relatively short period (3 to 6 mo) after initiating treatment with insulin, sulfonylureas, and other insulin secretagogues like glinides and thiazolidinediones. Participants in the Diabetes Prevention Program with impaired glucose tolerance who took metformin (850 mg BID) lost 2.1 kg compared with a weight loss of 0.1 kg in the placebo group (69). A recent study comparing sitagliptin plus metformin with pioglitazone in drug-naive patients with T2DM showed that the sitagliptin-metformin combination resulted in weight loss (−1.4 kg) whereas pioglitazone led to weight gain (3.0 kg) (70). A retrospective analysis of exenatide (n = 6280), sitagliptin (n = 5861), and insulin (n = 32 398) indicated that exenatide-treated subjects lost an average of 3.0 kg, sitagliptin-treated subjects lost 1.1 kg, and insulin-treated subjects gained 0.6 kg (71).

In a 1-year trial comparing two doses of liraglutide (1.2 and 1.8 mg) with glimepiride 8 mg, subjects lost 2.05 and 2.45 kg in the 1.2- and 1.8-mg groups, respectively, compared with a 1.12-kg weight gain in the glimepiride group. Glycated hemoglobin (HbA1c) significantly (P = .0014) decreased by 0.84% with liraglutide 1.2 mg and by 1.14% with liraglutide 1.8 mg (P < .0001) compared to 0.51% with glimepiride (72). An analysis of 17 randomized placebo-controlled trials showed that all GLP-1 agonists reduced HbA1c levels by about 1% (62). The DPP-4 inhibitors sitagliptin and vildagliptin have also been shown in a meta-analysis of 25 studies to lower HbA1c by approximately 0.7 and 0.6%, respectively, in comparison with placebo (73).

A recent review of direct comparisons with active glucose-lowering agents in drug-naive patients demonstrated that DPP-4 inhibitors reduce HbA1c slightly less than metformin (by approximately 0.28) and provide similar glucose-lowering effects as a thiazolidinedione. DPP-4 inhibitors have better gastrointestinal tolerability than metformin yet are weight neutral (74, 75). Another meta-analysis found that an increase in body weight (1.8 to 3.0 kg) was observed with most second-line therapies, the exceptions being DPP-4 inhibitors, α-glucosidase inhibitors, and GLP-1 analogs (+0.6 to −1.8 kg) (76). Pramlintide, indicated as an adjunct to insulin, may also aid with weight loss. A meta-analysis demonstrated a weight loss of −2.57 kg for those taking pramlintide vs the control groups (77).

The SGLT-2 inhibitors dapagliflozin and canagliflozin are a new class of antidiabetic drugs that reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion (78). A recent systematic review and meta-analysis (79) looks at not only the effect of these medications on glycemic indices but also their effects on body weight. Compared with placebo, the mean percentage change in body weight from baseline in eight studies of > 12 weeks comparing the SGLT-2 inhibitor to placebo was −2.37% (95% confidence interval [CI], −2.73 to −2.02). Canagliflozin appears to produce slightly more weight loss on average because three studies with dapagliflozin vs placebo showed mean loss of −2.06% of initial body weight (95% CI, −2.38 to
HbA1c reductions of 0.62 to 0.68% in the 120-showed weight loss (95% CI, −3.09 to −2.13); however, this was not statistically significant. This analysis may underestimate the weight loss effects of these drugs because studies of 12 weeks were included. In 52-week observations, there is no weight regain after maximal loss at 24 weeks.

In addition, because weight-sparing medications are unique in that they do not independently cause hypoglycemia, they have a lower potential for hindering an exercise program. Exercise adjustment is generally necessary only with insulin and with medications that can promote endogenous insulin secretion despite decreasing glucose levels, such as the sulfonylurea and glinide classes of agents (80). Hence, prioritizing metformin, incretin-based medications, and SGLT-2s as therapeutic strategies can reduce exercise-related hypoglycemia and potentially increase the safety and efficacy of exercise in patients with diabetes, thus supporting this important weight-reduction strategy (67, 68).

2.2 In obese patients with T2DM requiring insulin therapy, we suggest adding at least one of the following: metformin, pramlintide, or GLP-1 agonists to mitigate associated weight gain due to insulin. The first-line insulin for this type of patient should be basal insulin. This is preferable to using either insulin alone or insulin with a sulfonylurea. We also suggest that the insulin therapy strategy be considered a preferential trial of basal insulin prior to premixed insulins or combination insulin therapy.

Evidence

Insulin remains the most effective agent to control serum glucose (81). However, multiple large studies typically show weight gain associated with insulin use, either as monotherapy or in combination with oral antidiabetic agents (82–85). Treatment with both metformin and insulin, or when metformin is prescribed in addition to an insulin program, yields similar glycemic benefit to insulin alone without excessive additional weight gain, as shown by meta-analyses and randomized trials (86–88).

Amylin analogs are FDA approved for use in combination with existing insulin treatment. A dose-finding study with pramlintide added to a variety of insulin regimens showed weight loss (−1.4 kg) in treatment groups (89), with HbA1c reductions of 0.62 to 0.68% in the 120-μg dose group. Additionally, weight gain was prevented when pramlintide was added to the basal insulins glargine or detemir. Other studies have found more substantial weight loss of over 3 kg with the use of pramlintide (90).

Other weight-sparing regimens have been studied, including the combination of basal insulin with the weight-neutral DPP-4 inhibitor sitagliptin (91) and weight-reducing combination therapy with liraglutide and metformin. Buse et al (92) investigated the addition of exenatide or placebo to regimens of insulin glargine alone, or in combination with metformin or pioglitazone or both, in adult T2DM patients with HbA1c of 7.1 to 10.5%. Despite superior HbA1c reduction, weight also decreased by 1.8 kg in the exenatide group compared with an increase of 1.0 kg in the placebo group (between-group difference, −2.7 kg; 95% CI, −3.7 to −1.7).

Finally, some weight benefits have been seen with the basal insulin analogs relative to biphasic and prandial insulin analog regimens. The Treating To Target in Type 2 Diabetes trial in patients receiving metformin/sulfonylurea compared the initiation of basal insulin detemir (twice daily, if required) to that of biphasic insulin aspart BID or prandial insulin aspart TID. Basal insulin use was associated with the least weight gain at 1 year (+1.9 vs +4.7 kg, detemir vs biphasic vs prandial, respectively) (93), and the weight advantage persisted during the 3-year trial (94).

2.3 We recommend ACE inhibitors, ARBs, and calcium channel blockers rather than β-adrenergic blockers as first-line therapy for hypertension in patients with T2DM who are obese.

Evidence

Angiotensin is overexpressed in obesity, directly contributing to obesity-related hypertension, providing support for the use of an ACE inhibitor as a first-line agent. Calcium channel blockers are also effective in the treatment of obesity-related hypertension and have not been associated with weight gain or adverse changes in lipids. ACE inhibitors and ARBs have not been associated with weight gain or insulin resistance and provide renal protection in diabetes (95).

If required, selective or nonselective β-blockers with a vasodilating component such as carvedilol and nebivolol are recommended because these agents appear to have less weight gain potential and less of an impact on glucose and lipid metabolism than other nonselective β-blockers (96, 97).

A study in patients taking metoprolol tartrate compared with those taking carvedilol for hypertension showed a mean weight gain of 1.19 kg, suggesting that weight gain is not a class effect of the β-adrenergic blockers (98). A meta-analysis of body weight changes in a series of randomized controlled hypertension trials of at least 6-month duration showed that body weight was higher in the β-blocker group, with a median difference of 1.2 kg between the β-blocker group and the control group (97). The Second Australian National Blood Pressure Trial re-
ported slightly better cardiovascular outcomes in hypertensive men treated with a regimen that began with an ACE inhibitor compared with a regimen starting with a diuretic (95).

2.4 When antidepressant therapy is indicated, we recommend a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the antidepressant to make an informed decision about drug choice. Other factors that need to be taken into consideration include the expected length of treatment. (1)

Evidence

The antidepressants vary considerably with respect to their long-term weight gain potential. Serretti and Mandelli (99) evaluated the relative risk of weight gain associated with drugs within the major classes of antidepressant medications in a recent meta-analysis. Paroxetine is considered to be the SSRI associated with the greatest long-term increase in body weight (100), amitriptyline is the most potent inducer of weight gain among the tricyclic antidepressants (99), and mirtazapine (a noradrenergic and specific serotoninergic antidepressant) is also associated with weight gain in the long term (101). Other specific tricyclics that have been associated with weight gain include nortriptyline (102), whereas the effect of imipramine seems to be neutral (99). SSRIs such as fluoxetine and sertraline have been associated with weight loss during acute treatment (4–12 wk) and with weight neutrality in the maintenance (>4 mo) phase (99). No significant effect could be observed for citalopram or escitalopram on body weight (99). Among the serotonon and norepinephrine re-uptake inhibitors, venlafaxine and duloxetine have been reported to slightly increase body weight over long-term treatment, although long-term data for venlafaxine are scarce (99). Bupropion selectively inhibits reuptake of dopamine and, to a lesser extent, norepinephrine. It is the only antidepressant that consistently causes weight loss (103). It was originally approved both for treating depression and for inducing smoking cessation. During clinical trials, it suppressed appetite and food cravings and significantly decreased body weight (103). The commissioned systematic review accompanying this guideline (3) was only able to demonstrate weight gain with amitriptyline (1.8 kg) and mirtazapine (1.5 kg) and weight loss with bupropion (−1.3 kg) and fluoxetine (−1.3 kg). The evidence for weight changes with other antidepressants was of lower quality.

2.5 We recommend using weight-neutral antidepressant alternatives when clinically indicated, rather than those that cause weight gain, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the alternative treatments to make an informed decision about drug choice. (1)

Evidence

Although better tolerated than the older antipsychotics, many of the new atypical antipsychotic agents have weight gain as a side effect (104). This weight gain is of clinical concern because it impedes patient compliance and has deleterious health consequences (104, 105) in patients who are often overweight or obese to begin with. The differential effect of atypical antipsychotics on histamine (H1) receptors, anticholinergic effects, and serotonin type 2C antagonistic effects may explain differences in weight gain among the drugs. Henderson et al (106) demonstrated that weight gain associated with clozapine treatment continued for as long as 46 months and was accompanied by a significant increase in triglyceride levels and a 37% increase in the incidence of T2DM over the 5-year period of observation. A randomized trial investigating the effectiveness of five antipsychotic medications found that a weight gain of >7% from baseline occurred in 30% of those taking olanzapine, 16% for quetiapine, 14% for risperidone, 12% for perphenazine, and 7% of those taking ziprasidone (107). Allison and Casey (104) noted that patients lost weight when switched from olanzapine to ziprasidone, and this weight loss was associated with improvements in their serum lipid profile and glucose tolerance. In a 6-week, double-blind trial, patients were randomly assigned to receive ziprasidone (n = 136) or olanzapine (n = 133). Body weight increased significantly in those taking olanzapine (3.6 kg) compared with those taking ziprasidone (1.0 kg) (108). A review of nine randomized controlled trials comparing ziprasidone with amisulpride, clozapine, olanzapine, quetiapine, and risperidone showed that ziprasidone produced less weight gain than olanzapine (five RCTs; n = 1659; mean difference, −3.82; 95% CI, −4.69 to −2.96), quetiapine (two randomized controlled trials [RCTs]; n = 754; relative risk, 0.45; 95% CI, 0.28 to 0.74), or risperidone (three RCTs; n = 1063; relative risk, 0.49; 95% CI, 0.33 to 0.74). Ziprasidone was also associated with less cholesterol increase than olanzapine, quetiapine, and risperidone (109). Finally, a review of 34 trials of antipsychotics in youth with psychotic and bipolar disorders found that weight gain ranged from 3.8 to 16.2 kg with olanzapine, 0.9 to 9.5 kg with clozapine, 1.9 to 7.2 kg with risperidone, 2.3 to 6.1 kg with quetiapine, and 0 to 4.4 kg with aripiprazole (110). Despite the variable effects on weight gain among the antipsychotic agents, the prediabetes ef-
fect may be similar via weight-independent mechanisms (111).

2.6 We recommend considering weight gain potential in choosing an AED for any given patient, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the drugs to make an informed decision about drug choice. (1|

Evidence

AEDs associated with weight loss are felbamate, topiramate, and zonisamide. AEDs associated with weight gain are gabapentin, pregabalin, valproic acid, vigabatrin, and carbamazepine. Weight-neutral AEDs are lamotrigine, levetiracetam, and phenytoin. In clinical practice, it is critical to weigh patients regularly, and AED selection should be based on each patient’s profile without sacrificing therapeutic efficacy (112).

Valproic acid has been shown to cause weight gain in both adults and children (113). A retrospective study of long-term weight gain in adult epileptic patients on valproic acid mono- or polytherapy showed that mild-to-moderate weight gain (5 to 10% of baseline weight) was shown in 24% of patients, whereas marked weight gain (>10% gain of baseline weight) was shown in 47% of patients (114). A study of patients taking gabapentin for 12 months or more showed that of 44 patients, 57% gained more than 5% of their baseline body weight; of these, 10 patients (23%) gained more than 10% of their baseline weight (115). Our commissioned systematic review (3) suggested weight gain with gabapentin (2.2 kg after 1.5 mo of use) and divalproex (relative risk for weight gain, 2.8; 95% CI, 1.30, 6.02). Carbamazepine is an older AED and has also been associated with weight gain, although not as significant as valproic acid or gabapentin (116). A study of 66 patients taking AEDs showed that 66.7% of those on carbamazepine had gained an average of 1.5 kg at a 6- to 8-month follow-up visit (117).

2.7 In women with a BMI > 27 kg/m² with comorbidities or BMI > 30 kg/m² seeking contraception, we suggest oral contraceptives over injectables due to weight gain with injectables, provided that women are well-informed about the risks and benefits (ie, oral contraceptives are not contraindicated). (2|

Evidence

Contraceptive drugs are available in different dosages and formulations and are composed of progestins alone or in combination with estrogens. Some progestins have androgenic/antiandrogenic properties. The research on contraceptives and weight gain is conflicting, and the studies conducted so far are difficult to compare because of the different formulations of contraceptives containing variable doses of estrogens, and with the progestins having different androgenic/antiandrogenic profiles. Moreover, randomized controlled trials comparing hormonal contraceptive methods with a placebo usually raise ethical issues. As recently documented by Gallo et al (118), only four trials included a placebo group or no intervention group, and no evidence has been found to support the association between combination (estrogen plus a progestin) hormonal contraception and weight change. In addition, the same authors, by examining 79 trials of combination contraceptives, concluded that no substantial difference in weight could be found. Moreover, discontinuation of combination contraceptives because of weight change did not differ between groups where this was studied (118).

There is limited evidence of weight gain when using progestin-only contraceptives. Mean gain was less than 2 kg for most studies up to 12 months (119). However, it should be noted that most of the trials were conducted in normal-weight women and excluded obese subjects.

Remarks

Selected studies have reported an increase in contraceptive failure in women with a BMI > 27 kg/m². Data on this issue are conflicting but should be discussed with the appropriate patients on an individual basis.

2.8 We suggest monitoring the weight and waist circumference of patients on antiretroviral therapy due to unavoidable weight gain, weight redistribution, and associated cardiovascular risk. (2|

Evidence

Treatments for human immunodeficiency disease include administration of antiretroviral therapy and protease inhibitors. Although effective for suppressing HIV viral activity, which should be associated with appropriate weight gain, such treatments are associated with increased deposition of visceral adipose tissue (120) and lipodystrophy (121). One study of 10 HIV patients treated with protease inhibitor-containing regimens found that patients gained an average of 8.6 kg (P = .006) after 6 months (120).
Evidence

When possible, chronic steroid therapy should be avoided in the treatment of chronic inflammatory disease to avoid weight gain in individuals who are overweight or obese. Weight gain and its effects on comorbidities should be considered among the commonly known side effects of glucocorticoid therapy. This is particularly important in rheumatic diseases because, for example, obesity in the setting of osteoarthritis leads to more severe disability and reduced exercise capacity, ambulatory capacity, and quality of life (122). A systematic review reported that, based on data from four RCTs in rheumatoid arthritis, glucocorticoids cause a weight increase of 4 to 8% (123, 124). An additional study showed that, when compared with sulfasalazine, glucocorticoid therapy was associated with a 1.7-kg weight gain after 1 year of treatment (125, 126), and another showed a 2.0-kg weight gain after 24 weeks in patients taking prednisone (127).

2.10 We suggest the use of antihistamines with less central nervous system activity (less sedation) to limit weight gain. (2)|

Evidence

Research is inconclusive regarding differences in the weight gain potential of sedating vs nonsedating antihistamines because weight has rarely been an outcome in studies of antihistamines, but it appears that the more potent the antihistamine, the greater the potential for weight gain (128). A recent study demonstrated that the odds ratio for being overweight was increased in prescription H1 antihistamine users (129). Furthermore, a study using data from the 2005–2006 National Health and Nutrition Examination Survey found that prescription H1 antihistamine users had a significantly higher weight, waist circumference, and insulin concentration than matched controls (129).

3.0 Off-label use of drugs approved for other indications for chronic obesity management

3.1 We suggest against the off-label use of medications approved for other disease states for the sole purpose of producing weight loss. A trial of such therapy can be attempted in the context of research and by healthcare providers with expertise in weight management dealing with a well-informed patient. (Ungraded Best Practice Recommendation)

Evidence

A variety of drug classes approved for other uses have been utilized off-label by some prescribers to promote weight loss in patients who are obese. Categories of drugs used may include the antiseizure medication topiramate as well as zonisamide, metformin, GLP-1 agonists such as exenatide and liraglutide, the antidepressant bupropion, as well as drugs for attention deficit hyperactivity disorder such as methylphenidate, and thyroid hormones. Combination treatments of these drugs also represent off-label use, although they have been utilized by some practitioners. Physicians without expertise in weight management or endocrinology are advised against prescribing off-label medications.

If a provider chooses to prescribe a medication for weight loss that is not FDA approved for this indication or is not approved for chronic administration, at minimum they should advise patients that this approach has not been evaluated for safety and efficacy and is not approved by the FDA. This discussion as well as details of the risks and benefits of the treatment approach that were presented to the patient should be documented in the medical record. The provider should discuss medications that are FDA approved for weight loss with the patient and document why an off-label medication was chosen over one of these. Practices such as selling weight loss medications out of the office should be avoided because they could be interpreted as representing a conflict of interest for the provider.

Long-term prescribing of phentermine

Although phentermine is FDA approved for weight loss, it is not approved for long-term use. This presents a conundrum for clinicians because it is clear that weight regain will likely occur once the medication is stopped. One approach that has been tried to avoid this situation is intermittent therapy (130). Although this approach appears to work and might be appropriate when a patient is intermittently exposed to environmental factors that promote weight gain, it is not a logical way to prescribe given what is understood about the effects of weight loss medications on weight regulation. The question then is whether or not it is reasonable to prescribe phentermine off-label long term. In making this decision with a patient, direction and guidance provided by State Medical Boards and local laws always take precedence. However, in the many locations where these sources have not provided clear advice, clinicians are left to make their own best professional judgments.

Phentermine is currently the most widely prescribed weight loss medication, and it is likely that much of this prescribing is off label. This is likely a reflection of the low cost of phentermine as compared to other weight loss medications. There currently are no long-term data on safety or efficacy, although recent data on 269 patients treated long term with phentermine suggest that the addiction potential is low (131). In addition, recent data on single and combination agents for weight loss document phen-
termine 15 mg alone as able to induce over 7% weight loss at 6 months (26). There currently is minimal evidence of any serious long-term side effects when phentermine is used alone for weight loss. Given the wide clinical prescribing of phentermine for more than 20 years and the lack of evidence of serious side effects, even in the absence of long-term controlled safety and efficacy data, it seems reasonable for clinicians to prescribe phentermine long term as long as the patient: 1) has no evidence of serious cardiovascular disease; 2) does not have serious psychiatric disease or a history of substance abuse; 3) has been informed about weight loss medications that are FDA approved for long-term use and told that these have been documented to be safe and effective whereas phentermine has not; 4) does not demonstrate a clinically significant increase in pulse or BP when taking phentermine; and 5) demonstrates a significant weight loss while using the medication. These aspects of care should be documented in the patient’s medical record, and the off-label nature of the prescribing should be documented at each visit. Medication should be started at 7.5 or 15 mg/d initially and only increased if the patient is not achieving clinically significant weight loss. Patients should be followed at least monthly during dose escalation and then at least every 3 months when on a stable dose.

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Addiction potential of phentermine prescribed during long-term treatment of obesity

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**Abstract**

**Objective:**
To investigate if phentermine treatment induces phentermine abuse, psychological dependence (addiction) or phentermine drug craving in overweight, obese and weight loss maintenance patients. To investigate whether amphetamine-like withdrawal occurs after abrupt cessation of long-term phentermine treatment.

**Design:**
Clinical intervention trial with interruption of phentermine treatment in long-term patients.

**Subjects:**
269 obese, overweight or formerly obese subjects (age: 20–88 years, BMI: 21–74 kg m⁻²) treated with phentermine long-term (LTP, N=117), 1.1–21.1 years, or short-term (ATP, N=152), 4–22 days, with phentermine doses of 18.75–112.5 (LTP) and 15–93.75 (ATP) mg per day.
Measurements:
Module K of the Mini International Neuropsychiatric Interview modified for phentermine (MINI-SUD), Severity of Dependence Scale (SDS), 45-item Cocaine Craving Questionnaire-NOW (CCQ-NOW) modified for phentermine (PCQ-NOW), and Amphetamine Withdrawal Questionnaire (AWQ) modified for phentermine (PWQ).

Results:
MINI-SUD interviews were negative for phentermine abuse or psychological dependence in all LTP patients. SDS examination scores were low for all LTP and ATP patients, indicating they were not psychologically dependent upon phentermine. PCQ-NOW scores were low for all LTP and ATP patients, indicating neither short-term nor long-term phentermine treatment had induced phentermine craving. Other than an increase in hunger or eating, amphetamine-like withdrawal symptoms did not occur upon abrupt phentermine cessation as measured by sequential PWQ scores.

Conclusions:
Phentermine abuse or psychological dependence (addiction) does not occur in patients treated with phentermine for obesity. Phentermine treatment does not induce phentermine drug craving, a hallmark sign of addiction. Amphetamine-like withdrawal does not occur upon abrupt treatment cessation even at doses much higher than commonly recommended and after treatment durations of up to 21 years.
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Competing interests
Dr Hendricks has received honoraria from Akramax Pharmaceuticals, Eurodrug Laboratories, Citius Pharmaceuticals and Vivus pharmaceuticals. Dr Greenway has received honoraria from Baronova, Basic Research, Citius, Diabetic Living, Eisai, GNC, Jenny Craig, Lithera, Merck, Naturalpha, Nume Health, Orexigen, Plensat, Takeda, Thetis, Unigene and Zafgen. The remaining authors declare no conflict of interest.

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Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort


Objective: The aim of this work was to study weight loss and risk of cardiovascular disease (CVD) or death associated with longer-term phentermine use.

Methods: Using electronic health record data, 13,972 adults were identified with a first phentermine fill in 2010 to 2015, creating exposure categories according to a patient’s duration of use (referent: ≤ 3 months). Multivariable linear models were used to compare percent weight loss across categories at 6, 12, and 24 months, and Cox proportional hazards models were used to compare risk of composite CVD or death, up to 3 years after starting phentermine.

Results: The cohort was 84% female and 45% white, with a mean (SD) baseline age 43.5 (10.7) years and BMI of 37.8 (7.2) kg/m². In multivariable models, longer-term users of phentermine experienced more weight loss; patients using continuously for >12 months lost 7.4% more than the referent group at 24 months (P < 0.001). The composite CVD or death outcome was rare (0.3%, 41 events), with no significant difference in hazard ratios between groups.

Conclusions: Greater weight loss without increased risk of incident CVD or death was observed in patients using phentermine monotherapy for longer than 3 months. Despite the limitations of the observational design, this study supports the effectiveness and safety of longer-term phentermine use for low-risk individuals.


Introduction

Lifestyle interventions remain the cornerstone of treatment for patients with obesity, typically yielding a peak weight loss of 5% to 10% after 6 months (1). However, up to one-third of patients do not respond to such programs (2,3), and weight regain is common following intervention cessation (4,5). Pharmacotherapy can increase the proportion of individuals who respond to lifestyle interventions as well as the duration and magnitude of response (6). Clinically significant durable weight loss has been demonstrated in placebo-controlled trials of antiobesity medications (7-14), but broader use of medications remains limited because of concerns about cost, efficacy, and adverse events (15).

The most commonly used weight-loss medication in the United States is phentermine (16,17), a sympathomimetic amine that acts by inhibiting appetite and that was originally approved for weight loss in 1959 (18,19). Most studies examining phentermine monotherapy have limited treatment duration to less than 12 weeks (20), aligning with a package insert that recommends that the medication be used as “a short-term adjunct (a few weeks)” to lifestyle-based programs (21). Concerns about longer-term phentermine use include increased risk...
of cardiovascular disease (CVD) (6,17) and potential for addiction (22).

Weight-loss treatment approaches are evolving to favor long-term therapy, aligning with the new chronic disease model of obesity. Newer antiobesity medications have, accordingly, been approved by the Food and Drug Administration (FDA) for long-term use (i.e., more than 12 months) (20). If phentermine monotherapy, which is widely available and low cost, was found to be safe and effective for long-term use, the impact for obesity treatment could be significant.

Using data from electronic health records (EHRs), we studied whether adults prescribed phentermine for longer than 12 weeks experienced differential weight loss, change in blood pressure (BP) or heart rate (HR), or increased risk of incident CVD or death compared with adults prescribed phentermine in an on-label short-term episode. Our primary hypothesis was that longer-term users would experience greater weight loss without increased risk of CVD or death.

Methods
Study design, health care systems, and data sources

The data sources for this retrospective cohort study were EHRs abstracted from the Patient Outcomes Research to Advance Learning (PORTAL) cohort, a collaborative data effort across several integrated health insurance and care-delivery systems in the United States as part of the National Patient-Centered Clinical Research Network (PCORnet) initiative (23,24). Data elements included membership status, demographics, vital signs, health care use, laboratory values, and pharmacy dispensing. This cohort included data from Kaiser Permanente (Southern California, Colorado, Northwest, Washington state, Hawaii, and Mid-Atlantic States [Maryland, Virginia, District of Columbia]) and from Denver Health and HealthPartners (Minnesota). The study was approved by the Kaiser Permanente Southern California Institutional Review Board, with other sites ceding primary review.

Study population

We identified adult health plan members 18 to 64 years old with a “first” phentermine fill (dose ≤ 37.5 mg/d) between January 1, 2010, and September 30, 2015. To find likely incident users, we limited selection to patients with at least 12 months of continuous baseline enrollment, during which there were no prior phentermine prescriptions (25). We chose the study end date to coincide with the International Classification of Diseases, Ninth Revision to Tenth Revision transition, after which changes in diagnosis coding could have led to systematic differences in detection of outcomes and covariates.

We required patients to have BMI ≥ 27 kg/m² within 3 months prior to their first phentermine fill. We excluded those with history of bariatric surgery or cancer diagnosis (other than nonmelanoma skin cancer). We also excluded anyone with baseline year evidence of pregnancy, use of other weight-loss medications, palliative care encounters, or diagnosis and/or procedure codes for any cardiovascular outcomes of interest, including myocardial infarction, stroke, angina, coronary artery bypass grafting, or carotid artery procedures (Figure 1). Weight, BP, and HR analyses were limited to individuals with at least one relevant measurement before and after initiating phentermine.

Exposure

Our exposure of interest was a patient’s pattern of phentermine use in follow-up, characterized based on duration and persistence of use. For each individual, we first created episodes of phentermine use and mapped them across follow-up time (26-28). See Supporting Information Figure S1 for details on how episodes were created.

Individuals with one phentermine treatment episode lasting ≤ 112 days and no subsequent use during follow-up were treated as our referent or “short-term” use group, reflecting FDA-approved use of the medication. This episode duration (≤ 112 days) was based on multiplying the on-label duration of 90 days by a factor of 1.25 to account for days in the episode when a patient was between fills (28). Patients with a single phentermine treatment episode lasting > 112 and up to 365 days, but with no subsequent treatment episodes, were labeled “medium-term continuous” users. Patients with a single continuous episode lasting > 365 days were labeled “long-term continuous” users.

In clinical practice, patients often take phentermine intermittently over time. To separately capture these individuals and allow for follow-up beyond the first treatment episode, we created two additional groups. Persons with two or more separate treatment episodes in which no episode exceeded 112 days were termed “short-term intermittent” users. Those with two or more episodes in which at least one episode exceeded 112 days were termed “medium-term intermittent” users.

We treated phentermine use as a time-varying exposure. A patient’s inclusion in a particular exposure category was dependent on his or her exposure pattern up to the time point of interest, meaning that patients could change exposure categories over time. For example, at the 6-month mark, we could not yet classify anyone as being in the long-term continuous group because less than a year of phentermine exposure had elapsed. Therefore, these individuals were included in our medium-term continuous group for 6-month analyses, only separating out as a distinct group after 12 months of continuous exposure to phentermine.

Outcomes

Our outcome for drug effectiveness was percent change in weight from baseline, measured at 6, 12, and 24 months after initial phentermine dispensing. We abstracted all weights recorded in the outpatient setting. We selected baseline weight (kilograms) as the nearest measure on or within 90 days prior to the index date. Because we were working with clinical data, follow-up did not occur precisely at 6, 12, or 24 months for most individuals. We accepted weights for each follow-up point based on a variable window that enlarged as follow-up time progressed. For our 6-month outcome, we accepted the nearest weight measure within − 30 to + 90 days; at 12 months, we accepted the nearest weight measure within − 90 to + 90 days; and at 24 months, we accepted the nearest weight measure within − 180 to + 180 days.

We examined changes in systolic BP (SBP), diastolic BP (DBP) (mmHg), and HR (beats per minute [bpm]) from baseline as intermediate outcomes for cardiovascular risk because of the sympathomimetic effect of phentermine. We derived change in HR, SBP, and DBP from outpatient measures, selecting the nearest measure per window per patient for analysis. Additional rules used for cleaning vital sign data are available in Supporting Information Table S1.

Our distal outcome measure for cardiovascular risk was a composite measure of incident myocardial infarction, stroke, angina, coronary artery...
bypass grafting, carotid artery intervention, or death. We abstracted all relevant International Classification of Diseases, Ninth Revision diagnosis or procedure and Current Procedural Terminology procedure codes (Supporting Information Table S2) and used a previously published method to assign incident events (29). Information about date of death came from a combination of EHR, administrative, and state mortality databases (30).

Covariates
All models included EHR-derived covariates for sex, race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other), age group (18-34, 35-49, 50-64), baseline BMI category (27-29.9, 30-34.9, 35-39.9, 40-49.9, or ≥ 50), hypertension, diabetes, smoking status, health care system, calendar year of phentermine initiation, and average daily dose category of phentermine (37.5 mg/d or < 37.5 mg/d). BP and HR models were adjusted for baseline tertile of each measure.

We used demographic information from geographic information systems to create a covariate for area-level measure of poverty (percent of households in census block below poverty level: <5%, 5% to <10%, 10% to <20% or ≥20%) (31). We assigned the rare patients missing phentermine dose (n = 39) or poverty (n = 538) the modal values for their region.

Statistical analysis
We built separate multivariable linear models at 6, 12, and 24 months of follow-up to examine the outcomes of percent change in weight and change in SBP, DBP, and HR. In weight analyses, we limited inclusion in the referent group to patients with at least one refill because patients with a single fill were likely intolerant to phentermine. Their inclusion would have biased weight loss results in favor of longer-term users.

We used Cox proportional hazards models with phentermine treated as a time-varying covariate to examine the composite outcome of incident CVD or death in a time-to-event fashion up to 3 years after the index date. Patients achieving any one of the submeasures composing our composite outcome were considered to have the outcome at that time.

Patients were not included in multivariable linear models if any of the following occurred before a time point of interest: health insurance plan disenrollment, >18 months since any clinical care or encounters...
TABLE 1 Characteristics of phentermine users according to final exposure categorization

<table>
<thead>
<tr>
<th></th>
<th>On-label users</th>
<th>Off-label users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-term referent</td>
<td>Short-term intermittent</td>
</tr>
<tr>
<td></td>
<td>(n = 6,764)</td>
<td>(n = 2,938)</td>
</tr>
<tr>
<td>Sexb</td>
<td>Female</td>
<td>5,611 (83.1%)</td>
</tr>
<tr>
<td>Race/ethnicityc</td>
<td>Non-Hispanic white</td>
<td>3,007 (44.5%)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic black</td>
<td>1,370 (20.3%)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>1,749 (25.9%)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>305 (4.5%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>324 (4.8%)</td>
</tr>
<tr>
<td>Age (y)c</td>
<td>43.7 (10.9)</td>
<td>42.3 (10.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)c</td>
<td>Mean (SD)</td>
<td>38.0 (7.5)</td>
</tr>
<tr>
<td></td>
<td>27-29.9</td>
<td>687 (10.2%)</td>
</tr>
<tr>
<td></td>
<td>30-34.9</td>
<td>1,977 (29.3%)</td>
</tr>
<tr>
<td></td>
<td>35-39.9</td>
<td>1,890 (28.0%)</td>
</tr>
<tr>
<td></td>
<td>40-49.9</td>
<td>1,733 (25.7%)</td>
</tr>
<tr>
<td></td>
<td>≥50.0</td>
<td>468 (6.9%)</td>
</tr>
<tr>
<td>Hypertension diagnosisd</td>
<td>1,443 (21.4%)</td>
<td>578 (19.6%)</td>
</tr>
<tr>
<td>Diabetes diagnosisd</td>
<td>824 (12.2%)</td>
<td>299 (10.2%)</td>
</tr>
<tr>
<td>Smoking statusc,e</td>
<td>Never users</td>
<td>4,211 (62.3%)</td>
</tr>
<tr>
<td></td>
<td>Ever users</td>
<td>2,298 (34%)</td>
</tr>
<tr>
<td></td>
<td>Missing/unknown</td>
<td>246 (3.6%)</td>
</tr>
<tr>
<td>Area families below poverty levelf</td>
<td>Missing</td>
<td>234 (3.5%)</td>
</tr>
<tr>
<td></td>
<td>&lt;5%</td>
<td>1,568 (23.2%)</td>
</tr>
<tr>
<td></td>
<td>5-&lt;10%</td>
<td>1,779 (26.3%)</td>
</tr>
<tr>
<td></td>
<td>10-&lt;20%</td>
<td>1,812 (26.8%)</td>
</tr>
<tr>
<td></td>
<td>≥20%</td>
<td>1,362 (20.2%)</td>
</tr>
<tr>
<td>Follow-up duration (y)c</td>
<td>1.6 (1.1)</td>
<td>2.2 (0.9)</td>
</tr>
<tr>
<td>Median percent of follow-up on phentermine</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>Daily phentermine dosec</td>
<td>&lt;37.5 mg</td>
<td>3,688 (54.6%)</td>
</tr>
<tr>
<td></td>
<td>37.5 mg</td>
<td>3,053 (45.2%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>14 (0.2%)</td>
</tr>
</tbody>
</table>

Data given as n (%) for categorical variables and mean (SD) for continuous variables.

aOn-label short-term users (referent) had a single phentermine use episode ≤ 112 days. Short-term intermittent users rotated on and off phentermine but never remained on the drug for longer than 112 days. Off-label user groups defined as follows: medium-term continuous users had a single phentermine treatment episode lasting >112 but ≤365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days. Note that “n” in each column corresponds to final exposure assignment at end of follow-up. Because of the time-varying nature of the exposure, relative size of groups and distribution of characteristics may differ between time points in early follow-up (e.g., at 6 and 12 months).

bIntended for descriptive purposes and not intended to represent interpretation of exposure.

cTobacco “ever users” includes current and historical smokers.

dTobacco use was defined as history of tobacco use, defined as one or two tobacco use event(s) in the month prior to index phentermine prescription.

eRacial and ethnic groups go from highest to lowest SES vertically.

Data is given as n (%) for categorical variables and mean (SD) for continuous variables. 

Revision codes in year prior to index phentermine prescription. 

p < 0.001 for difference across groups using χ² test for categorical and Kruskal-Wallis test for continuous variables.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter estimate (95% CI)</td>
<td>n (% of enrolled with weight data available)</td>
<td>Parameter estimate (95% CI)</td>
</tr>
<tr>
<td>Intercept</td>
<td>−2.68 (−3.28 to −2.08)</td>
<td>n/a</td>
<td>−1.38 (−2.08 to −0.67)</td>
</tr>
<tr>
<td>Short-term continuous</td>
<td>−5.07 (−5.40 to −4.73)</td>
<td>2,352 (74%)</td>
<td>−4.66 (−5.13 to −4.19)</td>
</tr>
<tr>
<td>Medium-term intermittent</td>
<td>−4.22 (−5.11 to −3.33)</td>
<td>179 (78%)</td>
<td>−5.63 (−6.13 to −5.13)</td>
</tr>
<tr>
<td>Long-term continuous</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*aSeparate models built for each time point, all adjusted for gender, race and ethnicity, smoking, diabetes, hypertension, baseline BMI, average medication strength, year of original prescription, and site.

*b n (%) by exposure category within each time point references those with a weight measure versus total number assigned to that exposure category at that time point.

*c Short-term users (referent) had a single phentermine use episode ≤112 days; short-term intermittent users rotated on and off phentermine but never remained on the drug for longer than 112 days. Off-label user groups were defined as follows: medium-term continuous users had a single phentermine treatment episode lasting >112 but ≤365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days.

*dParameter estimates for intercept approximate percent weight loss of referent group when all covariates are set to their referent value, and parameter estimates for comparison groups should be interpreted as difference in percent weight loss compared with referent group.

*eP < 0.0001 for comparing intercept to zero.

*f P < 0.0001 for comparing intercept to zero.

*g P < 0.0001 for comparing percent weight loss in comparison groups to referent group.

*n/a, not applicable.
in their health system, incident pregnancies, bariatric procedures, prescription of any weight-loss medication besides phentermine, prescription for phentermine > 37.5 mg/d, CVD outcome (e.g., myocardial infarction), or death. Patients were censored at these times in the Cox model.

Sensitivity analyses
Unmeasured patient characteristics or differential response to phentermine could predict greater medication persistence and more weight loss. Therefore, we conducted two sensitivity analyses to assess whether patients who used phentermine for longer did so because the medication was working better for them. In the first sensitivity analysis, we treated phentermine use over follow-up as a fixed exposure, allowing patients to populate their final exposure categories artificially early. We then conducted weight-loss analysis using these fixed exposure categories, beginning at 3 months, when phentermine duration should have been relatively equal between categories.

Second, we conducted a separate “responders-only” sensitivity analysis. In this analysis, we limited inclusion in the cohort to patients who achieved ≥3% weight loss by 3 months. Our goal with this analysis was to reduce the potential impact of phentermine nonresponders on lower weight loss in the referent group. The responder analysis was also conducted in two ways, treating phentermine as both time varying and fixed.

To test the sensitivity of our weight findings to varying acceptable time windows for follow-up measures, we reran models using acceptable windows of −/+/90 days, +90 days, −/+/60 days, +60 days, −30/+90 days, and −30/+60 days at each time point (6, 12, and 24 months).

To examine whether a higher-risk subgroup of patients might be more likely to experience adverse effects, we repeated HR and BP analyses on the subset of individuals with baseline hypertension diagnoses.

Results
Study population
We identified 13,972 incident phentermine users (Figure 1). Most were women (84%), and the mean (SD) baseline age was 43.5 (10.7) years; just under half (45%) were non-Hispanic white (Table 1). Baseline BMI was 37.8 (7.2) kg/m², 21% carried a diagnosis of hypertension at baseline, and 12% had a diagnosis of diabetes. Phentermine use groups differed by baseline characteristics, with on-label users slightly more likely to be minorities, younger, not diabetic, and never smokers compared with off-label groups. Off-label groups included a higher proportion of patients taking a lower daily dose of phentermine.

Weight loss
At 6, 12, and 24 months after phentermine initiation, weight loss was greater among off-label and intermittent short-term users than our referent short-term single episode users (Table 2). The mean weight change for short-term single episode (referent) phentermine use can be approximated by examining the intercept values for models at each time point (Table 2, Figure 2). By 6 months after drug initiation (or ~3 months after discontinuing phentermine), short-term users averaged 2.7% (95% CI: 2.1%-3.3%) total weight loss. By 12 months, their weight loss was 1.4% (95% CI: 0.7%-2.1%), and by 24 months, the weight change in this group was not different from zero.

The magnitude of difference in weight loss between comparison groups and the referent group varied with duration of follow-up (Table 2, Figure 2). At 6 months, short-term intermittent users lost 1.8% (95% CI: 1.4%-2.1%) additional body weight relative to short-term single episode (referent) users, while medium-term continuous users lost 5.1% (95% CI: 4.7%-5.4%) more. At 12 months, the medium-term intermittent group lost 5.6% (95% CI: 5.1%-6.1%) more weight than short-term single episode users. At 24 months after phentermine initiation,
TABLE 3 Difference in percent weight loss over follow-up: results from multivariable linear models using time-varying exposure among early phentermine responders

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter estimate (95% CI)</td>
<td>n (% of enrolled with weight data available)</td>
<td>Parameter estimate (95% CI)</td>
</tr>
<tr>
<td>Intercept</td>
<td>-6.26 (-7.09 to -5.43)</td>
<td>767 (70%)</td>
<td>-4.07 (-5.20 to -2.94)</td>
</tr>
<tr>
<td>Short-term</td>
<td>Referent</td>
<td>767 (70%)</td>
<td>Referent</td>
</tr>
<tr>
<td>Short-term intermittent</td>
<td>-1.54 (-2.12 to -0.97)</td>
<td>565 (78%)</td>
<td>-1.75 (-2.49 to -1.02)</td>
</tr>
<tr>
<td>Medium-term continuous</td>
<td>-3.35 (-3.82 to -2.88)</td>
<td>1574 (78%)</td>
<td>-3.64 (-4.33 to -2.95)</td>
</tr>
<tr>
<td>Medium-term intermittent</td>
<td>-2.25 (-3.34 to -1.15)</td>
<td>103 (82%)</td>
<td>-4.21 (-4.93 to -3.48)</td>
</tr>
<tr>
<td>Long-term continuous</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

aSeparate models built for each time point, all adjusted for gender, race and ethnicity, smoking, diabetes, hypertension, baseline BMI, average medication strength, year of original prescription, and site. Models include only patients who had documented weight loss of ≥3% by 3 months after starting phentermine.

bPercent (%) by exposure category within each time point references those with a weight measure versus total number assigned to that exposure category at that time point.

Short-term users (referent) had a single phentermine use episode ≤112 days; short-term intermittent users rotated on and off phentermine but never remained on drug for longer than 112 days. Off-label user groups were defined as follows: medium-term continuous users had a single phentermine treatment episode lasting >112 but ≤365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days.

Parameter estimates for intercept approximate percent weight loss of referent group when all covariates are set to their referent value, and parameter estimates for comparison groups should be interpreted as difference in percent weight loss compared with referent group.

P < 0.0001 for comparing intercept to zero.

P < 0.001 for comparing intercept to zero.

P < 0.0001 for comparing percent weight loss in comparison groups with referent group.

n/a, not applicable.
long-term continuous (>12 months) users lost 7.4% (95% CI: 5.8%-9.0%) more weight than short-term single episode users.

When we examined weight change at 3 months using final assigned exposure categories rather than time-varying exposure, individuals in the off-label and intermittent use categories already had greater weight loss than those in the referent group (Supporting Information Table S3). In these models, short-term users had lost 3.5% (95% CI: 3.1%-4.0%) body weight at 3 months, with additional weight loss by group as follows: short-term intermittent, 0.4% (95% CI: 0.1%-0.7%); medium-term continuous, 2.6% (95% CI: 2.3%-2.9%); medium-term intermittent, 3.0% (95% CI: 2.7%-3.3%); and long-term continuous, 3.4% (95% CI: 2.6%-4.3%). Referent and between-group patterns for weight loss at 6, 12, and 24 months (Table 3, Figure 3). Despite selecting for individuals with more initial success, weight loss in our comparison groups was still greater than the referent group at all time points in follow-up. Comparison groups displayed a similar magnitude of difference as observed in our main analysis (Table 3) but with greater overall weight loss for all groups (Figure 3). The sensitivity analysis for responders using end-group assignments and examining early (3 months) weight loss between groups showed slightly greater early weight loss among comparison groups compared with the referent group; however, between-group differences at this early time point were attenuated (Supporting Information Table S4).

Varying the time window for acceptable EHR weight measures did not appreciably change referent or between-group results compared with our main analysis despite a large amount of variability in missingness that occurred as a result of requiring narrower or wider time windows around each point (Supporting Information Table S5). Related to missingness, the reader will note that the number of patients in each exposure category varies over follow-up. In part, this is due to the time-varying nature of our exposure; however, additional reasons for missingness are summarized in Supporting Information Table S6.

Changes in BP and HR
At baseline, mean (SD) HR was 79 (12) bpm, and mean (SD) BP was 122 (12)/74 (9). Patients in the short-term single episode (referent) group had no significant change in HR at 6, 12, or 24 months (Table 4). The greatest relative HR increase among medium-term continuous users was at 6 months and was 1.6 (95% CI: 1.0-2.2) bpm higher than the referent group; among medium-term intermittent users, at 12 months, it was 1.1 (95% CI: 0.3-1.9) bpm higher than the referent group. Comparison group changes in HR did not differ from the referent group at 24 months.

SBP in the referent group was stable at 6 and 12 months, but at 24 months, it had increased by 1.8 (0.5-3.2) mmHg, relative to baseline. There was no between-group difference in SBP change at 6 months; however, the comparison groups on the whole had slightly lower BP than the referent group at 12 and 24 months, again with variability in magnitude of difference by group. For example, at 24 months, patients in the long-term continuous user group experienced SBP Δ~3.3 (−0.8 to −5.9) mmHg relative to the on-label users.

DBP in the referent (short-term) group was stable relative to baseline at 6, 12, and 24 months, and there were no significant between-group differences in DBP over follow-up.
### TABLE 4 Change in heart rate (HR) and blood pressure (BP) over follow-up: results from multivariable linear models using time-varying exposure

#### Heart rate results

<table>
<thead>
<tr>
<th>Time</th>
<th>Parameter estimate ΔHR (bpm) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔHR (bpm) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔHR (bpm) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>Intercept: 1.01 (−0.13 to 2.16)</td>
<td>n/a</td>
<td>0.64 (−0.51 to 1.80)</td>
<td>n/a</td>
<td>0.55 (−0.77 to 1.86)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Short-term: 0.81 (0.08 to 1.53)</td>
<td>4,268 (68%)</td>
<td>0.27 (−0.43 to 0.96)</td>
<td>3,672 (79%)</td>
<td>0.13 (−0.65 to 0.91)</td>
<td>2,534 (91%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term continuous: 1.61 (0.99 to 2.24)</td>
<td>2,363 (75%)</td>
<td>1.16 (0.40 to 1.92)</td>
<td>1,362 (79%)</td>
<td>−0.19 (−1.28 to 0.90)</td>
<td>610 (90%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term intermittent: −0.77 (−2.57 to 1.04)</td>
<td>181 (80%)</td>
<td>1.09 (0.28 to 1.90)</td>
<td>1,184 (88%)</td>
<td>0.67 (−0.14 to 1.49)</td>
<td>1,360 (95%)</td>
</tr>
<tr>
<td></td>
<td>Long-term continuous: n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>2.64 (0.15 to 5.14)</td>
<td>96 (90%)</td>
</tr>
<tr>
<td>12 months</td>
<td>Intercept: −0.99 (−2.13 to 0.14)</td>
<td>n/a</td>
<td>−0.19 (−1.37 to 0.99)</td>
<td>n/a</td>
<td>1.83 (0.48 to 3.19)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Short-term: −0.33 (−1.18 to 0.52)</td>
<td>4,377 (68%)</td>
<td>−0.57 (−1.44 to 0.29)</td>
<td>3,742 (79%)</td>
<td>0 (−0.98 to 0.98)</td>
<td>2,592 (92%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term continuous: −0.78 (−1.49 to −0.06)</td>
<td>1,468 (75%)</td>
<td>−0.41 (−1.11 to 0.30)</td>
<td>1,759 (83%)</td>
<td>0.2 (−0.60 to 1.00)</td>
<td>1,560 (94%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term intermittent: 0.08 (−0.46 to 0.61)</td>
<td>2,402 (76%)</td>
<td>−1.11 (−1.88 to −0.33)</td>
<td>1,395 (80%)</td>
<td>−0.94 (−2.05 to 0.17)</td>
<td>622 (90%)</td>
</tr>
<tr>
<td></td>
<td>Long-term continuous: n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>−0.12 (−0.93 to 0.69)</td>
<td>n/a</td>
</tr>
<tr>
<td>24 months</td>
<td>Intercept: −1.18 (−2.98 to 0.61)</td>
<td>183 (80%)</td>
<td>−0.92 (−1.74 to −0.09)</td>
<td>1,200 (88%)</td>
<td>−0.41 (−1.25 to 0.43)</td>
<td>1,383 (95%)</td>
</tr>
<tr>
<td></td>
<td>Short-term: −0.81 (−2.16 to 0.53)</td>
<td>2,363 (75%)</td>
<td>−0.19 (−0.79 to 0.41)</td>
<td>1,184 (88%)</td>
<td>0.12 (−0.49 to 0.73)</td>
<td>99 (91%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term continuous: n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>−3.31 (−5.85 to −0.76)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Medium-term intermittent: n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>−0.69 (−2.54 to 1.16)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

#### Blood pressure results

<table>
<thead>
<tr>
<th>Time</th>
<th>Parameter estimate ΔSBP (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔSBP (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔSBP (95% CI)</th>
<th>n (%) enrolled with VS data</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>Intercept: −0.99 (−2.13 to 0.14)</td>
<td>n/a</td>
<td>−0.19 (−1.37 to 0.99)</td>
<td>n/a</td>
<td>1.83 (0.48 to 3.19)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Short-term: −0.33 (−1.18 to 0.52)</td>
<td>4,377 (68%)</td>
<td>−0.57 (−1.44 to 0.29)</td>
<td>3,742 (79%)</td>
<td>0 (−0.98 to 0.98)</td>
<td>2,592 (92%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term continuous: −0.78 (−1.49 to −0.06)</td>
<td>1,468 (75%)</td>
<td>−0.41 (−1.11 to 0.30)</td>
<td>1,759 (83%)</td>
<td>0.2 (−0.60 to 1.00)</td>
<td>1,560 (94%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term intermittent: 0.08 (−0.46 to 0.61)</td>
<td>2,402 (76%)</td>
<td>−1.11 (−1.88 to −0.33)</td>
<td>1,395 (80%)</td>
<td>−0.94 (−2.05 to 0.17)</td>
<td>622 (90%)</td>
</tr>
<tr>
<td></td>
<td>Long-term continuous: n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>−0.12 (−0.93 to 0.69)</td>
<td>n/a</td>
</tr>
<tr>
<td>12 months</td>
<td>Intercept: −1.18 (−2.98 to 0.61)</td>
<td>183 (80%)</td>
<td>−0.92 (−1.74 to −0.09)</td>
<td>1,200 (88%)</td>
<td>−0.41 (−1.25 to 0.43)</td>
<td>1,383 (95%)</td>
</tr>
<tr>
<td></td>
<td>Short-term: −0.81 (−2.16 to 0.53)</td>
<td>2,363 (75%)</td>
<td>−0.19 (−0.79 to 0.41)</td>
<td>1,184 (88%)</td>
<td>0.12 (−0.49 to 0.73)</td>
<td>99 (91%)</td>
</tr>
<tr>
<td></td>
<td>Medium-term continuous: n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>−3.31 (−5.85 to −0.76)</td>
<td>n/a</td>
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<tr>
<td></td>
<td>Medium-term intermittent: n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>−0.69 (−2.54 to 1.16)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

---

*a* Separate models built for each time point, all adjusted for gender, race and ethnicity, smoking, diabetes, hypertension, baseline HR or BP tertile, average medication strength, year of original prescription, and site.

*b* n (%) by exposure category within each time point references those with a HR measure versus total number assigned to that exposure category at that time point.

*c* Short-term users (referent) had a single phentermine use episode ≤112 days; short-term intermittent users rotated on and off phentermine but never remained on the drug for longer than 112 days. Off-label user groups were defined as follows: medium-term continuous users had a single phentermine treatment episode lasting >112 but ≤365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days.

*d* Parameter estimates for intercept approximate change from baseline in BP or HR of referent group when all covariates are set to their referent value, and parameter estimates for comparison groups should be interpreted as difference in BP or HR compared with referent group.

*e* P < 0.0001 for comparing HR and BP change in comparison groups with referent group.

*f* P = 0.0001 for comparing HR and BP change in comparison groups with referent group.

*g* P = 0.005 for comparing BP change in comparison groups with referent group.

*h* P = 0.008 for comparing intercept to zero.

*i* P = 0.02 for comparing SBP change in comparison groups with referent group.

*j* P = 0.03 for comparing SBP change in comparison groups with referent group.

VS, vital signs; n/a, not applicable.
Among patients with baseline hypertension, BP increased more over time than in our main cohort (Supporting Information Table S7), but there were no 6- or 12-month differences by phentermine exposure category. By 24 months, SBP in longer-term phentermine use groups for hypertensive patients was lower than among short-term hypertensive users. Between-group comparisons for ∆HR among patients with hypertension were similar to our main analysis.

Incident CVD or death

Up to 3 years after the index date, incidence of composite adverse outcomes was low. Forty-one people out of 13,972 (0.3%) experienced an event (for group-specific event rates, see Supporting Information Table S8). Because there were no qualifying CVD or death events in the long-term continuous user group, these individuals were grouped with the medium-term continuous users for analysis. Multivariable Cox regression models treating phentermine use as a time-varying covariate found no significant difference in risk of incident CVD or death between groups (Table 5).

Discussion

In this large cohort study, a longer duration of phentermine use was associated with clinically significant greater weight loss up to 2 years after initiating medication, with no observed increase in risk for incident cardiovascular events or death over 3 years of follow-up. Discontinuation of phentermine consistently resulted in weight regain.

There are few prior studies examining long-term use of phentermine, particularly as monotherapy for obesity (6,20,22,32). However, in 2012, a new brand-named drug, Phentermine/Topiramate-CR, earned FDA approval for long-term (≥12 months) use as a weight-loss medication. Randomized trial data from patients taking this medication for up to 24 months showed sustained 9% to 11% weight loss without increased cardiovascular risk (33,34). While these findings suggested possible safety and effectiveness of using phentermine monotherapy for longer than 12 weeks, Phentermine/Topiramate-CR has a lower daily phentermine dose than is typical of monotherapy, necessitating additional studies on this topic to inform clinical care.

Experts now recognize obesity as a chronic disease, best treated with comprehensive intensive lifestyle intervention and long-term follow-up, using tools such as pharmacotherapy and bariatric surgery to supplement lifestyle change as needed (35). There is a need for longer-term effective, safe, and affordable pharmacotherapy that can be used as an adjunct to lifestyle change advice. Longer-term use of phentermine in the United States indeed appears to be a pervasive practice (36); 30% of our cohort was made up of individuals with at least one phentermine episode lasting >12 weeks.

Our findings show that patients prescribed phentermine for ≤3 months, as is currently directed by labeling, did not experience durable clinically significant weight loss. In contrast, patients using phentermine off-label for longer periods generally experienced greater weight loss that was sustained so long as they remained on medication. For example, medium-term users (those on phentermine for up to 12 months) averaged significantly greater weight loss than the referent group at 12 months but had regained nearly 70% by 24 months.

Findings from our analysis of phentermine responders, patients with at least 3% weight loss by 3 months after medication initiation, underscore the importance of not continuing to prescribe a medication to patients who do not appear to experience clinical benefit (Figure 2, Figure 3). Patients who responded early across all groups reached clinically significant levels of weight loss (≥5% on average) by 6 months and generally had more durable weight loss. This finding aligns with similar observations from the literature on diet-induced weight loss, in which early response tends to predict greater overall weight-loss success (2,37).

We observed a slight increase in average HR among phentermine users that normalized after discontinuation. This finding is consistent with the drug’s mechanism of action, and the magnitude of increase is similar to prior studies of phentermine-containing medications (33). The relative decrease in SBP associated with longer-term phentermine use, despite the sympathomimetic effect of the drug, may be attributable to greater weight loss, resulting in a net-lowering effect. We observed this relative BP lowering even among patients with baseline hypertension. We cannot exclude the occurrence of rare hypertensive events resulting in emergency department visits because our analyses relied on outpatient information.

Importantly, we did not observe an increase in risk of CVD or death related to the duration of phentermine use up to 3 years after initiating medication. Additional study of these rare outcomes is needed, including research with a larger higher-risk population of long-term users and greater duration of follow-up. Our overall low rate of the composite outcome (0.3% of all patients experienced an event) may be related to the patient population in this study; 85% were women, and we excluded individuals with prevalent CVD. However, our findings are consistent with those from placebo-controlled trials of Phentermine/Topiramate-CR, in which 7 of 2,581 (0.3%) of active drug patients experienced a similar composite outcome (34) and provide some reassurance about the relative safety of phentermine prescribing in low-risk individuals.

Our study has several important limitations. First, we cannot interpret the relationship between duration of phentermine use and percent weight loss as causal. Our referent group likely includes patients who discontinued phentermine because of ineffectiveness, and, conversely,
our comparison groups contained people who remained on medication precisely because it was effective for them. Our sensitivity analyses support this suspicion; differences in weight loss favored longer-term users even at the 3-month mark when phentermine duration was approximately equal between groups. We tried to mitigate this bias by limiting our weight analyses to patients with at least one refill and by conducting a responders-only analysis; however, the possibility for residual confounding and/or reverse causality remains.

Duration of follow-up differed between exposure categories and was systematically greater for longer-term phentermine users. This could have led to an ascertainment bias between categories, but it is not clear in which direction our results would be biased.

We did not address provider- or health-system-level variables, and it is possible that these factors differed systematically between groups in a way that favored longer-term phentermine users. For example, if physicians willing to prescribe phentermine for longer durations are more likely to be obesity specialists (36), or if this pattern of prescribing is more likely to be associated with participation in a comprehensive weight-management program, such differences could confound the relationship between phentermine use duration and weight loss.

Our data should be interpreted with regard to dispensing of phentermine and may not fully indicate whether patients reliably took the medication. Similarly, it is possible that some patients had phentermine or other weight-loss medications filled outside of our systems, going undetected in our data. Although we adjusted for daily dose of phentermine and censored for doses exceeding 37.5 mg/d, we did not specifically study appropriate dosing for longer-term use of this medication. Similarly, we did not examine coadministered medications that could have led to weight loss or gain or changing BP or HR as a side effect (e.g., topiramate, metoprolol). We did censor for incident use of any FDA-approved weight-loss medications in follow-up.

As with any EHR-based study, there was loss to follow-up in our cohort over time, with missingness possibly not at random. We did find that a large portion of the missingness (e.g., 32% at 24 months) was due to patients prescribed phentermine in later years reaching the end of the study period (September 30, 2015), which is unlikely to be a source of bias. On a related note, the number of patients in our “long-term continuous” use group was quite small relative to the other groups; therefore, additional study with a larger group of patients using phentermine for ≥12 months would help to bolster our findings.

Finally, we did not attempt to characterize other possible adverse outcomes of phentermine use such as anxiety, sleep disturbance, or addiction. A clinical trial with regular standardized outcome assessments at predetermined intervals would be important to accurately describe the risk of such events.

Conclusion

Recommendations to limit phentermine use to less than 3 months do not align with current concepts of pharmacological treatment for patients with obesity. Our results show that longer-term phentermine users experienced greater weight loss without apparent increases in cardiovascular risk. Given the chronicity of obesity and the paucity of good long-term treatment options for this condition, these data provide reassurance that longer-term phentermine monotherapy is a reasonable treatment option in low-risk individuals. Still, there is a need for randomized controlled trials to definitively establish the safety and effectiveness of protracted phentermine monotherapy.

Acknowledgments

We thank Dr. Sengwee Toh of the Department of Population Medicine at Harvard Pilgrim Healthcare Institute/Harvard Medical School for providing his input and expertise on pharmacoepidemiologic methods for this paper. Additionally, we thank the analysts in each PORTAL region for their time and effort in extracting the EHR data used in this study.

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References

Longer-Term Phentermine Use Lewis et al.


Long-Term Persistence of Hormonal Adaptations to Weight Loss


BACKGROUND
After weight loss, changes in the circulating levels of several peripheral hormones involved in the homeostatic regulation of body weight occur. Whether these changes are transient or persist over time may be important for an understanding of the reasons behind the high rate of weight regain after diet-induced weight loss.

METHODS
We enrolled 50 overweight or obese patients without diabetes in a 10-week weight-loss program for which a very-low-energy diet was prescribed. At baseline (before weight loss), at 10 weeks (after program completion), and at 62 weeks, we examined circulating levels of leptin, ghrelin, peptide YY, gastric inhibitory polypeptide, glucagon-like peptide 1, amylin, pancreatic polypeptide, cholecystokinin, and insulin and subjective ratings of appetite.

RESULTS
Weight loss (mean [±SE], 13.5±0.5 kg) led to significant reductions in levels of leptin, peptide YY, cholecystokinin, insulin (P<0.001 for all comparisons), and amylin (P=0.002) and to increases in levels of ghrelin (P<0.001), gastric inhibitory polypeptide (P=0.004), and pancreatic polypeptide (P=0.008). There was also a significant increase in subjective appetite (P<0.001). One year after the initial weight loss, there were still significant differences from baseline in the mean levels of leptin (P<0.001), peptide YY (P<0.001), cholecystokinin (P=0.04), insulin (P=0.01), ghrelin (P<0.001), gastric inhibitory polypeptide (P<0.001), and pancreatic polypeptide (P=0.002), as well as hunger (P<0.001).

CONCLUSIONS
One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss do not revert to the levels recorded before weight loss. Long-term strategies to counteract this change may be needed to prevent obesity relapse. (Funded by the National Health and Medical Research Council and others; ClinicalTrials.gov number, NCT00870259.)
Worldwide, there are more than 1.5 billion overweight adults, including 400 million who are obese. Although dietary restriction often results in initial weight loss, the majority of obese dieters fail to maintain their reduced weight. Understanding the barriers to maintenance of weight loss is crucial for the prevention of relapse.

Body weight is centrally regulated, with peripheral hormonal signals released from the gastrointestinal tract, pancreas, and adipose tissue integrated, primarily in the hypothalamus, to regulate food intake and energy expenditure. The number of identified peripheral modulators of appetite is expanding rapidly and includes leptin, ghrelin, cholecystokinin, peptide YY, insulin, pancreatic polypeptide, and glucagon-like peptide 1 (GLP-1).

Caloric restriction results in acute compensatory changes, including profound reductions in energy expenditure and levels of leptin and cholecystokinin and increases in ghrelin and appetite, all of which promote weight regain. It was recently shown that a disproportionate reduction in 24-hour energy expenditure persists in persons who have maintained a reduced body weight for more than 1 year; however, it is not known whether the changes in levels of appetite-regulating hormones that occur during weight reduction are sustained with prolonged maintenance of reduced weight. The present study was designed to address this question, which may be important for understanding the physiological basis of weight regain after weight loss.

**Methods**

**Participants and Study Oversight**

We recruited men and postmenopausal women with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) between 27 and 40 by means of newspaper advertisements. Smokers, persons with clinically significant illness, including diabetes, and those taking medications known to affect body weight were excluded. The study was approved by the Austin Health Human Research Ethics Committee, and all participants provided written informed consent.

**Study Design**

**Weight-Loss Phase**

For 8 weeks, participants were instructed to replace all three of their daily meals with a very-low-energy dietary formulation (Optifast VLCD, Nestlé) and 2 cups of low-starch vegetables, according to the manufacturer’s guidelines, which provided 2.1 to 2.3 MJ (500 to 550 kcal) per day. During weeks 9 and 10, participants who had lost 10% or more of their initial body weight were gradually reintroduced to ordinary foods, and weight was stabilized to avoid the potential confounding effect of active weight loss on hormone profiles. Meal replacements were stopped at the end of week 10.

**Weight-Maintenance Phase**

At the end of week 10, participants received individual counseling and written advice from a dietitian on a dietary intake that would be consistent with their calculated energy expenditure, with the aim of weight maintenance. No specific macronutrient ratios were prescribed, but carbohydrates with a low glycemic index and a reduced intake of fat were recommended. Participants were also encouraged to engage in 30 minutes of moderately intense physical activity on most days of the week. They visited the clinical research unit at Heidelberg Repatriation Hospital every 2 months, and were contacted by telephone between visits for continued dietary counseling.

**Data Collection**

Testing was performed after an overnight fast at baseline (week 0), week 10, and week 62. Participants wore light clothing and were barefoot when anthropometric measurements were made. Bioelectrical impedance was used to measure body weight and composition, with the use of a body-composition analyzer (TBF-300, Tanita). At each of these visits, the first measurement was made while the patient was fasting (baseline). A standardized breakfast was then provided, which consisted of a boiled egg, toast, margarine, orange juice, cereal biscuits (Weet-Bix, Sanitarium), and whole milk. This meal contained 2.3 MJ (550 kcal), with approximately 51% of the energy from carbohydrate, 33% from fat, and 16% from protein. Blood samples were collected 30, 60, 120, 180, and 240 minutes after the meal. Self-reported ratings of appetite were also recorded at these times with the use of a validated 100-mm visual-analogue scale.

**Biochemical Assays**

Fasting and postprandial plasma levels of acylated ghrelin, active GLP-1, total gastric inhibitory polypeptide, pancreatic polypeptide, amylin, and peptide YY were measured in the same assay with the...
use of the human gut hormone panel (LINCOplex Kit, Millipore). Plasma levels of insulin, leptin, and cholecystokinin were measured with the use of a radioimmunoassay. (Additional details on the assays are available in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

**STATISTICAL ANALYSIS**

Two analyses were conducted. In the intention-to-treat analysis, measures that were missing for participants who discontinued the study were replaced with baseline measures. In the second analysis, the only data included were from participants who completed the study (through the 12-month follow-up period). Since our aim was to examine the nature and duration of the physiological changes that occur as a result of diet-induced weight loss, only the data from participants who completed the study are provided for measures of biochemical values and appetite.

Continuous measures were compared with the use of nonparametric tests (the Wilcoxon signed-rank test for pairwise comparison of changes in measurements between study visits, and the Wilcoxon rank-sum test for comparisons between two independent groups). However for the sake of simplicity, descriptive statistics are reported as means ±SE unless stated otherwise. Exact P values for Wilcoxon tests were computed with the shift algorithm, which also corrected for ties. Comparisons of independent proportions were calculated with Fisher’s exact test. Spearman’s rank correlations and associated P values were computed with algorithm AS 89.18

Analyses of fasting and 4-hour postprandial hormone profiles and ratings on the visual-analogue scale were carried out by fitting linear mixed-effect models to the data. The linear mixed-effect model, a repeated-measures analysis, included fasting and postprandial measurements and both fixed effects (postprandial time, week, and interaction) and random effects (participant characteristics). Linear mixed-effect estimation was carried out with the use of restricted maximum-likelihood methods, and the overall significance of each fixed effect was assessed by means of Wald tests. When no significant interaction could be detected between postprandial time and week (indicating similar postprandial changes relative to fasting values at different weeks), the model was refitted without interaction, and Tukey’s test was used for multiple comparisons of means.

When interaction was present (suggesting an alteration in the postprandial hormone profile after weight loss), significant differences in linear mixed-effect coefficients at weeks 10 and 62, as compared with those at week 0, were reported for individual postprandial time points, and the linear mixed-effect model was restricted to weeks 10 and 62, for a more direct comparison between these weeks. The analysis of gastrointestinal hormones excluded one participant whose biochemical values were more than 5 SD beyond the mean. At baseline, measures of fasting biochemical data were missing for one participant. Less than 2% of the remaining data were missing. Linear mixed-effect analyses were applied to the raw data with no imputation of missing values. To ensure insensitivity of the results to missing data, analyses were repeated after imputation (see the Supplementary Appendix).

**RESULTS**

**STUDY PARTICIPANTS**

Among the 50 participants who began the study, 4 withdrew during the first 8 weeks, while they were on the very-low-energy diet. An additional 7 participants did not lose the required 10% of body weight. During the 12-month follow-up period, 5 participants withdrew. Baseline characteristics of all participants who commenced the study and of those who completed it are shown in Table 1. There were no significant differences in any baseline measurements between those who did and those who did not complete the study, but there was a trend toward a younger age among participants who did not complete the study.

**BODY MEASUREMENTS**

Changes in body weight (Fig. 1) were significant in both the intention-to-treat analysis and the analysis that included only those participants who completed the study. Although male participants were significantly heavier than female participants throughout the study period (mean [±SD] baseline weight, 105.9±12.6 kg vs. 90.5±11.0 kg; P<0.001), the pattern of weight change was similar for men and women; consequently, the data were combined for the purposes of analysis.

Changes in anthropometric measurements for the participants who completed the study are shown in Table 2. The mean weight loss at the end of week 10 was 13.5±0.5 kg (14.0% of initial weight). All anthropometric measurements de-
creased significantly between weeks 0 and 10 and remained significantly below baseline values at week 62. Only data from the 34 patients who completed the study are included in the analyses that follow.

**Hormonal Regulators of Appetite**

**Leptin**

During the weight-loss period, mean fasting plasma levels of leptin decreased by 64.5±3.4% (P<0.001). Levels rose between weeks 10 and 62, but at week 62, they remained 35.5±4.7% below baseline levels (P<0.001). Reductions in leptin levels from baseline at weeks 10 and 62 remained significant when adjusted for fat mass, and the ratio of leptin to fat mass was significantly lower at week 10 than at week 62 (Table 1 in the Supplementary Appendix). Percentage reductions in leptin and weight correlated strongly at week 10 (r = 0.78, P<0.001) and week 62 (r = 0.78, P<0.001). There was a strong linear relationship between the log-transformed percentage of leptin regained and weight regained, indicating that leptin levels and body weight rose concurrently.

**Gastrointestinal Hormones**

Mean fasting and postprandial levels of ghrelin, peptide YY, amylin, and cholecystokinin are shown in Figure 2. (Fig. 1 in the Supplementary Appendix provides these data for the remaining hormones studied, and Table 1 in the Supplementary Appendix provides information on the area under the curve and the median percentage changes in biochemical values from baseline.) The linear mixed-effect analysis of hormone levels according to postprandial period and study week revealed that postprandial changes were highly significant for each hormone studied (P<0.001 for all comparisons). The interaction between the postprandial period and study week was not significant for ghrelin, peptide YY, GLP-1, cholecystokinin, or pancreatic polypeptide, suggesting that there were similar patterns of postprandial hormone suppression or secretion at baseline and at weeks 10 and 62. For each of these hormones, however, each week was highly significant (P ≤ 0.001 for ghrelin, peptide YY, pancreatic polypeptide, and cholecystokinin; P = 0.008 for GLP-1), indicating differences in absolute hormone levels at each study week.

Mean levels of ghrelin rose significantly with weight loss (P<0.001 for the change from baseline to week 10). Although ghrelin levels fell between week 10 and week 62 (P<0.001), the mean level remained significantly higher at 62 weeks than at baseline (P<0.001). For peptide YY, mean levels were significantly lower at weeks 10 and 62 than at baseline (P<0.001 for both comparisons), with levels that were significantly lower at week 62 than those at week 10 (P=0.004). For amylin, the interaction between postprandial period and study week was close to being significant (P=0.05). Fast-
ing levels of amylin declined significantly with weight loss ($P=0.008$ for the change from baseline to week 10; $P=0.05$ for the change from baseline to week 62). The reduction from baseline in amylin secretion within the first 30 minutes after eating was significant at week 10 ($P=0.002$) and approached significance at week 62 ($P=0.08$). The mean level of cholecystokinin was significantly lower at weeks 10 and 62 than at baseline ($P<0.001$ and $P=0.04$, respectively), with no significant difference in levels between weeks 10 and 62.

For gastric inhibitory polypeptide, the interaction between postprandial period and study week was significant ($P=0.02$), owing to the greater secretion of this hormone in the first 60 minutes after meals at weeks 10 and 62 than at baseline ($P=0.004$ and $P<0.001$, respectively). Mean levels of gastric inhibitory polypeptide did not differ significantly between weeks 10 and 62. Mean levels of GLP-1 did not change significantly between baseline and week 10; the levels at week 62 were slightly but significantly lower than baseline levels ($P=0.005$).

Decreases in insulin levels after weight loss were evident, and the interaction between postprandial period and study week was significant ($P<0.001$), with significant reductions in meal-stimulated insulin release 30 and 60 minutes after eating, both from baseline to week 10 ($P<0.001$ for the two postprandial comparisons) and from baseline to week 62 ($P<0.001$ for the comparison at 30 minutes; $P=0.01$ for the comparison at 60 minutes). Mean levels of pancreatic polypeptide were significantly higher at week 10 and week 62 than at baseline ($P=0.008$ and $P<0.002$, respectively), with no significant difference between levels at weeks 10 and 62.

### APPETITE

Figure 3 shows mean ratings, on a visual-analogue scale, of fasting and postprandial hunger and desire to eat at baseline and at weeks 10 and 62. (Additional ratings are available in Fig. 2 and Table 2 in the Supplementary Appendix.) The linear mixed-effect analysis revealed that mean ratings of hunger, desire, and urge to eat, and prospective consumption were significantly higher at weeks 10 and 62.

### APPETITE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline to Wk 10 P Value</th>
<th>Wk 10 to Wk 62 P Value</th>
<th>Baseline to Wk 62 P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>$-13.5\pm0.5$ &lt;0.001</td>
<td>$5.5\pm1.0$ &lt;0.001</td>
<td>$-7.9\pm1.1$ &lt;0.001</td>
</tr>
<tr>
<td>Percent change in weight</td>
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<td>$-8.2\pm1.1$ &lt;0.001</td>
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<td>BMI</td>
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<td>$2.0\pm0.3$ &lt;0.001</td>
<td>$-2.8\pm0.4$ &lt;0.001</td>
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<td>Waist circumference (cm)</td>
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<td>$4.1\pm0.9$ &lt;0.001</td>
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<td>Hip circumference (cm)</td>
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<td>$2.5\pm0.8$ 0.002</td>
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<td>$5.9\pm3.1$ 0.05</td>
<td>$-7.7\pm3.2$ 0.03</td>
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<td>Diastolic</td>
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<td>$4.9\pm1.7$ 0.009</td>
<td>$-4.0\pm1.4$ 0.01</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>$-4.7\pm1.6$ 0.005</td>
<td>$1.9\pm1.8$ 0.30</td>
<td>$-2.8\pm1.8$ 0.04</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>$-9.8\pm0.7$ &lt;0.001</td>
<td>$4.5\pm0.8$ &lt;0.001</td>
<td>$-5.3\pm0.9$ &lt;0.001</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SE. P values are for the changes in body measurements within each time period.
62 than at baseline (P<0.001 for all comparisons), with no significant differences between mean ratings at weeks 10 and 62 and no significant interactions between postprandial period and study week. Ratings for preoccupation with thoughts of food, as compared with baseline ratings, tended to increase at week 10 (P = 0.09) and were significantly increased at week 62 (P = 0.008). Mean ratings for fullness did not change significantly from baseline to week 10 or week 62 but were significantly lower at week 62 than at week 10 (P = 0.03).

**DISCUSSION**

Although short-term weight loss is readily achieved through dietary restriction, only a small minority of obese people maintain diet-induced weight loss in the long term.29 A multitude of hormones, peptides, and nutrients are involved in the homeostatic regulation of body weight, many of which are perturbed after weight loss. Whether these changes represent a transient compensatory response to an energy deficit is unknown, but an important finding of this study is that many of these alterations persist for 12 months after weight loss, even after the onset of weight regain, suggesting that the high rate of relapse among obese people who have lost weight has a strong physiological basis and is not simply the result of the voluntary resumption of old habits.

Leptin, an adipocyte hormone, is an indicator of energy stores20 and acts in the hypothalamus to reduce food intake and increase energy expenditure.21,22 Ghrelin, peptide YY, gastric inhibitory polypeptide, GLP-1, cholecystokinin, pancreatic polypeptide, and amylin are released from the gastrointestinal tract and pancreas in response to nutrient intake; all but two inhibit intake.8,10,23-25 The exceptions are ghrelin, which stimulates hunger,7 and gastric inhibitory polypeptide, which may promote energy storage.26,27

Caloric restriction results in a rapid, profound reduction in circulating levels of leptin28,29 and energy expenditure30 and an increase in appetite.15 Other effects of diet-induced weight loss include increased levels of ghrelin14 and reduced levels of peptide YY31 and cholecystokinin.13 Our study shows that after diet-induced weight loss, there are alterations in the postprandial release of amylin and pancreatic polypeptide and, more important, that changes in levels of leptin, ghrelin, peptide YY, gastric inhibitory polypeptide, pancreatic polypeptide, amylin, and cholecystokinin, as well as changes in appetite, persist for 12 months. In ad-

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**Figure 2.** Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.
dition, these changes would be expected to facilitate regain of lost weight, with the exception of the change in the level of pancreatic polypeptide, which reduces food intake. However, our findings are consistent with a study of obese children in which levels of pancreatic polypeptide increased after diet-induced weight loss.

A greater-than-predicted decline in 24-hour energy expenditure after weight loss also persists for 1 year or more after the loss in weight has been maintained. In obese rats with diet-induced weight loss, normalization of enhanced metabolic efficiency lags behind weight regain.

Taken together, these findings indicate that in obese persons who have lost weight, multiple compensatory mechanisms encouraging weight gain, which persist for at least 1 year, must be overcome in order to maintain weight loss. These mechanisms would be advantageous for a lean person in an environment where food was scarce, but in an environment in which energy-dense food is abundant and physical activity is largely unnecessary, the high rate of relapse after weight loss is not surprising. Furthermore, the activation of this coordinated response in people who remain obese after weight loss supports the view that there is an elevated body-weight set point in obese persons and that efforts to reduce weight below this point are vigorously resisted. In keeping with this theory, studies have shown that after adjustment for body composition, people whose weight is normal and those who are obese have similar energy requirements for weight maintenance and equivalent reductions in energy expenditure after weight loss. If this is the case, successful management of obesity will require the development of safe, effective, long-term treatments to counteract these compensatory mechanisms and reduce appetite. Given the number of alterations in appetite-regulating mechanisms that have been described so far, a combination of medications will probably be required. Several such combinations are undergoing evaluation, but none have been approved by the Food and Drug Administration. Bariatric surgery has well-documented favorable effects on appetite-mediating hormones, hunger, body weight, hypertension, dyslipidemia, type 2 diabetes, and mortality. However, because of the attendant costs and long waiting periods, bariatric surgery is not readily accessible to most people.

There are several limitations of this study. First, the attrition rate was high, as it typically is in studies of long-term weight loss. The analyses included only those participants who completed the study, since our intention was to assess the duration of physiological responses to substantial weight loss. However, the possibility that changes in hormone levels and appetite differed in patients who discontinued the study cannot be ruled out. Second, the use of a multiplex assay inevitably results in measurements of individual hormones that are less accurate and precise than those obtained with an optimized assay. However, these factors are likely to minimize the detection of changes occurring after weight loss. Finally, the possibility that weight loss may alter central sensitivity to circulating hormones was not examined.

In conclusion, we found that the compensatory changes in circulating mediators of appetite that encourage weight regain after diet-induced weight loss do not revert to baseline values within 12 months after the initial weight reduction.
Supported by a project grant from the National Health and Medical Research Council (508920), a scholarship from the Endocrine Society of Australia, a Shields Research Scholarship from the Royal Australasian College of Physicians (to Dr. Sumithran), and funding from the Sir Edward Dunlop Medical Research Foundation (to Dr. Proietto).

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REFERENCES


It is the position of the Obesity Medicine Association (OMA) that long-term pharmacotherapy represents one important evidence-based treatment strategy for obesity. Obesity has been recognized as a disease by the American Medical Association. [i] Obesity is a chronic disease that worsens over time. Weight loss does not cure obesity – instead, it triggers adaptations that restore the lost weight. [ii] It is estimated that 85% of self-directed weight loss efforts are met by weight regain.

Pharmacotherapy has been approved by the FDA for chronic weight management. This is different than the prevailing opinion about medications for obesity treatment. Prior to 2012, most medications were indicated only for short-term use to induce weight loss. This is incongruent with current knowledge about the chronic disease of obesity. Pharmacotherapy has been shown to be both safe and effective. It doubles to triples the odds of losing 5-10% body weight (or more), and also the odds of keeping that weight off. Unfortunately, if treatment is stopped, weight is regained. [iii]

Recent studies have shown the older agents including Phentermine to be safe and effective for long-term use. A study published in 2019 of nearly 14,000 patients on long-term phentermine demonstrated it to be safe and effective for low-risk individuals with responders losing 10.5% body weight. [iv] And, the FDA approved a new version of Phentermine, marketed as Qsymia, for chronic use in 2012.

As a progressive, chronic disease, obesity gets worse over time. Therefore, we also believe that prevention of obesity is just as important as treatment. Drug labels recommend use at a Body Mass Index (BMI) of 27 or more with a compelling comorbidity, or 30 or more without. However, as with other chronic diseases, we know that medications can also be useful in prevention. For example, in an individual with pre-diabetes, metformin can be used off-label to prevent diabetes. Similarly, for a patient at high risk of obesity, medications may be helpful in prevention. Many studies have demonstrated the safety and efficacy of pharmacotherapy. Studies have also shown the older agents to be non-habit-forming. [v]

We would welcome further studies into the safety and efficacy of both old and new agents. In particular, we hope to see well-done, long-term studies on generic phentermine. Nevertheless, we also oppose the current practice of not treating obesity. For example, it is estimated that only 2% of patients with an on-label indication for obesity pharmacotherapy receive treatment. [vi] A more recent study shows only 1.6% of 2.2 million eligible patients are prescribed pharmacotherapy for obesity. [vii] This is in contrast to 85% of those with type 2 diabetes.

Obesity threatens the health of our nation. It is estimated that due to this rise in obesity, by 2030, type 2 diabetes rates will rise from 8.6% to 25% of the population. [viii] Obesity is costing our nation 1.72 trillion dollars annually (47.1% of healthcare spending on chronic disease) and is responsible for 320,000 deaths per year. [ix] Normalizing the BMI can save $14,059 in healthcare costs and $28,020 in societal costs per patient over their lifetime. [x]
Only by reducing the burden of the obesity epidemic can we prevent improve these numbers. While we understand that this will take significant work in the public health sector, we cannot continue to deny treatment to those who need it.

Our view is not alone – recent studies published in Obesity Journal, and also in Endocrine Journal [xi] recommend chronic treatment, even with older agents including phentermine. In spite of this, many providers continue to stop treatment after 3 months, 12 months, or after weight loss stops. Some do this out of fear of repercussion from their state medical, pharmacy and nursing boards. In fact, some states have laws making it illegal to use anti-obesity medications in an off-label way, and specifically single-out phentermine, threatening to take physician licenses if prescribing phentermine for over 3 months. Nurse practitioners and Physician Assistants also sometimes have limitations depending on their local and national certifying organizations that block their ability to provide the current standard of care with regards to anti-obesity pharmacotherapy.

The OMA applauds the AMA for adopting as policy that it is inappropriate for state or federal rules to interfere with evidence-based treatments for obesity that would prohibit a physician from providing the current standard of care with regards to obesity treatment. It is the position of the OMA that long-term prescribing of medications constitutes the current standard of care for obesity treatment, and the OMA opposes these restrictive rules.

Therefore, it is the position of the OMA that:

1) The current standard of care with respect to obesity pharmacotherapy is that medications should be prescribed long-term.
2) It is medically inappropriate for licensing boards to interfere with a provider’s ability to offer standard of care treatment to patients affected by obesity.
3) Short-term use of obesity pharmacotherapy is not recommended as it has not been proven to provide a benefit.

[i] AMA Policy H440.842, 2013 Annual Meeting of the HOD
The Mitigating Effect of Phentermine and Topiramate on Weight Regain After Roux-en-Y Gastric Bypass Surgery

Nawfal W. Istfan 1, Wendy A. Anderson 2, Donald T. Hess 2, Liqun Yu 1, Brian Carmine 2, and Caroline M. Apovian 1

Objective: Weight regain (WR) after Roux-en-Y gastric bypass surgery (RYGB) starts to occur 2 years after surgery, ultimately affecting at least 25% of patients. A limited number of studies have evaluated the impact of antiobesity medications (AOMs) on this phenomenon.

Methods: This study reviewed the electronic medical records of 1,196 patients who underwent RYGB between 2004 and 2015. WR was evaluated by comparing each patient’s weight during subsequent postoperative office visits to nadir weight (lowest weight after RYGB, n = 760), taking into consideration the interval during which WR occurred. Patients who were prescribed AOMs and came to follow-up visits were classified as adherent users, whereas those who missed their follow-up visits were considered nonadherent. This study used a linear mixed model, Cox regression, and generalized equation estimator to determine the impact of AOMs on WR trajectory, hazard ratio for time to event, and odds ratio for repeated event occurrence, respectively.

Results: Despite the lack of a unified protocol for using AOMs, the three statistical models converged to show that phentermine and topiramate, used individually or in combination, can significantly reduce WR after RYGB.

Conclusions: Phentermine and topiramate are effective in mitigating WR after RYGB. Further studies are needed to help ascertain optimal use of AOMs after bariatric surgery.

Introduction

Bariatric surgery has evolved as a main treatment strategy for patients with severe obesity, especially in the presence of chronic comorbid conditions such as type 2 diabetes (T2D) and obstructive sleep apnea. One attribute that has increased the popularity of surgical management of obesity is the expectation of durable weight loss (WL), especially for patients with a history of weight cycling. However, several studies have identified an increasing prevalence of weight regain (WR) and subsequent reemergence of obesity-related comorbidities after bariatric surgery (1,2). The lack of a standard measure of WR after bariatric surgery has led to different methods of literature reporting, such as percentage of presurgery weight, nadir weight, or maximum weight lost. It is estimated that in the 5 years following Roux-en-Y gastric bypass surgery (RYGB), approximately one-half of patients would have regained 15% of the nadir weight, and two-thirds would have regained >20% of the weight lost (2). Given the increasing number of bariatric surgery procedures being performed, the unfavorable impact of WR and the potential for recurrence of metabolic sequelae are likely to be substantial.

We recently showed that, in an 11-year cross-sectional analysis of our ethnically diverse patient population undergoing RYGB, mean WR relative to nadir was approximately 10%, with the highest quartile showing WR in excess of 14.3% of nadir weight. These estimates, which were based on the most recent office visit for each patient, represent a regain of >24% in one-half of the patients and >45% of the weight lost in the highest quartile. Significant factors affecting WR following RYGB were race, age, and presurgical BMI (3).

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This retrospective study examined the utility of antiobesity medications (AOMs) in treating WR in the same multiethnic patient population after RYGB. We used linear mixed models to evaluate trajectories of weight change relative to the patients’ nadir weight. As in our previous study, we classified the rates of WR by quartiles and evaluated the impact of AOMs using three different statistical modeling methodologies. The results of these analyses converge to show that AOMs could play an important role in mitigating WR after RYGB. Although WR has been shown to occur after both sleeve gastrectomy and RYGB, our center is similar to others in that the RYGB population spans a longer follow-up period because sleeve gastrectomy became popular more recently. Therefore, we restricted our analysis to those patients who underwent RYGB during this time period.

Methods

Patients

This retrospective study used the electronic medical record data of adult patients who had undergone bariatric surgery, specifically RYGB, at Boston Medical Center (BMC) between 2004 and 2015. This study was approved by the BMC and Boston University Medical Campus Institutional Review Board under protocol H-26417.

Clinical data

Race and ethnicity were self-identified as Caucasian (CA), black/African American (AA), Hispanic (HA), Asian, American Indian/Native American, Native Hawaiian/Pacific Islander, or not available/declined information. Data were extracted by the Boston University Clinical Data Warehouse and included age at the time of surgery, date of enrollment in the bariatric program, date of the surgery, weight, height, and BMI.

We reviewed data from all patients who underwent bariatric surgery at BMC during this period (n = 1,516). We limited our study to patients who underwent RYGB from the three most common racial and ethnic groups in our population (n = 1,196): AA, HA, and CA. Patients who became pregnant after surgery or underwent surgical revisions were excluded. Presurgical medical International Classification of Diseases, Ninth Revision codes were used to identify comorbid conditions, including T2D (250 and 790.29), osteoarthritis (715.9 and 716.9), hypertension (401.1, 401.9 and 796.2), dyslipidemia (272), and obstructive sleep apnea (780.57, 780.53 and 327.23).

The zip code for each patient was used to estimate the socioeconomic status (SES) based on the zip code median income. Data on the median income by zip code in 2014 were obtained from the United States Census Bureau (4). Patients were classified into SES quartiles based on the zip code median income. Use of AOMs was determined from the use in these analyses: before surgery and 1 to 2 years, 2 to 3 years, 3 to 4 years, 4 to 5 years, 5 to 6 years, and beyond 6 years after surgery.

Patients who had not yet achieved nadir weight (n = 436) were excluded from the following calculations. We calculated WL as the difference between the presurgical weight and the nadir weight for each participant (n = 760). We defined WR as the difference between the weight obtained at each subsequent office visit following the nadir date and the nadir weight in kilograms. WR was evaluated relative to amount of weight lost (WR/WL, expressed as a percentage) and relative to nadir (WR/nadir, expressed as a percentage) for each patient based on the recorded weights at each office visit after nadir. Hence, WR/WL and WR/nadir are both repeated measures for each participant.

The rate of WR was calculated based on both WR/WL and WR/nadir at each subsequent weight measurement relative to the time elapsed since nadir (reported as percentage per 30-day interval). Differences in continuous variables between categorical groups were assessed by ANOVA. Categorical outcomes were assessed by cross-tabulation and χ² distribution analysis. Multinomial logistic regressions were used to compare groups with more than two categorical outcomes across groups.

The 25%, 50%, and 75% values of the WR/nadir weight distribution based on the last observed weight were used to define thresholds and group patients into quartiles of low, moderate, and high rates of WR. We performed a Cox regression model to determine the proportional hazard ratio of WR at each of these three thresholds. Hence, event occurrence was defined as the time to first occurrence for a patient whose WR/nadir exceeded each specific cut-off threshold corresponding to the 25th, 50th, and 75th WR/nadir distribution (WR/nadir of 1.49%, 6.25%, and 14.29%, respectively). Race, sex, SES, and each comorbid condition were entered individually into the Cox regression as categorical predictors; age and WL were entered as continuous predictors. The final multivariable Cox regression included all the factors with P values < 0.05. Because AOMs were prescribed intermittently, we further analyzed the rates of WR at each visit as “repeated exposures” using a generalized equation estimator with an independent correlation structure to correct within-participant correlation. The odds ratio (OR) for occurrence of an event was determined by binomial logistic regression analysis. We used specific WR rates as “events” based on the quartile distribution of all WR rates for the study population, as described above. All data analyses were performed using SPSS version 25 (IBM Corp., Armonk, New York).

Results

A summary of the clinical characteristics of patients who achieved nadir weight and are at risk of WR after RYGB is presented in Table 1. Of the 760 in this cohort, 350 (46.1%) were documented users of AOMs. Of the AOM users, 119 (34.0%) were prescribed phentermine alone, 74 (21.1%) used topiramate alone, and 154 (44.0%) were prescribed a combination of phentermine and topiramate. Only three patients (0.9%) were prescribed lorcaserin and none were prescribed generic or brand-name bupropion/naltrexone or brand-name phentermine/topiramate. Liraglutide 3.0 was not an available option at the time. There were no
significant differences in presurgery BMI and prevalence of the comorbidities included in the analysis between the AOM users and nonusers. There were more AOM users among HA and AA patients than among CA patients. Relative to CA patients, the ORs for patients to be prescribed AOMs were 2.42 (CI: 1.74-3.36, \( P < 0.001 \)) for AA patients and 2.85 (CI 1.85-4.39, \( P < 0.001 \)) for HA patients. Patients in the lowest SES category were more likely to be prescribed AOMs (OR: 1.90, CI: 1.26-2.87, \( P = 0.000 \)).

Table 1  Characteristics of patients who achieved nadir weight stratified by AOM use

<table>
<thead>
<tr>
<th></th>
<th>No medication</th>
<th>Adherent</th>
<th>Nonadherent</th>
<th>Total</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>410 (53.9%)</td>
<td>157 (20.7%)</td>
<td>193 (25.4%)</td>
<td>760</td>
<td>0.007</td>
</tr>
<tr>
<td>Age, y</td>
<td>47.0 ± 0.5</td>
<td>44.2 ± 0.8</td>
<td>45.2 ± 0.9</td>
<td>45.9 ± 0.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>76.1</td>
<td>91.1</td>
<td>81.9</td>
<td>80.7</td>
<td>0.000</td>
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<td>Male</td>
<td>23.9</td>
<td>8.9</td>
<td>18.1</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>Presurgical weight, kg</td>
<td>92.4 ± 2.6</td>
<td>100.3 ± 3.9</td>
<td>90.5 ± 4.0</td>
<td>93.6 ± 1.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Presurgical BMI, kg/m(^2)</td>
<td>46.8 ± 0.4</td>
<td>46.5 ± 0.7</td>
<td>47.2 ± 0.7</td>
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<td>0.77</td>
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<td>Race, %</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>CA</td>
<td>44.6</td>
<td>39.5</td>
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</tr>
<tr>
<td>AA</td>
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<td>30.8</td>
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<tr>
<td>HA</td>
<td>10.5</td>
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<td>SES, %</td>
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<td>1</td>
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<td>56.0</td>
<td>56.3</td>
<td>NS</td>
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<tr>
<td>Dyslipidemia, %</td>
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<td>48.4</td>
<td>28.0</td>
<td>42.1</td>
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<tr>
<td>Hypertension, %</td>
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</tr>
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<td>OSA, %</td>
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<td>35.0</td>
<td>37.3</td>
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<tr>
<td>Osteoarthritis, %</td>
<td>10.7</td>
<td>8.9</td>
<td>12.4</td>
<td>10.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean ± SE. SES: 1, <$47,297; 2, $47,297-$60,774; 3, $60,775-$76,924; 4, >$76,924. AA, African American; AOM, antiobesity medication; CA, Caucasian; HA, Hispanic; NS, not significant; OSA, obstructive sleep apnea; Sig, significance; SES, socioeconomic status; T2D, type 2 diabetes.

Because WR increases with time, differences between the quartiles could be explained by the duration of the observation period during which WR was assessed (the last office visit for each patient). Patients in the highest quartile of total WR were more likely to have undergone RYGB earlier (years after procedure: 4.3 ± 0.2, 3.1 ± 0.1, 4.3 ± 0.2, and 5.5 ± 0.2 years for the lowest to highest quartile, respectively; \( P < 0.0001 \)). Therefore, we normalized the WR/nadir values as monthly rates. The corresponding cut-off WR rates (percentage per 30 days) were 0.18%, 0.58%, and 1.22%.

To further evaluate the effect of AOMs on WR, we determined the increase in weight relative to nadir at the last available weight for each patient. These estimates of WR (percentage of nadir weight) were then classified by quartiles. Cut-off points for the 25th, 50th and 75th percentiles of WR were 1.5%, 6.25%, and 14.3% relative to the nadir, respectively. As a percentage of the amount of weight lost, WR was 1.8% ± 0.2%, 17.2% ± 0.8%, 30.3% ± 1.4%, and 41.1% ± 5.1%, respectively, for the four quartiles. Thus, 50% of the patients (upper two quartiles) regained at least one-third of the weight they had previously lost. The clinical characteristics of these quartiles of WR were published previously (3). Briefly, the quartiles were similar in age and sex distribution; significant differences were noted in race, presence of T2D, and use of AOMs. The upper two quartiles were more likely to include AA than CA patients (likelihood ratio: 1.553, CI: 1.023-2.358, \( P = 0.039 \) in the third quartile and likelihood ratio: 2.154, CI: 1.37-3.385, \( P = 0.001 \) in the fourth quartile). The quartile with the highest WR was also more likely to include patients with T2D (likelihood ratio: 1.689, CI: 1.114-2.571, \( P = 0.013 \)) and patients who were prescribed AOMs but were identified to be nonadherent (likelihood ratio relative to patients without AOM prescription: 1.683, CI: 1.041-2.557, \( P = 0.033 \)).

We used three statistical models to evaluate the impact of AOMs on monthly WR rates for each of the quartile cut-off values shown. In the first model, a linear mixed model, adjusted for age, sex, race, and SES, was used to evaluate WR progression. Differences in WR between AOM users and nonusers were statistically significant only in the highest (most rapid) WR quartile. The results of the subgroup
of patients who regained weight relative to the nadir at a rate ≥1.22% per month (highest WR quartile) are presented in Figure 2. WR progression was smaller in the group of patients who were prescribed AOMs and were classified as adherent when compared with the nonadherent patients or nonusers of AOMs \( (P = 0.012) \). By the end of the observation period, WR relative to nadir was approximately 10% lower among adherent AOM users in comparison with nonadherent users.

In the second model, we evaluated whether AOMs can impact the occurrence of WR/nadir of at least 1.22% per month. The results of Cox regression analysis are presented in Figure 3, showing a proportional hazard ratio of 0.729 (CI: 0.556-0.957, \( P = 0.023 \)) for the adherent AOM users compared with the nonusers of AOMs. Patients who were prescribed AOMs but classified as nonadherent had a proportional hazard ratio of 0.844 (CI: 0.659-1.081, \( P = 0.18 \)). Similar analyses for the lower three quartiles of WR did not reveal statistically significant differences.

It is important to note that use of AOMs in this patient population was intermittent because patients were likely to discontinue the medications and resume them at subsequent times. The decision to prescribe and when to prescribe AOMs were variable among providers and patients. Thus, multiple exposures to AOMs occurred “randomly” per patient during the observation interval. Therefore, to further evaluate the effectiveness of AOMs, we used the generalized equation estimator approach with an independent correlation structure to correct within-participant correlation. In a binary logistic model, adjusted for age, sex, race, and SES, the OR for occurrence of WR of ≥1.22% per month relative to nadir was 0.579 (CI: 0.371-0.877, \( P = 0.01 \)) in the adherent AOM group and 0.872 (CI: 0.593-1.284, \( P = 0.5 \)) compared with the non-AOM users. These results imply that AOMs effectively reduced the risk of recurrent bouts of rapid WR in our patient population.

**Discussion**

This large retrospective study of WR after RYGB suggests that the use of AOMs and adherence to those medications is effective in mitigating WR after RYGB. Our results relate specifically to the use of phentermine and topiramate, either individually or in combination. We were unable to compare the effectiveness of other AOMs because of the small numbers prescribed to this cohort at the time of analysis. The analytical approach in the current study focuses on the progression of body-weight changes throughout an 11-year observation period in an ethnically diverse patient population. Although it is conventional to evaluate the effectiveness of AOMs by the amount...
Figure 2 Trajectory of total weight regain in the highest quartile. Data are shown as percentage of nadir weight. Highest quartile is defined by a rate of weight regain equivalent to 1.22% of nadir weight per 30-day-interval. SES, socioeconomic status.

Figure 3 Cox regression for weight regain relative to nadir normalized for a 30-day interval stratified by antiobesity medication use. Data are for the top quartile (weight regain ≥ 1.22% of nadir weight). RYGB, Roux-en-Y gastric bypass. [Color figure can be viewed at wileyonlinelibrary.com]
of weight lost, this approach was not applicable in the current study. There were no specific clinical parameters that guided the providers’ prescriptions of AOMs; and in most cases, the decision to take or withhold AOMs was effectively a random event. Therefore, to overcome this limitation, we used three independent statistical models, which consistently demonstrated that AOMs decrease cumulative WR by about 10% relative to nadir weight and reduce the odds of rapid WR after RYGB. As detailed elsewhere, rapid WR in our cohort is defined as a rate of increase in body weight of 1.22% per month relative to nadir weight (3). These results take into account that patients typically lost weight when taking AOMs and regained weight during intervals when the medications were not prescribed and that patients in the current study started AOMs at different stages and used them over variable and intermittent periods. Therefore, controlled prospective clinical trials are needed to further evaluate the impact of AOMs on WL parameters and long-term weight outcomes after bariatric surgery procedures.

Wider awareness of the clinical implications associated with obesity has increased the acceptance of surgical interventions. The beneficial effects of RYGB on T2D are clear, and studies with only 1 to 2 years of follow-up have purported that RYGB is associated with long-term weight stability. However, recent reports of WR after RYGB highlight the need for adjunct treatment strategies to maximize the long-term benefit and reduce the recurrence risk of comorbid conditions. Estimated proportions of patients who have “significant” WR have varied from 17% to 30% at 2 years from RYGB (5-8) to 59% in 1 small study with >20% WR at least 1 year from RYGB (9) to 79% by self-report (10). These estimates depend on the definition of significant WR, the duration of the study, and the method of reporting WR (11-14). Without a standard definition of WR, it is difficult to compare data from different studies. For example, in the Swedish Obese Subjects (SOS) study, long-term weight outcomes are reported as weight changes relative to the presurgical weight (15-18). This approach emphasizes the beneficial long-term outcomes of bariatric surgery because it continues to show significant WL 10 years following the surgical procedure. However, data presented as such do not provide clear and direct measures of the amount of WR. A discussion of the different ways of reporting WR and how they relate to clinical outcomes is presented by King et al (2). We have previously argued that because WR is the consequence of a specific physiological process characterized by a state of positive energy balance, it is better evaluated in terms of actual weight increase rather than by a decrease in previously achieved WL. Thus, we regard WR/nadir as a more clinically relevant parameter of the metabolic condition associated with WR in the post-RYGB phase. Because total WR increases with time, we determined WR/nadir as a rate per 30 days to normalize for differences in observation intervals between groups. Further details characterizing WR in our patient population are presented elsewhere (3).

It is important to emphasize that the relapse of obesity is better defined by the recurrence of clinically significant comorbid conditions rather than by WR itself. Long-term observations, such as those from the SOS study, consistently document the beneficial impact of bariatric surgery on mortality, diabetes, and vascular disease (16,17,19,20). The relationship between WR and recurrence of specific comorbidities remains unclear. Although the SOS study has associated diabetes remission with the degree of WL at 2 and 10 years after surgery (21), it is difficult to evaluate the impact of WR from that study because of the specific way data are reported, as noted above. However, the potential for relapse is concerning and has prompted additional surgical procedures (“revisional surgery”) (22) aiming to increase malabsorption (“distalization”) (23), increase the restriction at the gastro-jejunal anastomosis (24) (sclerotherapy) (25), and correct anatomical defects such as gastro-gastric fistulas (26). Unfortunately, position statements and guidelines related to the implementation of surgical revisions continue to rely on expert opinion (27) rather than on controlled prospective studies. Thus, nonsurgical interventions remain crucial for counteracting the growing problem of WR following bariatric surgery.

Interventions targeting disordered or maladaptive eating patterns such as night eating, grazing, and nibbling behaviors, which are widely reported among patients following bariatric surgery (6,28,29), have been effectively used to help mitigate WR (30). However, use of AOMs has been limited. One possible reason is that many patients are more likely to be followed up by bariatric surgeons who have limited experience in the use of anorexigenic pharmacotherapy. Additionally, guidelines for use of AOMs after bariatric surgery have not been established, thus leading to skepticism about their utility. Several possible physiological changes could potentially impact the effectiveness of AOMs after bariatric surgery. For example, changes in the regulation of satiety and the preexisting history of substantial WL after bariatric surgery could alter the effectiveness of AOMs. The current study further confirms that AOMs remain effective and are useful tools to help temper the brunt of WR among patients with history of RYGB, and potentially other bariatric surgery procedures. In our own experience, postsurgical AOM use in our clinic had been very limited prior to 2009 and had increased approximately fourfold by 2015, when >10% patients were prescribed phentermine, topiramate, or a combination of these two medications during postsurgery office visits.

Few other studies have demonstrated that AOMs remain effective after bariatric surgery (31-36). To our knowledge, compared with the prior studies cited, ours is the largest retrospective study to date and one that features an underserved ethnic patient population. It is important to note the unique setting of this retrospective study. As previously described in more detail elsewhere (3), race is an important determinant of WR after RYGB with AA patients being at high risk. In our center, we typically find that AA and HA patients are more likely to be prescribed AOMs than CA patients after RYGB, presumably because of their higher propensity for WR. Thus, it is possible that higher rates of WR among AA and HA patients could have influenced decisions to prescribe AOMs in our patient population. However, these prescriptions were not based on predetermined criteria or algorithms but were rather initiated by individual patient-physician interactions during routine office visits. Differences in AOM prescription practices between providers could further contribute to the variance in the clinical outcomes in the current study. However, despite these drawbacks, we are able to show that AOMs are important tools in the long-term management of patients with obesity and WR following RYGB and work as effectively as they do in medically managed patients with obesity. We also note that our previous findings of racial disparities of WR after RYGB may have been tempered by the higher rate of AOMs prescribed to AA and HA patients in our patient population.

There are few prospective trials investigating “rescue” pharmacotherapy with AOMs following bariatric surgery, with only six published to date with small numbers of patients (37-43). One of the studies used an AOM which has since been withdrawn from the market, fenfluramine (40), and two other trials used AOMs after the adjustable laparoscopic gastric band, which is rarely used today (41,42). The advent of larger randomized controlled clinical trials...
evaluating the use of single and combination AOMs as rescue therapy for WR after bariatric surgery will be crucial to the development of treatment guidelines. The judicious use of multimodal medical and surgical treatment (43) for extreme obesity will further promote the advancement of the field of obesity medicine and mitigate the rising prevalence of this disease worldwide.

Strengths of this study are its large multiethnic patient population and its duration of 11 years. Details pertaining to factors that contribute to WR after RYGB have already been published. Its limitations include the retrospective nature of clinical observations, the lack of a unified protocol for use of AOMs, that the data pertain only two AOMs, and the randomization of decisions made by providers and patients to use or abstain from AOMs.

Conclusion
Bariatric surgery is the most effective treatment strategy to combat obesity and achieve long-term resolution and/or improvement of most cardiometabolic dysfunction associated with it. However, as a chronic disease, obesity is subject to relapse years after bariatric surgery and it could require further medical interventions. Here we show that phentermine and topiramate could play a role in the management of weight relapse after RYGB. However, the full potential of these agents and newer AOMs to counter weight recidivism and prevent the recurrence of obesity-related comorbidities needs to be further explored in prospective clinical trials. Guidelines for initiating and monitoring the potential long-term use of AOMs after bariatric surgery need to be established.

Acknowledgments
The authors thank Ashley McCarthy for her helpful feedback.

References

Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study\(^1\)–\(^3\)

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ABSTRACT

Background: Obesity is a serious chronic disease. Controlled-release phentermine/topiramate (PHEN/TPM CR), as an adjunct to lifestyle modification, has previously shown significant weight loss compared with placebo in a 56-wk study in overweight and obese subjects with ≥2 weight-related comorbidities.

Objective: This study evaluated the long-term efficacy and safety of PHEN/TPM CR in overweight and obese subjects with cardiometabolic disease.

Design: This was a placebo-controlled, double-blind, 52-wk extension study; volunteers at selected sites continued with original randomly assigned treatment [placebo, 7.5 mg phentermine/46 mg controlled-release topiramate (7.5/46), or 15 mg phentermine/92 mg controlled-release topiramate (15/92)] to complete a total of 108 wk. All subjects participated in a lifestyle-modification program.

Results: Of 866 eligible subjects, 676 (78%) elected to continue in the extension. Overall, 84.0% of subjects completed the study, with similar completion rates between treatment groups. At week 108, PHEN/TPM CR was associated with significant, sustained weight loss (intent-to-treat with last observation carried forward; \(P < 0.0001\) compared with placebo); least-squares mean percentage changes from baseline in body weight were –1.8%, –9.3%, and –10.5% for placebo, 7.5/46, and 15/92, respectively. Significantly more PHEN/TPM CR–treated subjects at each dose achieved ≥5%, ≥10%, ≥15%, and ≥20% weight loss compared with placebo (\(P < 0.001\)). PHEN/TPM CR improved cardiovascular and metabolic variables and decreased rates of incident diabetes in comparison with placebo. PHEN/TPM CR was well tolerated over 108 wk, with reduced rates of adverse events occurring between weeks 56 and 108 compared with rates between weeks 0 and 56.

Conclusion: PHEN/TPM CR in conjunction with lifestyle modification may provide a well-tolerated and effective option for the sustained treatment of obesity complicated by cardiometabolic disease. This trial was registered at clinicaltrials.gov as NCT00796367. Am J Clin Nutr 2012;95:297–308.

INTRODUCTION

Obesity is a global epidemic (1, 2). This chronic disease increases morbidity and mortality, in large part due to associated comorbidities, including T2D\(^1\), CVD, metabolic syndrome, liver disease, and cancer (1–7). The first-line strategy for the treatment of obesity and prevention of cardiometabolic disease is achieving weight loss through lifestyle interventions, which consist of reductions in caloric intake (by 500–1000 calories/d), increases in physical activity, and changes in health behaviors (8). However, adherence to lifestyle changes can be challenging for a wide variety of reasons, such as a lack of readiness for change on the part of the patient, physical restrictions that limit activity, and a shortage of therapeutic venues that include a multidisciplinary health care team essential to treatment effectiveness. When lifestyle changes alone do not provide the desired weight loss, the addition of pharmacotherapy or bariatric surgery provides a viable option for patients meeting eligibility criteria. However, effective pharmacologic options are limited, and indication for bariatric surgery is limited to patients with a high BMI due to the inherent risks of invasive procedures (9, 10). Thus, it is imperative that effective, long-term pharmacologic strategies are identified that may be used in conjunction with lifestyle changes to combat the obesity epidemic.

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\(^4\) Abbreviations used: AE, adverse event; bpm, beats per minute; C-SSRS, Columbia Suicide Severity Rating Scale; CVD, cardiovascular disease; Hb A\(_{1c}\), glycated hemoglobin; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least-squares; PHEN/TPM CR, controlled-release phentermine/topiramate; SAE, serious adverse event; TEAE, treatment-emergent adverse event; T2D, type 2 diabetes; 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; 15/92, 15 mg phentermine/92 mg controlled-release topiramate.

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Currently, orlistat (Xenical; Genentech), a gastric and pancreatic lipase inhibitor, is the only approved agent for the long-term pharmacologic treatment of obesity in the United States (10). Phentermine (Apidex-P; Teva), a central norepinephrine-releasing drug, is approved for short-term (a few weeks) treatment of obesity as monotherapy (37.5 mg/d) (10, 11). Topiramate (Topamax; Janssen Pharmaceuticals), an anticonvulsant (200–400 mg/d) that is also approved for the prophylaxis of migraine headaches (100 mg/d), has shown weight-loss properties but is not currently approved as a therapy for obesity (10, 12–16). A low-dose combination of phentermine plus controlled-release topiramate (PHEN/TPM CR) as an adjunct to lifestyle modification was previously shown to reduce body weight through 56 wk of treatment in the CONQUER study (17). The SEQUEL study, an extension of the CONQUER study, was designed to assess the longer-term efficacy and safety of lifestyle intervention and 2 doses of PHEN/TPM CR for an additional 52 wk (ie, a total treatment duration of 108 wk).

SUBJECTS AND METHODS

Subjects

All subjects were eligible to enroll in the extension study if they completed the CONQUER study on treatment and complied with protocol requirements. Inclusion and exclusion criteria for CONQUER required subjects to have a BMI (in kg/m²) of ≥27 and ≤45 as well as ≥2 weight-related comorbidities, as previously described in detail (17). To continue into the SEQUEL extension study, female subjects of childbearing potential were required to continue contraception in the form of a double-barrier method, stable hormonal contraception plus single barrier, or tubal ligation. Exclusion criteria included having a BMI ≤22 at the completion of the CONQUER study, continuously not taking the study drug for >4 wk at the completion of the CONQUER study, developing a condition during the CONQUER study that would interfere with compliance or attainment of study measures, or participating in another formal weight-loss program.

Study design

SEQUEL was a double-blind, placebo-controlled, 52-wk extension of the CONQUER study. On completion of the 56-wk CONQUER study (17), sites that met the criteria described below were eligible to offer enrollment in SEQUEL. Participants in SEQUEL continued with the original treatment to which they were randomly assigned during CONQUER: lifestyle intervention plus placebo, lifestyle plus 7.5 mg phentermine/46 mg controlled-release topiramate, or lifestyle plus 15 mg phentermine/92 mg controlled-release topiramate, hereafter referred to as placebo, 7.5/46, and 15/92, respectively. Of the 93 CONQUER sites, 36 were selected for the extension study on the basis of their high initial enrollment numbers and rates of retention, and these sites remained blinded to assigned treatment through the end of SEQUEL. This study was conducted between December 2008 and June 2010 and was approved by institutional review boards at each site. All subjects provided written informed consent for participation in the SEQUEL extension. This trial was registered with clinicaltrials.gov as NCT00796367.

Randomization and interventions

Subjects were randomly assigned by using a computer-generated algorithm and were stratified according to their sex and diabetic status. Study drugs and placebo were administered as capsules that were identical in size and appearance. Eligible subjects maintained their originally assigned once-daily treatment from the CONQUER study (2:1:2 randomization for placebo, 7.5/46, or 15/92) (17). Investigators and subjects remained blinded to treatment assignment. The screening visit for the extension study occurred at the final CONQUER visit, and study visits occurred at 4-wk intervals thereafter. All subjects continued to receive standardized diet and lifestyle-modification counseling based on the LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) program (18). Dose reductions or interruptions were allowed for subjects who experienced AEs or who had tolerability issues. Subjects discontinuing the study drug were encouraged to remain in the study, complete study assessments, and continue with the lifestyle counseling according to the LEARN program.

Study endpoints

The CONQUER study had 2 predefined, coprimary endpoints, which were retained as the primary outcome measures in the SEQUEL extension study: mean percentage weight loss and percentage of subjects achieving ≥5% weight loss from baseline (week 0 of CONQUER) to week 108. Secondary endpoints included the following: weight loss in kilograms; percentage of subjects achieving ≥10%, ≥15%, or ≥20% weight loss; and change in waist circumference from baseline to week 108. Other efficacy endpoints included changes from baseline to week 108 in blood pressure, serum lipid variables, glycemic measures, concomitant medications for weight-related comorbidities, and rate of progression to diabetes among subjects without diabetes at baseline. All subjects were assessed for diabetic status at baseline per the 2007 American Diabetes Association guidelines, as follows: fasting blood glucose ≥126 mg/dL or 2-h blood glucose ≥200 mg/dL after an oral-glucose-tolerance test (19). Hb A1c concentrations were also obtained to assess degree of hyperglycemia but were not used as a diagnostic criterion for diabetes at baseline (20). Subjects were considered to have progressed to T2D if their blood glucose was ≥126 mg/dL under fasting conditions during ≥2 consecutive measurements and/or ≥200 mg/dL at 2 h after an oral-glucose-tolerance test. Safety assessments included AEs, physical examination, clinical and laboratory measurements, vital signs, and electrocardiography. At each visit, depressive symptoms were assessed by using the 9-item Patient Health Questionnaire self-reported assessment for depressive symptoms, and the presence of suicidal ideation or behavior was assessed by using the C-SSRS, an 11-item, clinician-administered assessment.

Statistical analysis

Analyses of change in weight, waist circumference, and other continuous efficacy measures were conducted in a modified ITT sample with the LOCF method to impute missing values. The modified ITT sample was defined as all subjects who received at least one study drug dose with at least one postbaseline measurement of body weight. ANCOVA was used to evaluate percentage weight loss, with treatment, sex, and diabetic status as
fixed effects and baseline weight as a covariate. LS means, corresponding SEs, 2-sided 95% CIs, and 2-sided \( P \) values for percentage weight loss within each treatment group were derived from the ANCOVA. Analyses of percentage of categorical weight loss were conducted by using logistic regression, with treatment, sex, and diabetic status as fixed effects and baseline weight as a covariate. For each treatment comparison, the estimated OR, SE, 95% Wald CI, and \( P \) value were determined. Multiple imputation was used as a sensitivity analysis to supplement the ITT-LOCF approach, and an analysis of subjects who completed the study while actively taking the study drug was also performed to understand the effect of treatment after 108 wk of exposure.

The annualized incidence rate of T2D was calculated as the number of newly diagnosed subjects divided by the number of subject-years of follow-up for each treatment group. The number of subject-years of follow-up was calculated as the sum of the number of days across all subjects from the randomization date in CONQUER to the onset date of T2D or to the date of completion or discontinuation from SEQUEL (for subjects who did not develop T2D) divided by 365.25.

Safety analyses were based on incidence of AEs, changes in laboratory evaluations, vital signs, electrocardiograms, physical examination findings, and results from the 9-item Patient Health Questionnaire and the C-SSRS during both the CONQUER and SEQUEL studies. TEAEs were defined as AEs occurring between week 0 of CONQUER and \( \leq 28 \) d after the last dose of double-blind study drug in SEQUEL. Analysis of TEAEs was also performed from the start date of study drug in the SEQUEL study and \( \leq 28 \) d after the last dose of study drug in the SEQUEL study. All other safety variables were measured between baseline (week 0 of CONQUER) and week 108 or early termination.

RESULTS

Disposition of study subjects and baseline characteristics

Of the 866 subjects who completed the CONQUER trial at eligible SEQUEL sites, 676 (78.1\%) elected to enroll in SEQUEL and continue receiving their blinded treatment as an adjunct to lifestyle modification for an additional 52 wk (Figure 1). A greater proportion of subjects in the 15/92 treatment arm (85.5\%) consented to continue with treatment than did subjects in the 7.5/46 treatment arm (79.4\%), whereas the placebo group had the lowest proportion of subjects electing to continue in the protocol (69.4\%). Overall, 84.0\% (568/676) of subjects completed the extension study, including 86.3\% (196/227) of those assigned to placebo, 82.5\% (127/154) of those assigned to 7.5/46, and 83.1\% (245/295) of those in the 15/92 group. Seven (3.1\%) subjects in the placebo arm, 7 (4.5\%) subjects in the 7.5/46 arm, and 13 (4.4\%) in the 15/92 arm, discontinued the study drug due to an AE (Figure 1). Three subjects in the placebo arm and one subject in the 7.5/46 arm stopped treatment due to lack of efficacy, whereas no subjects in the 15/92 arm discontinued due to lack of efficacy. A higher number of subjects were lost to follow-up in the 15/92 group (20 subjects) than in either the placebo or 7.5/46 groups (4 subjects each).

Baseline demographic, anthropometric, and clinical characteristics, including comorbidities, were similar among subjects in all 3 treatment arms of the SEQUEL study, and in each of the treatment arms the characteristics of the subjects in SEQUEL were similar to and representative of the larger CONQUER cohort (Table 1). Whereas the proportion of subjects with hypertension and dyslipidemia was similar between groups and between CONQUER and SEQUEL, a greater percentage of subjects enrolling in SEQUEL had T2D at baseline compared with the original CONQUER cohort (21.5\% compared with 15.8\%, respectively). In total, 451 (66.8\%) subjects in SEQUEL met the American Heart Association and National Heart, Lung, and Blood Institute criteria (21, 22) for metabolic syndrome at baseline, including 152 (67.0\%) in the placebo group, 107 (69.9\%) in the 7.5/46 group, and 192 (65.1\%) in the 15/92 group.

Weight loss

Subjects in both PHEN/TPM CR arms showed significantly greater percentage weight loss than did those in the placebo arm, and the weight loss was sustained during 108 wk (Figure 2: \( P < 0.0001 \) compared with placebo at all time points assessed). At week 108, the LS mean percentage changes from baseline in body weight in the ITT-LOCF analysis were significantly greater in the PHEN/TPM CR groups compared with placebo: –1.8\%, –9.3\%, and –10.5\% for placebo, 7.5/46, and 15/92, respectively (\( P < 0.0001 \) compared with placebo for all comparisons). For subjects who completed the study while still taking the study drug at week 108, the LS mean percentage changes from baseline in body weight were also significantly greater in the PHEN/TPM CR groups compared with placebo: –2.2\%, –9.3\%, and –10.7\% for placebo, 7.5/46, and 15/92, respectively (\( P < 0.0001 \) compared with placebo for all comparisons). Absolute LS mean weight loss using ITT-LOCF data were –2.1, –9.6, and –10.9 kg for the placebo, 7.5/46, and 15/92 groups, respectively (\( P < 0.0001 \) compared with placebo for all comparisons). Greater proportions of subjects treated with each dose of PHEN/TPM CR experienced weight losses of \( \geq 5\% \), \( \geq 10\% \), \( \geq 15\% \), and \( \geq 20\% \) when compared with placebo-treated subjects (Figure 3; \( P < 0.0001 \) for all comparisons except for weight loss \( \geq 20\% \) for the 7.5/46 group, \( P = 0.0072 \); ITT-LOCF). There were also significant reductions in waist circumference at Week 108 in subjects treated with PHEN/TPM CR, with mean reductions of –3.6, –9.8, and –10.6 cm for placebo, 7.5/46, and 15/92 treatment arms, respectively (\( P < 0.0001 \) compared with placebo; ITT-LOCF).

An analysis of weight loss as a function of baseline BMI category (<30, \( \geq 30 \) and <35, \( \geq 35 \) and <40, \( \geq 40 \) and <45) was performed (see Supplemental Figure 1 under “Supplemental data” in the online issue). PHEN/TPM CR was clearly effective in all BMI categories and produced greater weight loss than did placebo (\( P \leq 0.0061 \)). However, a significant treatment effect by baseline BMI category was observed (\( P = 0.0327 \)). Whereas the 7.5/46 and 15/92 doses were statistically similar in their effectiveness in the lower baseline BMI categories, the 15/92 group showed significantly greater percentage weight loss than did the 7.5/46 group in the most severely obese subjects (baseline BMI \( \geq 40 \) and <45; \( P = 0.0016 \) compared with 7.5/46). Among all subjects with class II obesity or greater at baseline (ie, BMI \( \geq 35 \) (8)), LS mean percentage weight losses at week 108 were significantly greater for PHEN/TPM CR compared with placebo (\( P < 0.0001 \); ITT-LOCF): –3.4\%, –10.1\%, and –12.6\% for placebo, 7.5/46, and 15/92 treatment arms, respectively.
In a prespecified subgroup analysis of weight loss in subjects with T2D at baseline, the PHEN/TPM CR–treated subjects also showed greater weight loss when compared with placebo-treated subjects. At week 108, subjects with T2D in the placebo group \( (n = 55) \) lost 2.0% of their body weight, whereas subjects with T2D in both the 7.5/46 \( (n = 26) \) and 15/92 \( (n = 64) \) groups lost 9.0% of their body weight \( (P = 0.0003 \) for 7.5/46 and \( P < 0.0001 \) for 15/92 compared with placebo).

**Changes in weight-related comorbidities**

Consistent with study entry criteria, enrolled subjects were generally affected by cardiometabolic disease. Many subjects were receiving medications to control blood pressure, lipid variables, and glucose concentrations, and all subjects were actively managed throughout the trial to control these comorbidities. Blood pressure in subjects with hypertension was generally well controlled with \( \geq 2 \) antihypertensive medications, the most common of which were angiotensin-converting enzyme inhibitors, thiazide diuretics, and selective \( \beta \)-blockers. More than one-third of subjects with dyslipidemia were receiving statins; specifically, 78 (34.4%), 58 (37.9%), and 93 (31.5%) subjects randomly assigned to the placebo, 7.5/46, and 15/92 subgroups, respectively, were taking statins. The second most common lipid-controlling treatment was fish oil or a specific omega-3 formulation. Subjects with diabetes \( (n = 145) \) were required to be managed with a regimen of diet and exercise or metformin monotherapy; 38 (69.1%), 15 (57.7%), and 39 (60.9%) were randomly assigned to placebo, 15/92, and 15 mg phentermine/92 mg controlled-release topiramate, respectively, used metformin during the SEQUEL study. Therefore, to assess effects of PHEN/TPM CR, changes in both cardiometabolic disease variables and medication requirements were assessed.

**Blood pressure**

Both systolic and diastolic blood pressure decreased by 3–5 mm Hg at 108 wk compared with baseline in all treatment arms \( (P < 0.0001 \) for all comparisons compared with baseline except for placebo compared with baseline for systolic blood pressure, \( P = 0.0002 \); NS for PHEN/TPM CR groups compared with placebo; **Figure 4A**). Although the degree of blood pressure reduction did not differ significantly between treatment arms,
subjects randomly assigned to placebo experienced a net increase in the number of antihypertensive medications used, whereas there was a net decrease in the number of medications in subjects receiving 7.5/46 or 15/92 (Figure 4B). Specifically, 7.5% \((n = 17)\) of subjects in the placebo group experienced a decrease in concomitant antihypertensive medication use compared with 13.1% \((n = 20)\) in the 7.5/46 group and 15.6% \((n = 46)\) in the 15/92 group. At the same time, more subjects receiving placebo experienced an increase in antihypertensive medication use than did subjects treated with PHEN/TPM CR: 11.0% \((n = 25)\), 9.2% \((n = 14)\), and 5.8% \((n = 17)\) for the placebo, 7.5/46, and 15/92 groups, respectively.

### TABLE 1
Baseline data by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (CONQUER study)</th>
<th>Long-term treatment (SEQUEL study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo ((n = 994))</td>
<td>Placebo ((n = 227))</td>
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<tr>
<td></td>
<td>7.5/46 ((n = 498))</td>
<td>7.5/46 ((n = 153))</td>
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<tr>
<td></td>
<td>15/92 ((n = 995))</td>
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<tr>
<td>Age (y)</td>
<td>51.2 ± 10.3(^2)</td>
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<tr>
<td>Women ([n %()])</td>
<td>695 (69.9)</td>
<td>147 (64.8)</td>
</tr>
<tr>
<td>Race ([n %()])</td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>861 (86.6)</td>
<td>198 (87.2)</td>
</tr>
<tr>
<td>African</td>
<td>114 (11.5)</td>
<td>28 (12.3)</td>
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<td>Asian</td>
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<td>1 (0.7)</td>
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<td>American Indian or Alaskan native</td>
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<td>0.9 (0.7)</td>
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<td>0</td>
</tr>
<tr>
<td>Other</td>
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</tr>
<tr>
<td>Weight (kg)(^4)</td>
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<td>113.0 ± 12.5</td>
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<td>Blood pressure (mm Hg)(^4)</td>
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<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.9 ± 13.5</td>
<td>128.5 ± 14.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81.1 ± 9.2</td>
<td>79.9 ± 9.7</td>
</tr>
<tr>
<td>Heart rate (bpm)(^4)</td>
<td>72.1 ± 9.9</td>
<td>70.6 ± 10.5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)(^4)</td>
<td>205.3 ± 41.7</td>
<td>203.5 ± 41.9</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)(^5)</td>
<td>123.8 ± 36.1</td>
<td>123.1 ± 36.6</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)(^6)</td>
<td>48.8 ± 13.8</td>
<td>49.5 ± 14.7</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)(^7)</td>
<td>163.6 ± 75.8</td>
<td>154.4 ± 66.7</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)(^8)</td>
<td>106.5 ± 23.5</td>
<td>109.3 ± 24.4</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)(^9)</td>
<td>5.9 ± 0.8</td>
<td>6.0 ± 0.9</td>
</tr>
<tr>
<td>Subjects with ([n %()])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression history</td>
<td>179 (18.0)</td>
<td>42 (18.5)</td>
</tr>
<tr>
<td>Hypertension(^10)</td>
<td>524 (52.7)</td>
<td>72 (46.4)</td>
</tr>
<tr>
<td>Hypertriglyceridemia(^11)</td>
<td>354 (35.6)</td>
<td>30 (31.4)</td>
</tr>
<tr>
<td>T2D(^12)</td>
<td>159 (16.0)</td>
<td>26 (17.0)</td>
</tr>
</tbody>
</table>

\(^1\) Baseline values for SEQUEL subjects were measured at the start of CONQUER. bpm, beats per minute; PHEN/TPM CR, controlled-release phentermine/topiramate; T2D, type 2 diabetes; 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; 15/92, 15 mg phentermine/92 mg controlled-release topiramate.

\(^2\) Mean ± SD (all such values).

\(^3\) Among CONQUER subjects, baseline weight, BMI, waist circumference, blood pressure, and heart rate values were missing for 2 subjects: one in the placebo group and one in the 15/92 group.

\(^4\) Among CONQUER subjects at baseline, there were missing values for 2 subjects (one for placebo, one for 15/92).

\(^5\) Among CONQUER subjects at baseline, there were missing values for 7 subjects (4 for placebo, 3 for 15/92).

\(^6\) Among CONQUER subjects at baseline, there were missing values for 2 subjects (one for placebo, one for 15/92).

\(^7\) Among CONQUER subjects at baseline, there were missing values for 2 subjects (one for placebo, one for 15/92).

\(^8\) Among CONQUER subjects at baseline, there were missing values for 11 subjects (4 for placebo, 7 for 15/92).

\(^9\) Among CONQUER subjects at baseline, there were missing values for 9 subjects (5 for placebo, 4 for 15/92).

\(^10\) Subjects with hypertension were those with systolic blood pressure \(\geq 140\) and \(\leq 160\) mm Hg (\(\geq 130\) and \(\leq 160\) mm Hg if diabetic) or diastolic blood pressure \(\geq 90\) and \(\leq 100\) mm Hg (\(\geq 85\) and \(\leq 100\) mm Hg if diabetic) or who were taking \(\geq 2\) antihypertensive medications and had blood pressure \(<140/90\) mm Hg.

\(^11\) Subjects with hypertriglyceridemia were those with fasting triglycerides between 200 and 400 mg/dL or who were taking \(\geq 2\) lipid-lowering medications and had fasting triglycerides of \(<200\) mg/dL.

\(^12\) Subjects with diabetes were those with an established diagnosis of T2D, managed with lifestyle measures, metformin therapy, or both.
Lipid variables

Treatment with 7.5/46 and 15/92 led to progressively greater reductions in triglycerides and greater increases in HDL cholesterol than did placebo, despite the fact that the placebo group required a markedly greater net increase in the number of lipid-lowering medications used compared with the PHEN/TPM CR groups. LDL cholesterol decreased in all treatment arms, with the greatest reduction in the placebo group, whereas reduction in non–HDL cholesterol was similar in all groups (Figure 4, C and D). Similar to the changes seen in concomitant antihypertensive medication use, more subjects receiving PHEN/TPM CR had a decrease in lipid-lowering medications than did subjects receiving placebo: 3.1% (n = 7), 5.9% (n = 9), and 5.8% (n = 17) for the placebo, 7.5/46, and 15/92 groups, respectively. Conversely, 20.3% (n = 46) of placebo-treated subjects increased lipid-lowering medication use compared with 11.1% (n = 17) in the 7.5/46 group and 10.5% (n = 31) in the 15/92 group.

Glycemic variables

PHEN/TPM CR treatment was associated with beneficial effects on glucose homeostasis at 108 wk (Table 2). When compared with placebo, treatment with PHEN/TPM CR reduced both fasting glucose and fasting insulin concentrations, which is indicative of an improvement in insulin sensitivity (23). In subjects without T2D at baseline, the favorable effects of weight loss on insulin sensitivity and glycemia were associated with decreased progression to T2D during the 2-y course of this study. The annualized incidence rates for progression to T2D...
among subjects without diabetes at baseline were 3.7%, 1.7%, and 0.9% in the placebo, 7.5/46, and 15/92 treatment groups, respectively. These data indicate a 54% reduction in the progression to T2D in subjects receiving 7.5/46 and a 76% reduction in subjects taking 15/92 compared with placebo (Figure 5).

When only subjects with T2D at baseline were considered, the initial mean Hb $\text{A}_1c$ at week 0 was similar in each of the 3 treatment groups (6.9% in subjects randomly assigned to placebo, 7.3% in the 7.5/46 treatment arm, and 6.9% in the 15/92 treatment arm). At 108 wk, Hb $\text{A}_1c$ did not substantially change from baseline in the placebo group (0%), whereas treatment with 7.5/46 and 15/92 led to reductions of 0.4% and 0.2%, respectively (Figure 4E). In these actively managed subjects, these reductions in Hb $\text{A}_1c$ were achieved without any net increase in

FIGURE 4. Effects of PHEN/TPM CR on cardiometabolic variables. LS mean changes (95% CI) in (A) blood pressure, (B) antihypertensive medications, (C) lipid variables, (D) lipid-lowering medications, (E) Hb $\text{A}_1c$, and (F) antidiabetic medications from baseline (week 0) to week 108 (ITT-LOCF). Changes in Hb $\text{A}_1c$ represent the T2D subgroup. Changes in concomitant medications represent the safety study. Standardized lifestyle intervention was used across all treatment groups. *Percentage increase minus percentage decrease; $P < 0.05$ for between-group differences. $P < 0.01$ compared with placebo; $P < 0.0001$ compared with placebo. Hb $\text{A}_1c$, glycated hemoglobin; HDL-C, HDL cholesterol; ITT, intent-to-treat; LDL-C, LDL cholesterol; LOCF, last observation carried forward; LS, least-squares; PHEN/TPM CR 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; PHEN/TPM CR 15/92, 15 mg phentermine/92 mg controlled-release topiramate; T2D, type 2 diabetes.
antidiabetic medications in the 15/92 group [3.1% (n = 9) experienced a decrease and 3.1% (n = 9) experienced an increase] and a small net increment in the 7.5/46 group [0.7% (n = 1) decreased and 2.6% (n = 4) increased use] compared with larger net increases in medications required in the placebo group [1.3% (n = 3) decreased and 8.4% (n = 19) increased use; Figure 4F].

Analysis of all primary and secondary variables by using multiple imputation instead of LOCF to accommodate for dropout yielded results consistent with those presented above (see Supplemental Tables 1 and 2 under “Supplemental data” in the online issue). Similar results were also observed in the set of subjects who completed the study while still taking the study drug (see Supplemental Tables 3 and 4 under “Supplemental data” in the online issue).

Safety and tolerability

AEs

PHEN/TPM CR was well tolerated over 108 wk, as shown by the TEAEs (Table 3). The most commonly reported TEAEs were upper respiratory tract infection, constipation, paraesthesia, sinusitis, and dry mouth. The type of TEAEs occurring between weeks 56 and 108 were similar to those reported in the overall CONQUER sample from weeks 0 to 56 (17). However, as delineated in Table 3, the incidence of individual TEAEs was markedly lower in the second year (weeks 56–108) than in the first year (weeks 0–56). The incidence of SAEs from weeks 0 to 108 was 6.2% for placebo, 5.9% for 7.5/46, and 8.1% for 15/92. The incidence of SAEs during the period of study extension

![TABLE 2](image)

**Effects on glucose homeostasis at week 108 (ITT-LOCF)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 227)</th>
<th>7.5/46 (n = 153)</th>
<th>15/92 (n = 295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>109.3 ± 24.37²</td>
<td>110.7 ± 25.28</td>
<td>108.2 ± 24.05</td>
</tr>
<tr>
<td>LS change at 108 wk</td>
<td>3.7 (0.8, 6.5)³</td>
<td>0.1 (−3.4, 3.7)</td>
<td>−1.2 (−3.8, 1.4)</td>
</tr>
<tr>
<td>P value vs placebo</td>
<td>N/A</td>
<td>0.0872</td>
<td>0.0048</td>
</tr>
<tr>
<td>Fasting insulin (μIU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.5 ± 12.01</td>
<td>16.8 ± 12.25</td>
<td>17.7 ± 14.61</td>
</tr>
<tr>
<td>LS change at 108 wk</td>
<td>−2.6 (−3.9, −1.3)</td>
<td>−5.3 (−6.9, −3.7)</td>
<td>−5.2 (−6.4, −4.0)</td>
</tr>
<tr>
<td>P value vs placebo</td>
<td>N/A</td>
<td>0.0051</td>
<td>0.0012</td>
</tr>
<tr>
<td>Hb A₁c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.0 ± 0.90</td>
<td>6.0 ± 0.90</td>
<td>6.0 ± 0.85</td>
</tr>
<tr>
<td>LS change at 108 wk</td>
<td>0.2 (0.09, 0.2)²</td>
<td>0.01 (−0.08, 0.1)</td>
<td>0.00 (−0.07, 0.07)</td>
</tr>
<tr>
<td>P value vs placebo</td>
<td>N/A</td>
<td>0.0042</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

¹ Values represent changes from baseline (week 0) to week 108 (ITT-LOCF). Hb A₁c, glycated hemoglobin; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least-squares; N/A, not available; PHEN/TPM CR, controlled-release phentermine/topiramate; 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; 15/92, 15 mg phentermine/92 mg controlled-release topiramate.
² Mean ± SD (all such values).
³ Mean; 95% CI in parentheses (all such values).

![FIGURE 5](image)

**FIGURE 5.** Annualized incidence rate for progression to T2D. Data represent subjects without T2D at baseline. Standardized lifestyle intervention was used across all treatment groups. *P = 0.1514 compared with placebo; †P = 0.0078 compared with placebo. PHEN/TPM CR 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; PHEN/TPM CR 15/92, 15 mg phentermine/92 mg controlled-release topiramate; T2D, type 2 diabetes.
(weeks 56–108) was also similar across treatment groups: 4.0%, 2.6%, and 4.1% for placebo, 7.5/46, and 15/92, respectively—none of which was reported by investigators to be related to study treatment. The percentage of subjects discontinuing due to AEs by week 108 was also similar across treatment groups: 3.1%, 4.5%, and 4.4% of subjects in the placebo, 7.5/46, and 15/92 arms, respectively (Figure 1). There were no deaths in the extension study. During SEQUEL, there were 2 pregnancies, one carried to term in the 15/92 group and one resulting in miscarriage at ~6 wk gestation in the placebo group. The pregnancy that was carried to full term resulted in a healthy macrosomic infant with no observed teratogenic effects.

**Physical examination and laboratory variables**

The reductions in blood pressure at week 108 (Figure 4A) were accompanied by a mean increase in heart rate of 0.4 bpm in placebo subjects, 1.3 bpm in 7.5/46 subjects, and 1.7 bpm in 15/92 subjects; there were no AEs reported that were relevant to changes in heart rate, and there were no associated adverse clinical sequelae. No dose-related changes were observed in shift summaries of selected laboratory variables, and no subjects experienced an SAE or discontinued the study drug due to laboratory abnormalities. At week 108, there was a greater increase in serum bicarbonate with placebo than with PHEN/TPM CR. The mean changes in bicarbonate from baseline to week 108 were 2.2, 0.7, and 0.2 mEq/L for placebo, 7.5/46, and 15/92, respectively (baseline mean bicarbonate concentration was 26.5 mEq/L in all 3 treatment groups). Although absolute changes were small, more subjects treated with PHEN/TPM CR experienced a decrease from baseline in serum bicarbonate of >5 mEq/L at 2 consecutive visits during the 2-y study course than did those in the placebo group; this was observed in 4 subjects (1.8%) in the placebo-treated group, 20 (13.1%) in the 7.5/46-treated group, and 48 (16.3%) in the 15/92-treated group over 108 wk. When looking only at weeks 56–108, 7 (4.6%) subjects in the 7.5/46 group and 12 (4.1%) subjects in the 15/92 group were observed to have a >5-mEq/L decrease in serum bicarbonate from baseline compared with 0 (0%) in the placebo arm. The decreases in bicarbonate generally occurred during the first 3 mo of CONQUER, did not require clinical intervention, and were not progressive during the 2-y study, tending to normalize over time.

**Psychiatric effects and suicidal behavior**

There was no increase in serious suicidal ideation or suicidal behavior based on the C-SSRS questionnaire during the 108 wk of observation in subjects treated with PHEN/TPM CR. Six subjects responded “yes” to the C-SSRS categories of suicidal ideation and suicidality (3 placebo-treated subjects, 1 7.5/46-treated subject, and 2 15/92-treated subjects, but all were below the threshold for “serious” as defined by the instrument). There were 5 subjects with worsening suicidal ideation (2 in the placebo-, 1 in

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**TABLE 3**

All adverse events with frequency of ≥5% in any PHEN/TPM CR group<sup>1</sup>

<table>
<thead>
<tr>
<th></th>
<th>Weeks 0–56</th>
<th></th>
<th></th>
<th>Weeks 56–108</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHEN/TPM CR</td>
<td>Placebo (&lt;n = 227&gt;)</td>
<td>7.5/46 (&lt;n = 153&gt;)</td>
<td>15/92 (&lt;n = 295&gt;)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (7.1)</td>
<td>25 (16.3)</td>
<td>62 (21.0)</td>
<td>7 (3.1)</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>6 (2.6)</td>
<td>21 (13.7)</td>
<td>62 (21.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5 (2.2)</td>
<td>21 (13.7)</td>
<td>59 (20.0)</td>
<td>1 (0.4)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>47 (20.7)</td>
<td>23 (15.0)</td>
<td>55 (18.6)</td>
<td>42 (18.5)</td>
<td>26 (17.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>35 (15.4)</td>
<td>20 (13.1)</td>
<td>39 (13.2)</td>
<td>26 (11.5)</td>
<td>13 (8.5)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4 (1.8)</td>
<td>18 (11.1)</td>
<td>39 (13.2)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (8.4)</td>
<td>17 (11.1)</td>
<td>39 (13.2)</td>
<td>18 (7.9)</td>
<td>12 (7.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (9.3)</td>
<td>8 (5.2)</td>
<td>28 (9.5)</td>
<td>6 (2.6)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>15 (6.6)</td>
<td>12 (7.8)</td>
<td>24 (8.1)</td>
<td>8 (3.5)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (5.3)</td>
<td>14 (9.2)</td>
<td>21 (7.1)</td>
<td>3 (1.3)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>19 (8.4)</td>
<td>11 (7.2)</td>
<td>21 (7.1)</td>
<td>7 (3.1)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (2.6)</td>
<td>9 (5.9)</td>
<td>20 (6.8)</td>
<td>2 (0.9)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (5.7)</td>
<td>5 (3.3)</td>
<td>19 (6.4)</td>
<td>4 (1.8)</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8 (3.5)</td>
<td>9 (5.9)</td>
<td>17 (5.8)</td>
<td>7 (3.1)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (4.9)</td>
<td>7 (4.6)</td>
<td>17 (5.8)</td>
<td>2 (0.9)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>6 (2.6)</td>
<td>7 (4.6)</td>
<td>17 (5.8)</td>
<td>4 (1.8)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20 (8.8)</td>
<td>13 (8.5)</td>
<td>13 (4.4)</td>
<td>14 (6.2)</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>Influenza</td>
<td>11 (4.9)</td>
<td>11 (7.2)</td>
<td>13 (4.4)</td>
<td>8 (3.5)</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11 (4.9)</td>
<td>8 (5.2)</td>
<td>13 (4.4)</td>
<td>13 (5.7)</td>
<td>14 (9.2)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>12 (5.3)</td>
<td>3 (2.0)</td>
<td>12 (4.1)</td>
<td>6 (2.6)</td>
<td>2 (1.3)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Preferred terms were defined by the MedDRA Coding Dictionary, version 10.1 (26). PHEN/TPM CR, controlled-release phentermine/topiramate; 7.5/46, 7.5 mg phentermine/46 mg controlled-release topiramate; 15/92, 15 mg phentermine/92 mg controlled-release topiramate.
the 7.5/46-, and 2 in the 15/92-treated groups). During the 2-y period, the incidence of reported anxiety-related AEs correlated with increasing dose: 3.1%, 6.5%, and 9.5% for placebo, 7.5/46, and 15/92 arms, respectively. Most anxiety events were mild in severity. Three subjects in the 15/92 group experienced a severe anxiety-related TEAE, with one subject discontinuing treatment. There were no anxiety-related SAEs. The occurrence of depression-related TEAEs was comparable in the placebo (7.9%) and 15/92 (8.1%) groups and occurred at a lower rate in the 7.5/46 group (3.9%).

**DISCUSSION**

The previously published CONQUER study reported that treatment of overweight and obese adults with PHEN/TPM CR as an adjunct to lifestyle intervention promoted weight loss and reduced manifestations of cardiometabolic disease over 56 wk when compared with lifestyle intervention plus placebo (17). This extension study, SEQUEL, maintained the blinded treatment groups for an additional 52 wk and showed that these beneficial therapeutic effects were sustained during a 2-y period.

After 108 wk, the addition of PHEN/TPM CR to a standardized lifestyle modification led to substantial weight loss that coincides with the weight-loss target of 10% recommended by the National Heart, Lung, and Blood Institute for overweight and obese individuals (8). The percentage changes in body weight from baseline were –1.8%, –9.3%, and –10.5% in subjects treated with placebo, 7.5/46, and 15/92, respectively (ITT-LOCF); and 10% weight loss was achieved by >50% of PHEN/TPM CR–treated subjects, whereas <12% of subjects receiving placebo met this goal. Importantly, both doses of PHEN/TPM CR were significantly more effective than placebo regardless of baseline BMI and were similarly effective at baseline BMI values extending from <30 to <40. In those subjects with class III obesity (BMI ≥40), the 15/92 dose produced an even more pronounced degree of weight loss, exceeding that observed with 7.5/46. These data are indicative of therapeutic efficacy for PHEN/TPM CR over a wide range of initial BMI, although higher doses might be more effective in cases of more severe obesity.

By design, subjects in the SEQUEL study were highly affected by cardiometabolic disease, and many were treated with numerous concomitant medications to control blood pressure, lipid variables, and glycemic variables, which were actively managed throughout the trial. PHEN/TPM CR improved these comorbidities and decreased the need for associated medications in comparison with the placebo group. For example, after 2 y of therapy, diastolic and systolic blood pressure showed equal reductions in the placebo and PHEN/TPM CR groups; however, this was accompanied by a net decrease in concomitant antihypertensive medication use in PHEN/TPM CR treatment groups, whereas antihypertensive medications were increased in the placebo group. Reducing the need for medications used to specifically control these comorbidities not only reduces the medication burden associated with cardiometabolic disease but could also improve subject compliance by decreasing their medication regimen complexity and reducing the overall treatment costs (24, 25).

When compared with placebo, PHEN/TPM CR–treated subjects exhibited lower fasting glucose and fasting insulin values compared with subjects receiving placebo, which is indicative of an improvement in insulin sensitivity (23), and experienced greater reductions in waist circumference, a measure of central adiposity related to increased morbidity and mortality (21, 22, 27). Because insulin resistance and central adiposity are integral to the development of cardiometabolic disease, it appears that PHEN/TPM CR–induced weight loss is accompanied by favorable effects on pathophysiologic processes that could reduce risk of metabolic syndrome, T2D, and CVD (8, 21, 22). In support of this, we observed that, among subjects without T2D at baseline, treatment with PHEN/TPM CR reduced progression to T2D by 54% with the 7.5/46 dose and by 76% with the 15/92 dose when compared with the placebo intervention. Previous studies have shown that lifestyle-intervention programs reduce progression to T2D among high-risk individuals with impaired glucose tolerance, and the degree of protection correlated with the amount of weight loss (28–31). Along these same lines, incremental improvements in cardiometabolic disease risk factors have also been shown to correlate with an increasing degree of weight loss, together with associated reductions in morbidity and mortality (5, 32, 33).

Approximately 20% of subjects had T2D at study entry and had been treated with lifestyle modifications alone, single-agent metformin, or both. In the T2D subgroup, PHEN/TPM CR led to significant reductions in Hb A₁c after 2 y compared with placebo. Improvements in fasting glucose, fasting insulin, and Hb A₁c were experienced without any net change in concomitant antidiabetic medications in subjects with T2D who were randomly assigned to 15/92 and a modest net increase in medications in those assigned to 7.5/46, whereas the placebo group experienced a substantial net increase in required antidiabetic medications to achieve guideline-dictated goals. Thus, weight loss associated with PHEN/TPM CR had a favorable impact on glycemic control in the subjects with T2D, without a need for added oral hypoglycemic agents.

Discontinuation rates during the extension study were similar between placebo and PHEN/TPM CR–treated subjects. The type of AEs reported during weeks 56–108 in the extension study were similar to those in the first 56 wk of the study; however, the incidence rates were lower in the second year of the study. In some subjects, PHEN/TPM CR treatment was associated with reductions in serum bicarbonate, particularly in the first 3 mo of the study, which is likely a manifestation of the carbonic anhydrase activity of topiramate. However, this effect was not progressive in these subjects, and serum bicarbonate tended to return toward normal during the remaining 2 y of the study without the need for clinical intervention. PHEN/TPM CR increased mean heart rate by 1.3–1.7 bpm over baseline; this increase was not accompanied by any related AE reporting and was accompanied by reductions in systolic and diastolic blood pressure. Rigorous assessments of suicidality were conducted by using the C-SSRS, which showed no increase in suicidal ideation associated with PHEN/TPM CR and no difference from placebo in AE reporting for incident depression. PHEN/TPM CR was associated with a dose-dependent increase in the incidence of anxiety. However, these anxiety-related TEAEs were mostly mild in nature and led to only one discontinuation of study drug. Finally, during the 108-wk trial, there were 2 pregnancies, with one pregnancy carried to term in a subject who was randomly assigned to 15/92, resulting in a healthy infant without any observed congenital malformations.
Limitations of this study were that not all CONQUER subjects were eligible to enroll into the SEQUEL extension because only high-enrolling centers were used. Furthermore, participation in the second-year extension study was optional. These aspects may have resulted in bias toward the inclusion of subjects with positive treatment outcomes, because one would expect that subjects who achieved satisfactory weight loss would be more likely to enroll for a second year. However, the baseline clinical characteristics of the subgroup entering the SEQUEL study were similar to those of the CONQUER cohort, with the exception of a greater percentage of subjects with T2D in SEQUEL. Another point pertains to the higher rate of subjects lost to follow-up in the 15/92 arm than in the placebo or 7.5/46 arms. Because the real reason for study discontinuation in these subjects is not known, this could result in an underestimation of important reasons for patients dropping out, including AEs or lack of efficacy. A third limitation of this study is that hyperglycemia, high blood pressure, and dyslipidemia were actively managed on the basis of national treatment guidelines, resulting in the confounding impact of medication changes on the secondary cardiometabolic variables. Actual treatment effects may have been different if related medications and doses were required to be fixed, thereby better isolating an effect of PHEN/TPM CR.

Medical options to promote sustained weight loss are limited. The lipase inhibitor orlistat is currently the only approved medication for chronic treatment of obesity in the United States (10). Bariatric surgery is an option for long-term weight loss but is generally limited to selected subjects with complicated or severe obesity because of the inherent risks of invasive surgical procedures and the requirements for long-term medical follow-up (9, 10, 34, 35). Results of this study suggest that PHEN/TPM CR together with lifestyle measures may be an additional therapeutic option for achieving long-term weight-loss in moderately to severely obese subjects.

In conclusion, PHEN/TPM CR used as an adjunct to lifestyle intervention for the treatment of obesity was well tolerated and produced significant, dose-related weight loss that was maintained during a 108-wk period. PHEN/TPM CR was also associated with sustained improvements in the clinical manifestations of weight-related cardiometabolic disease, including hyperglycemia, dyslipidemia, and elevated blood pressure, despite reduced use of concomitant medications. Importantly, these effects of PHEN/TPM CR led to a reduction in the rate of progression to T2D, with the greatest benefits seen in subjects receiving PHEN/TPM CR 15/92. Thus, PHEN/TPM CR may provide a well-tolerated, effective, and sustainable treatment option for obese subjects with cardiometabolic disease. Furthermore, the unmet clinical need for effective weight-loss medications, together with the favorable risk-benefit profile in the current study, suggests that PHEN/TPM CR in conjunction with a lifestyle-intervention program could be a valuable therapeutic approach to counteract increasing rates of obesity and its related complications.

We acknowledge and thank the SEQUEL subjects, investigators, and study coordinators; the Medpace team (study Contract Research Organization); The Lockwood Group (for manuscript development assistance); and Vivus Inc internal contributors.

The authors’ responsibilities were as follows—KMG, DBA, DHR, MS, CAP, WWD, and CHB: designed the research; WTG, KMG, and ML: conducted the research; WTG, KMG, DBA, DHR, CAP, MS, WWD, and CHB: analyzed and interpreted data; WTG, DHR, ML, KMG, DBA, CAP, MS, WWD, and CHB: drafted and edited the manuscript; and MS: had primary responsibility for final content and is the guarantor of the manuscript, having had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. The external authors as well as those employed by the funding sponsor participated in protocol design, data analyses, interpretation, and preparation of the manuscript. W TG participated in clinical trials with Merck & Co, Inc; Amylin Pharmaceuticals; Vivus Inc; Abbott; and Daiichi-Sankyo. He has served as an advisor, consultant, and/or speaker for Abbott Nutrition, Daiichi-Sankyo, Johnson & Johnson, LipoScience, Tethys, and Vivus Inc. He is a scientific advisory board member for Daiichi-Sankyo and Tethys, and he holds stock in Bristol-Myers Squibb; Isis/Genzyme; Merck & Co, Inc; Pfizer Inc; Novartis Pharmaceuticals Corp; and Vivus Inc. DHR served as a consultant for Vivus but did not receive any payment for service. ML is a scientific advisory board member for Vivus Inc. KMG received research support from Forest Laboratories, the National Institute of Diabetes and Digestive and Kidney Diseases, and Vivus Inc and owns stock in Orexigen Therapeutics. DBA received grants, honoraria, donations, and consulting fees from numerous food, beverage, and pharmaceutical companies, as well as other commercial and nonprofit entities with interests in obesity, including but not limited to Arena Pharmaceuticals, Jason Pharmaceuticals Inc, Pfizer Inc, and Vivus Inc. He served as a board member for the Pfizer Inc VPO program. WWD, CHB, and CAP are employees of Vivus Inc. MS was employed as the lead statistician for Medpace Inc, the study Contract Research Organization, throughout the study design, execution, and analysis; he had no additional conflicts to disclose.

REFERENCES


November 30, 2020

Ms. Kimberly Anderson, Esq.
State Medical Board of Ohio
30 East Broad Street
3rd Floor
Columbus, OH 43215

RE: Rules: 4731-11-04 and 4731-11-04.1

Submitted electronically via: Kimberly.Anderson@med.ohio.gov

Dear Ms. Anderson:

Cleveland Clinic is a not-for-profit, integrated healthcare system dedicated to patient-centered care, teaching and research. With a footprint in Northeast Ohio, Florida and Nevada, Cleveland Clinic Health System operates 18 hospitals with approximately 4,900 staffed beds, 21 outpatient Family Health Centers, 11 ambulatory surgery centers and numerous physician offices. Cleveland Clinic employs over 3,400 salaried physicians and scientists. Last year, our system cared for 2.4 million unique patients, including 10 million outpatient visits and 309,000 hospital admissions and observations.

Below are our comments in respect to the above captioned rule.

Cleveland Clinic has been caring for patients struggling with obesity for many years. Every day, Cleveland Clinic sees nearly 14,000 unique patients who suffer with obesity (BMI >30 kg/m²). Of those, 1,500 have a BMI over 35 kg/m² and 1,000 have a BMI at or above 40kg/m². To support these patients, Cleveland Clinic employs more than 40 physicians who are specifically licensed in obesity medicine and who are certified by the American Board of Obesity Medicine. Finally, Cleveland Clinic established a fellowship in obesity medicine that will begin in 2021. Today there are 17 medical subspecialty programs in obesity medicine and more than 4,000 certified ABOM in the United States. Cleveland Clinic also employs more than 10 advanced practice providers (APPs) whose practice is dedicated to seeing patients with obesity and who are licensed by the Ohio State Medical Board to prescribe anti-obesity medications.

Cleveland Clinic appreciates the recent meeting with representatives from the State Medical Board on November 23, 2020 to discuss the proposed amendments to rule OAC 4731-11-04 and 4731-11-04.1. This is an important step towards the improving the appropriate treatments for patients with obesity. As a follow-up to our discussion last week, we offer below general comments on the Board’s regulation of anti—obesity medications, as well as specific comments on the proposed rule changes.

First and foremost we want to emphasize that obesity is a chronic disease and is associated with more than 200 other medical comorbidities including diabetes, fatty liver disease, sleep apnea, hypertension, along with an increased mortality. Historically, the disease of obesity was thought to be a lifestyle...
choice, a behavior problem that exists in weak individuals who don’t have the coping mechanisms or
gwillpower to resist high-calorie foods and are too lazy to pursue routine exercise. It made sense at that
time for physicians to recommend that everyone “restrict” food intake and to treat “overeating” with
appetite suppressants, as if all patients with obesity have a problem with hunger. The belief was that
patients should be able to lose weight and keep it off with behavioral changes. However, in the
scientific world, this belief is not commonly accepted. We understand the disease of obesity as the
failure of normal weight and energy regulatory mechanisms and that appetite is tightly regulated
through metabolic adaptation. The cornerstone for treatment of obesity is behavioral modification
and lifestyle changes, including physical activity, sleep and stress. We know it is difficult to maintain
weight loss with lifestyle intervention alone, and many regain their lost weight, in part due to adaptive
physiologic responses (e.g. a decrease in metabolism and an increased appetite) that occur with weight
loss.

Anti-obesity medications (AOM) are not “diet pills” or “appetite suppressants” and are often required
as adjuvant therapy for weight loss induction and maintenance; these medications have the potential
to augment further weight loss when combined with a lifestyle intervention and are paramount for
prescribed AOM not only in our practice, but in the United States is Phentermine. Phentermine is
not only effective, it is also inexpensive, safe, and has a very low potential of addiction. Limiting the
use of Phentermine to three months is simply not a current standard of practice for the chronic disease
management of obesity and thus clearly not in the best interests of patients. This is especially
detrimental to those of low socioeconomic status and others whose insurance does not cover AOMs,
who could benefit from the long-term use of this affordable and effective medication. Over the last
two decades, as more knowledge of the disease of obesity is understood, the management of obesity
has shifted away from using AOMs for short-term weight loss and adapted a chronic disease
management model which incorporates combination therapies of behavioral, pharmacological and
surgical interventions to achieve sustainable weight loss in the setting of metabolic adaptation. Obesity
as a medical specialty is growing exponentially nationwide and its care has shifted since these rules
were written many years ago.

Lastly, the emergence of the COVID-19 pandemic has presented an unprecedented challenge to our
healthcare system. Many institutions have rapidly changed their healthcare delivery models by quickly
adopting robust telemedicine offerings to patients. Telemedicine is a growing segment of medical care
with the potential to improve access by removing geographic barriers and extending care to home.
This is accomplished by using new technologies via a modality that patients are already using in their
personal lives. Telemedicine has the potential to decrease costs and increase access while maintaining
quality of care. The federal government and the Medical Board recently relaxed standards for
prescribing controlled substances, so providers are now able to prescribe Phentermine (and other anti-
obesity medications) via telemedicine. We urge the Board to make permanent the option to prescribe
anti-obesity medications via telemedicine, which would greatly benefit the care of patients suffering
with obesity.

Below we have included comments on specific sections of each of the rules.

4731-11-04 (Rule Title) Controlled substances: utilization of short term anorexiant for weight
reduction sympathomimetics for overweight and obesity.
Cleveland Clinic Comments
We suggest that the title of the rule should be changed to read Controlled substances: utilization of sympathomimetics for overweight and obesity.

4731-11-04 Controlled substances: utilization of short term anorexiants for weight reduction

Proposed Language
4731-11-04(C)(1) The physician shall personally meet face-to-face or via telemedicine with the patient, at a minimum, every thirty days when controlled substances are being utilized for weight reduction, and shall record in the patient record information demonstrating the patient's continuing efforts to lose weight, the patient's dedication to the treatment program and response to treatment, and the presence or absence of contraindications, adverse effects, and indicators of possible substance abuse that would necessitate cessation of treatment utilizing controlled substances.

Cleveland Clinic Comments
We suggest that the Medical Board allow patients to meet with their physicians via telemedicine as patients oftentimes find it difficult to come to the office because they are struggling to get time off of work or they face challenges with transportation. It should be noted that patients with severe obesity may be reluctant to come to hospitals as they may be challenged with mobility, the lack of an appropriate physical environment (e.g. waiting room chairs, exam tables, etc.) in clinics, or stigmatizing encounters. Providing patients with the option of telemedicine will alleviate these concerns and remove a substantial barrier to their success while still maintaining the important patient-physician relationship.

Proposed Language
4731-11-04(C)(2) The controlled substance short term anorexiant is prescribed strictly in accordance with the F.D.A. approved labeling. If the F.D.A. approved labeling of the controlled substance short term anorexiant being utilized for weight loss states that it is indicated for use for "a few weeks," the total course of treatment using that controlled substance shall be closely monitored for the first three months of treatment not exceed twelve weeks. That time period includes any interruption in treatment that may be permitted under paragraph (C)(3) of this rule.

Cleveland Clinic Comments: We suggest the above modifications be made to the current language. There are a number of studies (please see relevant studies cited at the end of this document) that demonstrate that addiction to these anti-obesity medications is low and their efficacy in treatment is high. Further, studies also show that patients who are able to stay on the medications are able to maintain their weight loss. The requirement that patients only use these for short-term treatment of their obesity is not a standard of care and would continue to be a substantial barrier to care for those patients who actually respond well to the medications. Stopping an effective obesity treatment is counterintuitive. We don’t do this in other chronic diseases, therefore we should not consider short term treatment models for obesity.

Proposed Language
4731-11-04 (C)(3) A physician shall not initiate a course of treatment utilizing a controlled substance short term anorexiant for purposes of weight reduction if the patient has received any controlled substance for purposes of weight reduction within the past six months. However, the physician may resume utilizing a controlled substance short term anorexiant following an interruption of treatment of more than seven days if the interruption resulted from one or more of the following:
(a) Illness of or injury to the patient justifying a temporary cessation of treatment; or
(b) Unavailability of the physician; or
(c) Unavailability of the patient, if the patient has notified the physician of the cause of the patient's unavailability

4731-11-04 (C)(4) After initiating treatment, the physician may elect to switch to another anti-obesity medication based on sound medical judgment, but the total course of treatment for any short term anorexiant combination of controlled substances each of which is indicated for "a few weeks" shall not exceed twelve weeks.

Cleveland Clinic Comments
As mentioned previously, we believe that references to short-term use of the anti-obesity medications should be modified because studies have demonstrated the long-term safety and efficacy of the medications. The anti-obesity medication called Qsymia which is a combination of Phentermine and Topiramate is approved for chronic treatment of obesity therefore it does not seem logical for Phentermine monotherapy to be restricted.

Proposed Language
4731-11-04 (5) The physician shall not initiate or shall discontinue utilizing all controlled substance short term anorexiants for purposes of weight reduction immediately upon ascertaining or having reason to believe:
(5)(c)
(c) That the patient has failed to lose weight while under treatment with a controlled substance or controlled substances over a period of thirty days during the current course of treatment, which determination shall be made by weighing the patient at least every thirtieth day, except that a patient who has never before received treatment for obesity utilizing any controlled substance who fails to lose weight during the first thirty days of the first such treatment attempt may be treated for an additional thirty days;

Cleveland Clinic Comments
We are concerned that the rule requires patients to be removed from an anti-obesity medication if they do not lose weight. We suggest that this language be removed because in our experience, there may be several other variables (e.g. changes in lifestyle factors including sleep, physical activity, stress and diet, the presence of medications that cause weight gain or the weight trajectory of the patient prior to initiation of an anti-obesity medication) that may confound the weight outcome. For example, some patients prior to starting an anti-obesity medication are rapidly gaining weight and the medication may lead to weight stabilization. In this instance, we believe patients should be allowed to remain on the medication so that they can begin their treatment and move towards weight loss.

4731-11-04.1 Controlled substances: utilization for chronic weight management
Cleveland Clinic Comments
It should be noted that there are several anti-obesity medications (orlistat, naltrexone-bupropion, phentermine-topiramate XR, liraglutide) currently used to treat the chronic disease of obesity. Almost all of these are not controlled substances and therefore should be either described separately or excluded from this rule. These medications should be considered much like any other medication used to treat chronic diseases, for example, anti-hypertensive medications or diabetes medications.
Similar to our comments above, and especially because of what we have learned during the COVID-19 pandemic in terms of the successful use of telemedicine, we believe the Medical Board should include telemedicine as an option for patients to support their weight loss journey.

**Proposed Language**

4731-11-04.1(B)(1) The physician shall meet face-to-face with the patient for the initial visit and at least every thirty days either face-to-face or telemedicine during the first three months of treatment. If the F.D.A. approved labeling for the controlled substance anorexiant anti-obesity medication requires induction of treatment at one dose and an increase to a higher dose after a stated period of less than thirty days, the physician may give the patient a prescription for the higher dose at the initial visit and the first thirty day period then starts from the date the prescription for the higher dose may be filled.

**Other Cleveland Clinic Comments – Phentermine Designation**

We believe that the Medical Board should designate Phentermine as a chronic weight loss medication. We understand the concern of its addiction potential, but there have been no studies that support this statement. Below we have provided our reasoning and supporting research for our position.

Clinical guidelines support long-term use
The 2015 Endocrine Society has clinical guidelines on the pharmacologic management of obesity stating that there is minimal evidence of any serious, long-term side effects with Phentermine and that it is reasonable for clinicians to prescribe Phentermine long-term for the treatment of obesity. The guidelines include safety recommendations for long-term prescribing. The review article below also describes the off-label use of phentermine in clinical practice.

**References**


Hendricks EJ. Off-label drugs for weight management. https://www.dovepress.com/off-label-drugs-for-weight-management-peer-reviewed-article-DMSO Available at: https://www.dovepress.com/off-label-drugs-for-weight-management-peer-reviewedarticle-DMSO

Phentermine has demonstrated safety in long-term use
In a 28 week, randomized, controlled trial comparing phentermine/topirimate extended release (Qsymia® compared to phentermine 15mg daily or topirimate, the 15mg phentermine for 6 months led to 7% weight loss and was safe. This is the same dose available in Qsymia® formulation with is FDA approved for long-term use. Due to the high cost of Qsymia®, it would benefit patients to have phentermine available for long-term use.

**References**

Studies demonstrate long-term safety and efficacy

A retrospective study from an electronic medical record of 13,972 adults comparing those with longer term use to those with short-term use (<3 months) demonstrated that long-term users of phentermine experienced more weight loss: patients using continuously for >12 months experienced 7.4% weight loss, and at 24 months it was much greater than the short-term group. Composite cardiovascular death (CVD) or death outcome was rare (0.3%, 41 deaths) with no significant difference between groups comparing short term, vs long-term use. Patients using phentermine for longer periods experienced greater weight loss that was sustained while staying on the medication.

Reference

Phentermine has demonstrated that it has very low addictive potential.

In the Rule 4731-11-04, one of the current parameters is usage beyond 12 weeks. In the following study, 269 patients were treated for 1.1-21.1 years and the study showed that phentermine did not induce drug cravings or withdrawal symptoms.

Reference

Thank you for conducting a thoughtful process that allows us to provide input on such important issues and for your consideration of this information. Please do not hesitate to contact us if you need additional information.

Sincerely,

Barto Burguera, M.D. Ph.D
Chairman Endocrinology & Metabolism Institute
Professor of Medicine, Cleveland Clinic Lerner College of Medicine

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Director, Obesity EMI Programs

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Clinical Pharmacy Specialist

W. Scott Butsch, M.D. MSc. FTOS
Director of Obesity Medicine, Bariatric and Metabolic Institut
Dear Sirs,

I would like to take an opportunity to comment on the upcoming review for Rule 4731-11-04 and its restrictive nature regarding the long-term use of certain anti-obesity medications such as phentermine, diethylpropion and phendimetrazine.

Since June of 2013, Obesity has been regarded as a multi-faceted chronic disease in need of chronic treatment regimens including diet, exercise, pharmacology and surgery. National organizations such as the Obesity Medicine Association have long advocated for long term use of pharmacotherapy as adjunctive treatment of obesity as part of a comprehensive obesity management program that includes a thorough medical evaluation and lifestyle changes. The data is quite clear that combination treatments of diet exercise and pharmacotherapy are more successful than either diet and exercise or pharmacotherapy alone.
Currently the medication options for treatment of obesity include FDA approved anti-obesity medications such as phentermine, diethylpropion, phendimetrazine, orlistat, Qsymia, contrave and saxenda. As a chronic disease with a high relapse rate when therapy is discontinued, (similar to what is seen in hypertension or hyperlipidemia) obesity requires long term therapies to maintain successful treatment. The current evidence points to issues with “set point” where the hypothalamus protects the current weight even if it is not a healthy one. Thus, weight loss leads to metabolic adaptation to drive the individual back to an unhealthy weight. These homeostatic mechanisms underline the need to utilize chronic therapies to maintain progress towards a healthy weight. (NEJM 10/27/2011 sumithran)

Due to expansion in the understanding of the mechanisms related to appetite regulation and energy homeostasis, across the country the use of anti-obesity medications has changed since their original FDA labeling. The original labeling of short-term appetite suppressant for 12 weeks based on short term studies from 50yrs ago reflect a time where obesity was more poorly understood and not todays knowledge base. The newer generation of anti-obesity medications with their emphasis on long term management reflect that fact.

There are several facts to consider: several of the older medications have been on the US market for more than 50 years with no evidence of harm when prescribed appropriately by trained practitioners whether used short or long term. This is evidenced across the country where these tools are used under physician judgement with consent for off- label use and risk benefit conversations with patients in the context of a comprehensive program. Additionally, newer data suggest better efficacy when medications such as phentermine are used long term up to 2 years. One study showed patients on phentermine for 2 years continuously lost 7.4 percent more weight than those only using medication for 3 months with no increase in adverse outcomes (Obesity March 21, 2019).

Currently Ohio has an obesity rate of 34% by 2019 data and there are concerns that this rate will approach 40% possibly by end of 2020. We know that COVID has an increased mortality in the obese population. We also know that weight loss of 5-10% is recognized in decreasing the health risks for obesity. As an Ohio native, I would advocate that limiting access to potential tools for the treatment of this disease is worrisome for doing more harm than good.
I realize that there are concerns for addiction or addictive behaviors with this class of medication but that appears to be overinflated. Registries in ERs historically have not demonstrated any evidence for high addictive behaviors with this class of medications. In fact, one study published in the International Journal of Obesity did not find any phentermine abuse or psychological addiction even when individuals were on higher than commonly recommended doses and treatment durations of up to 21 years. (International Journal of Obesity (2014) 38,292-298).

Since overweight and obesity are chronic medical conditions, there should be no time limitations on the use of existing pharmacotherapy for obesity. This is under the assumption that the patients have been monitored as recommended by the FDA for the first twelve weeks, evaluated for efficacy and side effect profiles of the therapy. Additionally, continued monitoring is warranted that is individualized to patient’s needs, disease state and comorbid conditions. Continued assessments of medications and dosages for their appropriateness for the patient’s current level of risk associated with the patient’s therapy plan is critical for optimum treatment.

In summary, I urge the state medical board to allow patients with overweight and obesity the opportunity for the same long term treatment options as other chronic diseases. Allowing obesity medicine specialists to utilize phentermine and other short term obesity drugs for long term treatment of this chronic disease would be extremely beneficial step toward the goal of combating obesity here in Ohio. This approach would be more in line with the current knowledge base for the disease of obesity rather than using antiquated rules assigned to a presumed cosmetic issue from the 1950s-1960s. That just makes common sense.

RESPECTFULLY,

BRUCE BARKER MD
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Dear Ms. Anderson:

The Ohio Association of Physician Assistants (OAPA) would like to ONCE AGAIN address rules OAC 4731-11-02, 4731-11-03, 4731-11-04, 4731-11-04.1, 4731-11-07 and 4731-11-11 which the Medical Board is proposing to continue without any changes; and further OAPA would like to submit suggested amendments to 4731-11-04.1.

In 2018, the 132nd General Assembly passed Senate Bill 259 which expands the authority of physician assistants to prescribe drugs and therapeutic devices by eliminating the State Medical Board’s authority to adopt a physician assistant formulary, which in turn expands the supervising physician’s authority and decision-making process in granting physician-delegated prescriptive privileges to physician assistants. OAPA recognizes Senate Bill 259 does not eliminate the Board’s statutory authority to adopt rules in accordance with ORC 4730.39 governing physician-delegated prescriptive authority, provided any rules adopted are consistent with the intent and spirit of the statutes. OAPA believes a physician assistant has the authority to prescribe any drugs or therapeutic devices that are within the supervising physician’s scope of practice in accordance with ORC 4730.41 and 4730.42. Further, OAPA believes the Board should not have authority to promulgate rules that would restrict a supervising physician from delegating to a physician assistant the responsibility of prescribing, administering and/or monitoring the therapeutic efficacy of any drug or therapeutic device the supervising physician is authorized to prescribe within their scope of practice that have not been specifically restricted by federal law.

OAPA could not find any federal rules and regulations that restricts a physician assistant from prescribing stimulants or anorexiants for either short-term weight reduction or chronic weight management. Nor could OAPA find any pharmaceutical manufacturers suggestion that only a physician shall be allowed to prescribe anorexiants for the same.

OAC 4730-2-07 (A)(3) currently states that physician assistants and supervising physicians must follow the requirements set in all sections of OAC 4731-11. OAPA understands that multiple sections of OAC 4730 of the physician assistant rules have been proposed to be amended to comply with the recent changes made in Senate Bill 259 and are currently being reviewed by the Common Sense Initiative Office, however; the requirements set forth in OAC 4730-2-07 to comply with OAC 4731-11 have not been proposed to be either amended or eliminated.
Therefore, OAPA is suggesting the following amendments to OAC 4731-11-04.1:

**4731-11-04.1 Controlled substances: utilization for chronic weight management.**

(A) A PROVIDER (PHYSICIAN, PHYSICIAN ASSISTANT AND/OR APRN) physician shall determine whether to utilize a controlled substance anorexiant for purposes of chronic weight management as an adjunct to a reduced calorie diet and increased physical activity. The determination shall be made in compliance with the provisions of this rule.

(1) Before initiating treatment utilizing any controlled substance anorexiant, the PROVIDER shall complete all of the following requirements:

(a) Obtain a thorough history;

(b) Perform a physical examination of the patient;

(c) Determine the patient’s BMI;

(d) Review the patient’s attempts to lose weight in the past for indications that the patient has made a substantial good faith effort to lose weight in a regimen for weight reduction based on caloric restriction, nutritional counseling, intensive behavioral therapy, and exercise without the utilization of controlled substance anorexiants. The review shall include available records from the PROVIDER’S own prior treatment of the patient, prior treatment provided by another PROVIDER physician or physician assistant relating to the patient’s use of drugs or alcohol;

(e) Rule out the existence of any recognized contraindications to the use of the controlled substance anorexiant to be utilized;

(f) Assess and document the patient’s freedom from signs of drug or alcohol abuse;

(g) Access OARRS and document in the patient’s record the receipt and assessment of the information received; and

(h) Develop and record in the patient record a treatment plan that includes, at a minimum, a diet and exercise program for weight loss.

(2) The PROVIDER physician shall not initiate treatment utilizing a controlled substance anorexiant upon ascertaining or having reason to believe any one or more of the following:

(a) The patient has a history of, or shows a propensity for, alcohol or drug abuse, or has made any false or misleading statement to the PROVIDER physician or physician assistant relating to the patient’s use of drugs or alcohol;

(b) The patient has consumed or disposed of any controlled substance other than in strict compliance with the treating PROVIDER’S physician’s directions; or

(c) The PROVIDER physician knows or should know the patient is pregnant.

(3) The PROVIDER physician shall not initiate treatment utilizing a controlled substance anorexiant if any of the following conditions exist:

(a) The patient has an initial BMI of less than thirty, unless the patient has an initial BMI of at least twenty-seven with comorbid factors.

(b) The review of the patient’s attempts to lose weight in the past indicates that the patient has not made a substantial good faith effort to lose weight in a regimen for weight reduction based on caloric restriction, nutritional counseling, intensive behavioral therapy, and exercise without the utilization of controlled substance anorexiants. The review shall include available records from the PROVIDER’S own
prior treatment of the patient, prior treatment provided by another PROVIDER; prior participation in a weight-loss program, or prior treatment by a dietitian.

(4) The PROVIDER physician shall prescribe the controlled substance anorexiant strictly in accordance with the F.D.A. approved labeling;

(5) Throughout the course of treatment with any controlled substance anorexiant the PROVIDER physician shall comply with rule 4731-11-11 of the Administrative Code, and the physician assistant shall comply with rule 4730-2-10 of the Administrative Code.

(B) A PROVIDER physician shall provide treatment utilizing a controlled substance anorexiant for weight management in compliance with paragraph (A) of this rule and the following:

(1) The PROVIDER physician shall meet face-to-face with the patient for the initial visit and at least every thirty days during the first three months of treatment. If the F.D.A. approved labeling for the controlled substance anorexiant requires induction of treatment at one dose and an increase to a higher dose after a stated period of less than thirty days, the PROVIDER physician may give the patient a prescription for the higher dose at the initial visit and the first thirty day period then starts from the date the prescription for the higher dose may be filled.

(2) Following the initial visit and two follow-up visits, the treatment may be continued under one of the following means:

(a) The physician may authorize refills for the controlled substance anorexiant up to five times within six months after the initial prescription date;

(b) The treatment may be provided by a physician assistant in compliance with this rule, the supervisory plan or policies of the healthcare facility, and the physician assistant formulary adopted by the board.

(3) When treatment for chronic weight management is provided by a physician assistant, the following requirements apply:

(a) The supervising physician shall personally review the medical records of each patient to whom the physician assistant has prescribed a controlled substance anorexiant following each visit; and

(b) A physician assistant shall not initiate utilization of a different controlled substance anorexiant but may recommend such change for the supervising physician's initiation.

(4) (2) A PROVIDER physician shall discontinue utilizing any controlled substance anorexiant immediately upon ascertaining or having reason to believe:

(a) That the patient has repeatedly failed to comply with the PROVIDER’S physician’s treatment recommendations; or

(b) That the patient is pregnant.

(C) A violation of any provision of this rule, as determined by the board, shall constitute the following as applicable:

(1) For a PROVIDER physician:

(a) “Failure to maintain minimal standards applicable to the selection or administration of drugs,” as that clause is used in division (B)(2) of section 4731.22 of the Revised Code;

(b) “Selling, giving away, personally furnishing, prescribing, or administering drugs for other than legal and legitimate therapeutic purposes,” as that clause is used in division (B)(3) of section 4731.22 of the Revised Code; and
(c) "A departure from, or the failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances, whether or not actual injury to a patient is established," as that clause is used in division (B)(6) of section 4731.22 of the Revised Code.

(2) For a physician assistant:
(a) "A departure from, or failure to conform to, minimal standards of care of similar physician assistants under the same or similar circumstances, regardless of whether actual injury to a patient is established," as that clause is used in division (B)(19) of section 4730.25 of the Revised Code;
(b) "Failure to comply with the requirements of this chapter, Chapter 4731. of the Revised Code, or any rules by the board," as that clause is used in division (B)(2) of section 4730.25 of the Revised Code; and
(c) "Violating or attempting to violate, directly or indirectly, or assisting in or abetting the violation of, or conspiring to violate, any provision of this chapter, Chapter 4731. of the Revised Code, or the rules adopted by the board," as that clause is used in division (B)(3) of section 4730.25 of the Revised Code.

Note: OAPA has not suggested inserting the terms "physician assistant" in every section of OAC 4731-11 because the requirements set forth in OAC 4730-2.07 clearly imply that every standard of care a physician shall be held to when prescribing controlled substances, a physician assistant should be held to the same standards. And, as physician assistant is currently included in OAC 4731-11-04.1 (A) (2) (a) and (5), (B)(2)(a)(b) and (3)(a)(b), OAPA believes it is necessary to amend by deleting these subsections as to keep the language consistent throughout all sections of OAC 4731-11.

The passage of Senate Bill 259 has greatly expanded Physician Assistant scope of practice and prescriptive authority to be equivalent to and consistent with their supervising physician scope of practice. There are no citation in either ORC 4730 or OAC 4730 that specifically requires a supervising physician to "personally review the medical records of each patient to whom the physician assistant has prescribed a controlled substance anorexiant following each visit", or for any other particular type of patient care service, condition, diagnosis, drugs and therapeutic devices or treatment. The responsibilities of the supervising physician are clearly delineated in ORC 4730.21. OAPA believes the language in OAC 4731-11-04.1 requiring a physician to "personally review each medical record for each visit" is overly restrictive and inconsistent with the intent of ORC 4730.21. OAPA also believes the current language in OAC 4731-11-04.1 has already caused confusion amongst some physicians and administrators that have questioned if physician assistants are not mentioned in the other sections of OAC 4731-11 are they excluded from being able to be delegated the authority to prescribe stimulants and/or anorexiant as described in OAC 4731-11-03 and OAC 4731-11-04.

In conclusion, OAPA believes to achieve clarity with our regulatory terminology in Ohio, future consideration should be the utilization of more generic term such as practitioner, prescriber, provider or prescribing provider when crafting new language for Ohio statutes or rules governing the prescriptive authority and/or scope of practice for physicians, physician assistants and advanced practice registered nurses. The Medical Board’s request for review OAC 4731-11 has clearly evoked the need to consider making these changes.
If it has not been done already, OAPA respectfully requests this proposed rule be reviewed by the Physician Assistant Policy Committee of the Medical Board so they may make recommendations to the board in accordance with ORC 4730.06 (A) (2). OAPA greatly appreciate the opportunity to comment on these proposed rules. If you have any questions or need further information, please do not hesitate to contact us.

Sincerely,

[Signature]

Elizabeth W. Adamson
Executive Director
Please see the following comments from the Obesity Action Coalition regarding the Medical Board’s proposed rules surrounding obesity pharmacotherapy:

——

On behalf of the more than 70,000 members of the Obesity Action Coalition (OAC), a national non-profit organization dedicated to giving a voice to the individual affected by the disease of obesity, we are pleased to provide the following comments regarding the State Medical Board of Ohio’s review of the prescribing restrictions for anti-obesity agents outlined under rule:

4731-11-04, OAC, Controlled Substances: Utilization of short term anorexiant for weight reduction

4731-11-04.1, OAC, Controlled substances: Utilization for chronic weight management

The OAC is extremely appreciative of Dr. Soin for his time last week to allow the Medical Board to learn additional information regarding the impact that these regulations will have on obesity medicine specialists and the patients they treat. Dr. Soin asked several important and thoughtful questions of the attendees on the call last week and we are thankful for his deep interest in affording stakeholders sufficient time to educate the Board regarding how obesity care has evolved over the last decade.

While the OAC is thankful that the Board continues to review these regulations, we remain deeply concerned that the Board could be willing to continue a discriminatory approach toward prescribing rules associated with anti-obesity medications – especially given the tremendous advances that have been made this decade in understanding both the science and physiology surrounding obesity. Even more troubling is that the Board is poised to affirm this approach despite growing evidence that the link between obesity and even overweight places affected individuals as significant risk of severe outcomes, such as death and hospitalization should they contract COVID-19.

Throughout the past decade, the Food and Drug Administration has approved a number of anti-
obesity medications and many more agents are progressing through the development process. Some of these new treatment tools employ combinations of older drugs, including phentermine. Despite this progress, patients continue to face discriminatory hurdles to care – barriers that are based more on historical misconceptions than evidence-based science. Preconceptions that those who are affected by obesity came to it through character flaw, lack of willpower, poor lifestyle choices or all of the above.

Those who are affected by obesity deserve both respect and access to the full continuum of care for this complex and chronic disease — in the same fashion that others currently enjoy who struggle with chronic disease states such as high cholesterol, heart disease or diabetes. We are hopeful that the Board will work with both healthcare professionals and patients to better understand the significant changes that have occurred in the obesity treatment landscape since these rules were last substantively amended more than a decade ago. It is critical that the Medical Board shift its view from acute care management of obesity to one that embraces a chronic care philosophy needed to address the complexity of the chronic disease of obesity.

Again, thank you for this opportunity to provide feedback regarding this issue. We urge the State Medical Board to rescind these bias and discriminatory prescribing rules. Failure to do so could be devastating — especially during this deadly pandemic.

Christopher Gallagher

Washington Representative

Obesity Action Coalition

www.obesityaction.org

The Obesity Action Coalition (OAC) is a more than 70,000 member-strong 501(c)(3) National non-profit organization dedicated to giving a voice to the individual affected by the disease of obesity and helping individuals along their journey toward better health through education, advocacy and support. Our core focuses are to raise awareness and improve access to the prevention and treatment of obesity, provide evidence-based education on obesity and its treatments, fight to eliminate weight bias and discrimination, elevate the conversation of weight and its impact on health and offer a community of support for the individual affected.

On Nov 23, 2020, at 5:12 PM, Jill.Reardon@med.ohio.gov wrote:

Thank you so much for your attendance at our meeting on the Medical Board’s proposed weight loss rules. Your input as experts in the area of weight loss are
We will review the previous input you may have given the board on these rules and continue to accept any additional comments by email until close of business on Monday, November 30, 2020. Additionally, the rules are currently pending at the Common Sense Initiative and after the rules complete that process, there will be two more opportunities for public comment during the JCARR process. As was mentioned by Dr. Soin, this subject will be discussed at our next Medical Board meeting to be held on December 9th, during the Policy Committee. Here is the link to find the time of the meetings and the agendas: Medical Board of Ohio list of Board meetings and agendas. The Medical Board has a YouTube channel that will show the hearing live as well. For your reference here is the link to the YouTube channel: Ohio Medical Board of Ohio YouTube Channel.

If you would like to be included on a list to receive notification of rule filings, please send an e-mail to Judith.Rodriguez@med.ohio.gov to add your name and e-mail address to that list.

Again, thank you again for your time and input and best wishes for a Happy Thanksgiving.

Jill

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Chris Gallagher
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From: Ted Kyle <ted.kyle@conscienhealth.org>
Sent: Monday, November 30, 2020 3:31 PM
To: Reardon, Jill <Jill.Reardon@med.ohio.gov>
Cc: Chris Gallagher <chris@potomaccurrents.com>; GRIEBEM@ccf.org; Butsch, Winfield <BUTSCHW@ccf.org>; Anderson, Stan <stanand1@sbcglobal.net>; JJohns@amcno.org; Jennifer Hayhurst (jhayhurst@osma.org) <jhayhurst@osma.org>; Cjnorthup@premierhealth.com; Blair Barnhart-Kinkle <barnhab@ccf.org>; Michael Evans (EVANSM10@ccf.org) <EVANSM10@ccf.org>
Subject: Re: Interested party meeting regarding proposed weight loss rules

Here is the article on longer term phentermine use that I mentioned on our call last week.

Perhaps the most important thing to bear in mind is that obesity is a complex, chronic disease that requires long-term care. Back in the 1950s, when phentermine was first approved, people thought that weight loss was the answer to obesity. Now obesity care specialists understand that long-term weight management is essential. Discontinuing an anti-obesity medicine after a person loses weight is like discontinuing a medicine for hypertension after a person's blood pressure goes down. In both cases a person’s condition returns to its former state.

Thus in the late 1990s, FDA updated its guidance on meds for obesity to reflect the need for long-term therapy. All new obesity drugs, including the combination of phentermine and topiramate (Qsymia) are studied and approved for use in this way.

Because phentermine is so old and inexpensive, this is not how it has been labeled. But it is a mainstay for obesity medicine, because it is both effective and very inexpensive. By restricting its use to short-short term applications, Ohio regulations are preventing patients in Ohio from getting the most cost effective care possible. The only other alternative is newer and much more expensive drugs.

I ask that you include, by reference here (https://conscienhealth.org/2019/03/older-than-dirt-phentermine-works/), my commentary on this subject with these comments.

Thank you for your attention to this subject and for welcoming my input as a pharmacist and patient advocate.
Thank you so much for your attendance at our meeting on the Medical Board’s proposed weight loss rules. Your input as experts in the area of weight loss are invaluable.

We will review the previous input you may have given the board on these rules and continue to accept any additional comments by email until close of business on Monday, November 30, 2020. Additionally, the rules are currently pending at the Common Sense Initiative and after the rules complete that process, there will be two more opportunities for public comment during the the JCARR process. As was mentioned by Dr. Soin, this subject will be discussed at our next Medical Board meeting to be held on December 9th, during the Policy Committee. Here is the link to find the time of the meetings and the agendas: Medical Board of Ohio list of Board meetings and agendas. The Medical Board has a You Tube channel that will show the hearing live as well. For your reference here is the link to the You Tube channel: Ohio Medical Board of Ohio You Tube Channel.

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Again, thank you again for your time and input and best wishes for a Happy Thanksgiving.

Jill

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Jill,

Please let me know if I can be of service in the future and I thank you and Dr Soin for seriously considering a change in phentermine prescribing laws in Ohio. I was formerly at the University of Cincinnati as you may recall in my first message to you and one of the reasons I left to come to Massachusetts General Hospital was to be able to treat obesity in an adequate fashion that I was not able to do in Ohio.

Thank you again for your consideration and if I can be of service as an outside of Ohio now expert I am happy to help. With the obesity and COVID-19 pandemics intersecting it is more important than ever to treat obesity seriously and have access to medication that can do that. You may also want to hear from patients and we can also provide that testimony if it is helpful.

Happy Holidays!
Stay well!

Angela

Angela Fitch, MD, FACP, FOMA
Associate Director MGH Weight Center
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The Common Sense Initiative is established in R.C. 107.61 to eliminate excessive and duplicative rules and regulations that stand in the way of job creation. Under the Common Sense Initiative, agencies must balance the critical objectives of regulations that have an adverse impact on business with the costs of compliance by the regulated parties. Agencies should promote transparency, responsiveness, predictability, and flexibility while developing regulations that are fair and easy to follow. Agencies should prioritize compliance over punishment, and to that end, should utilize plain language in the development of regulations.
Reason for Submission-

1. R.C. 106.03 and 106.031 require agencies, when reviewing a rule, to determine whether the rule has an adverse impact on businesses as defined by R.C. 107.52. If the agency determines that it does, it must complete a business impact analysis and submit the rule for CSI review.

Which adverse impact(s) to businesses has the agency determined the rule(s) create?

The rule(s):

a. □ Requires a license, permit, or any other prior authorization to engage in or operate a line of business.

b. ☒ Imposes a criminal penalty, a civil penalty, or another sanction, or creates a cause of action for failure to comply with its terms.

c. □ Requires specific expenditures or the report of information as a condition of compliance.

d. □ Is likely to directly reduce the revenue or increase the expenses of the lines of business to which it will apply or applies.

Regulatory Intent

2. Please briefly describe the draft regulation in plain language. Please include the key provisions of the regulation as well as any proposed amendments.

Rule 4731-11-02 General provisions-No change

The rule provides general information regarding controlled substance prescribing for physicians.

Rule 4731-11-03-Utilization of anabolic steroids, schedule II controlled substances-Amend

The rule outlines the utilization of anabolic steroids and schedule II controlled substances. The rule is proposed to be amended to remove the reference to the rescinded intractable pain rules and to reference chronic pain as defined in Rule 4731-11-01, OAC and to correct a typographical error.

Rule 4731-11-04 Controlled substances: Utilization of short term anorexiant medication for weight reduction-Amend
The rules set forth the requirements for physicians to prescribe short-term anorexiants for weight loss. The rule is proposed to be amended to correct the spelling of dietitian in Section 4731-11-04(B)(1), OAC.

Rule 4731-11-04.1 Controlled substances: utilization for chronic weight management-Amend
The rule sets for the requirements for physicians and physician assistants in the utilization of controlled substances for chronic weight management. The rule is proposed to be amended to remove reference to the discontinued physician assistant formulary in Section 4731-11-04.1(B)(2)(b).

Rule 4731-11-07 Research utilizing controlled substances-No change
The rule outlines the research programs which are not impacted by the rules.

Rule 4731-11-11 Standards and procedures for review of “Ohio Automated Rx Reporting System” (OARRS)-Amend
The rule sets forth the standards and procedures to be followed by physicians prior to prescribing controlled substances and the red flags of abuse for physicians to monitor when prescribing controlled substances. The rule is proposed to be amended to update the reference to the Pharmacy Board rule for reported drugs in paragraph (A)(5) and to correct a typographical error.

3. Please list the Ohio statute(s) that authorize the agency, board or commission to adopt the rule(s) and the statute(s) that amplify that authority.
Statutory authority: 4731.295, 4731.281, 4731.05
Amplifying statutes: 4731.281, 4731.296, 4731.295, 4731.294, 4731.293, 4731.292, 4731.291, 4731.282

4. Does the regulation implement a federal requirement? Is the proposed regulation being adopted or amended to enable the state to obtain or maintain approval to administer and enforce a federal law or to participate in a federal program?
If yes, please briefly explain the source and substance of the federal requirement.
No. Although the Controlled Substance Act establishes the schedule for controlled drugs, the rules are not required by the federal law.

5. If the regulation includes provisions not specifically required by the federal government, please explain the rationale for exceeding the federal requirement.
Not applicable.
6. What is the public purpose for this regulation (i.e., why does the Agency feel that there needs to be any regulation in this area at all)?

The rules provide specific guidance to physicians in the prescribing of controlled substances, which are prescription drugs which can lead to addiction.

7. How will the Agency measure the success of this regulation in terms of outputs and/or outcomes?

The success of these regulations will be measured by physicians prescribing controlled substances in accordance with the rules; the rules being written in plain, understandable language; licensee compliance with the rules; and minimal questions from the licensees about the proposed rules.

8. Are any of the proposed rules contained in this rule package being submitted pursuant to R.C. 101.352, 101.353, 106.032, 121.93, or 121.931?

If yes, please specify the rule number(s), the specific R.C. section requiring this submission, and a detailed explanation.

No.

Development of the Regulation

9. Please list the stakeholders included by the Agency in the development or initial review of the draft regulation.

If applicable, please include the date and medium by which the stakeholders were initially contacted.

Interested parties that have requested notification of proposed rule changes, including Ohio State Medical Association, Ohio Association of Physician Assistants, Physician Assistant Policy Committee and the Pharmacy Board.

10. What input was provided by the stakeholders, and how did that input affect the draft regulation being proposed by the Agency?

Comments on Rule 4731-11-02: None

Comments on Rule 4731-11-03: None

Comments on Rule 4731-11-04 and 4731-11-04.1:

- Trace Curry, M.D. Eliminate the 12-week limit:
• Derrick Cetin, D.O. Current rule emphasizes when NOT to use rather than when to use. If patient just 1 day late for filling script, must be off for 6 months, they gain back weight. Should able to use the short acting medications such as phentermine long term to treat obesity as it should be as a chronic disease.

• Luke Selby, M.D., Chris Gallagher, Megan Skinner, APRN and Maria Schroff, M.D. Urges the Board to work with both patients and the healthcare community to better understand how Ohio’s overly restrictive and dated prescribing restrictions are impeding so many Ohioans from accessing the full continuum of care for obesity — in the same fashion that others currently enjoy who struggle with chronic disease such as high cholesterol, heart disease or diabetes.

• Neal Nesbett, M.D. Re-submission of 2013 letter as OSMA position has not changed. Rule is out-dated, particularly 3 months limitation and having see patient every 3 months.

• Beth Adamson, OAPA: Comments are applicable to 4731-11-04 and 4731-11-04.1. Supervising physician should be authorize PA to prescribe any drug within physician's normal practice and without requiring physician to review each chart after the PA sees the patient. Recommends use of a more inclusive term such as "practitioner" or "prescriber".

• Donna Leitzel, patient Rule imposes extraordinary restrictions on use of weight loss drugs.

• Ross Henchen, M.D., Cheryl Milani, MMS, PA-C, Alana Mercer, MSHS, PA-C: The rules are overly restrictive. Let PAs prescribe weight loss drugs; consider rescinding the rules completely and let physicians use medical judgment.

• Latyonya Fore, NP: Recommends removal of the verbiage “short term anorexiant for purposes of weight reduction” and replacing it with “anti-obesity medication for the purpose of treating overweight and obesity. Allow long-term use of "short-term" drugs. In 4731-11-04.1, allow PAs to prescribe and change medications as do APRNs.

• Barto Burguera M.D., Ph.D.: The rule should allow telemedicine visits for both 4731-11-04 and 4731-11-04.1. For 4731-11-04, drop the 12 weeks maximum, require closer monitoring for 12 weeks, but allow long term use. Should not require discontinuation based on failure to loose weight. Medical Board should designate phentermine to be a chronic weight loss drug. The letter Incudes references to several studies.

• Karen Schultz, CNS: Should amend both 4731-11-04 and 4731-11-04.1 to allow continuous treatment as phentermine is safe.

• Scott W. Butsch, M.D. Obesity is a chronic disease and the rules prevent appropriate treatment.

• Kay Mavko, R.D. Please correct spelling of dietitian. For both 4731-11-04 and 4731-11-04.1, add requirements for “nutritionally adequate calorie restricted diet”, “nutritional counseling and intensive behavioral therapy” and exercise program for weight loss.
• Stan Anderson, M.D. Obesity needs on-going treatment, OARRS should take care of "doctor shopping" concerns, easier to prescribe morphine than Schedule 4 weight loss drug, chronic weight management drugs too expensive for many patients
• Sandra Thornhill, P.A. Should rescind the rule, have a rule for obesity treatment instead. Limits patient's ability to lose any significant amount of weight. Rule limits PA practice and is contradictory to "new process of prescribing."
• Ethan Lazarus, M.D. Should allow long-term use of phentermine. Ohio physician who treats obesity according to standard of care violates the Ohio rule.
• Steven Schierholt, Executive Director, Board of Pharmacy: Supports continuing the rules are currently written.
• The Board’s Physician Assistant Policy Committee recommended two changes to rule 4731-11-04.1:
  (1) Remove reference to PA formulary in Rule 4731-11-04.1(B)(2)(b);
  (2) Modify requirement for supervising physician to have a discussion with the physician assistant rather than personally reviewing the medical records in paragraph (B)(3)(a) of Rule 4731-11-04.1.

Comments on Rule 4731-11-07: None

Comments on Rule 4731-11-11:
  • The Board of Pharmacy recommended changing paragraph (A)(5) to update the rule reference defining “reported drugs”.

The Board reviewed the comments at its Policy Committee meetings in September, October and November of 2019. The Board determined to accept the following changes:

4731-11-04: update spelling of dietitian;
4731-11-04.1: remove the reference to the discontinued physician assistant formulary;
4731-11-11: update the Pharmacy Board rule reference in paragraph (A)(5).

11. What scientific data was used to develop the rule or the measurable outcomes of the rule? How does this data support the regulation being proposed?
The Medical Board, which includes nine physicians, utilized its medical expertise in developing these rules.

12. What alternative regulations (or specific provisions within the regulation) did the Agency consider, and why did it determine that these alternatives were not appropriate? If none, why didn’t the Agency consider regulatory alternatives?
No alternative regulation was considered other than the amendments discussed above. The Board continues to have concerns regarding the safety of prescribing controlled substance medication and works closely with the Board of Pharmacy on this issue.

13. Did the Agency specifically consider a performance-based regulation? Please explain. 

*Performance-based regulations define the required outcome, but don’t dictate the process the regulated stakeholders must use to achieve compliance.*

The proposed rules are performance based.

14. What measures did the Agency take to ensure that this regulation does not duplicate an existing Ohio regulation?

The Medical Board is the only state agency that licenses physicians.

15. Please describe the Agency’s plan for implementation of the regulation, including any measures to ensure that the regulation is applied consistently and predictably for the regulated community.

The rule will be posted on the Medical Board’s website. Medical Board staff members are available by telephone and e-mail to answer questions.

**Adverse Impact to Business**

16. Provide a summary of the estimated cost of compliance with the rule. Specifically, please do the following:

a. Identify the scope of the impacted business community; and

The business community impacted is composed of physician licensees regulated by the Medical Board.

b. Identify the nature of all adverse impact (e.g., fees, fines, employer time for compliance,); and

The rules require periodic examinations for patients being prescribed controlled substance medications.

c. Quantify the expected adverse impact from the regulation.

*The adverse impact can be quantified in terms of dollars, hours to comply, or other factors; and may be estimated for the entire regulated population or for a*
“representative business.” Please include the source for your information/estimated impact.

There may be additional time for physicians treating patients with controlled substances for weight loss. However, these rules have been in place for many years, and there are no amendments requiring additional physician time.

17. Why did the Agency determine that the regulatory intent justifies the adverse impact to the regulated business community?

Controlled substances pose health and safety risks to patients and it is important to have comprehensive standards for the prescribing of these drugs.

**Regulatory Flexibility**

18. Does the regulation provide any exemptions or alternative means of compliance for small businesses? Please explain.

No. The regulation is applied equally for all physicians and physician assistants.

19. How will the agency apply Ohio Revised Code section 119.14 (waiver of fines and penalties for paperwork violations and first-time offenders) into implementation of the regulation?

Violations of these rules could result in disciplinary action, including fines. Any disciplinary action is imposed pursuant to Chapter 119 and the Medical Board’s laws and rules. Due process requires equal application of the laws and rules to all licensees.

20. What resources are available to assist small businesses with compliance of the regulation?

Board staff is available to answer questions regarding the rule. The rules are posted and are available on the Board’s website.
General provisions.

(A) A physician shall not utilize a controlled substance other than in accordance with all of the provisions of this chapter of the Administrative Code.

(B) A physician shall not utilize a controlled substance without taking into account the drug's potential for abuse, the possibility the drug may lead to dependence, the possibility the patient will obtain the drug for a nontherapeutic use or to distribute to others, and the possibility of an illicit market for the drug.

(C) A physician shall complete and maintain accurate medical records reflecting the physician's examination, evaluation, and treatment of all the physician's patients. Patient medical records shall accurately reflect the utilization of any controlled substances in the treatment of a patient and shall indicate the diagnosis and purpose for which the controlled substance is utilized, and any additional information upon which the diagnosis is based.

(D) A physician shall obey all applicable provisions of sections 3719.06, 3719.07, 3719.08 and 3719.13 of the Revised Code and the rules promulgated thereunder, all prescription issuance rules adopted under Chapter 4729. of the Revised Code, and all applicable provisions of federal law governing the possession, distribution, or use of controlled substances.

(E) Violations of this rule:

(1) A violation of any provision of this rule, as determined by the board, shall constitute any or all of the following: "failure to maintain minimal standards applicable to the selection or administration of drugs," as that clause is used in division (B)(2) of section 4731.22 of the Revised Code; and "a departure from, or the failure to conform to, minimal standards of care of similar physicians under the same or similar circumstances, whether or not actual injury to a patient is established," as that clause is used in division (B)(6) of section 4731.22 of the Revised Code.

(2) A violation of paragraph (C) of this rule shall further constitute "selling, prescribing, giving away, or administering drugs for other than legal and legitimate therapeutic purposes," as that clause is used in division (B)(3) of section 4731.22 of the Revised Code.
(A) A physician shall not:

1. Utilize anabolic steroids, growth hormones, testosterone or its analogs, human chorionic gonadotropin ("HCG"), or other hormones for the purpose of enhancing athletic ability.

2. Utilize the schedule II controlled substance cocaine hydrochloride for a purpose other than one of the following:
   a. As a topical anesthetic in situations in which it is properly indicated; or
   b. For in-office diagnostic testing for pupillary disorders.

3. Utilize a schedule II controlled substance stimulant in any of the following circumstances:
   a. For purposes of weight reduction or control;
   b. When the physician knows or has reason to believe that a recognized contra-indication to its use exists; or
   c. In the treatment of a patient who the physician knows or should know is pregnant, except if the following criteria are met:
      i. After the physician's medical assessment the physician and patient determine that the benefits of treating the patient with a schedule II controlled substance stimulant outweigh the risks, and
      ii. The basis for the determination is documented in the patient record.

(B) Utilizing a schedule II controlled substance stimulant:

1. Before initiating treatment utilizing a schedule II controlled substance stimulant, the physician shall perform all of the following:
   a. Obtain a thorough history;
(b) Perform an appropriate physical examination of the patient; and

c) Rule out the existence of any recognized contra-indications to the use of the controlled substance stimulant to be utilized.

(2) A physician may utilize a schedule II controlled substance stimulant only for one of the following purposes:

(a) The treatment of narcolepsy, idiopathic hypersomnia, and hypersonomias due to medical conditions known to cause excessive sleepiness;

(b) The treatment of abnormal behavioral syndrome (attention deficit disorder, hyperkinetic syndrome), and/or related disorders;

(c) The treatment of drug-induced or trauma-induced brain dysfunction;

(d) The differential diagnostic psychiatric evaluation of depression;

(e) The treatment of depression shown to be refractory to other therapeutic modalities, including pharmacologic approaches, such as antidepressants;

(f) As adjunctive therapy in the treatment of the following:

   (i) Chronic severe pain;

   (ii) Closed head injuries;

   (iii) Cancer-related fatigue;

   (iv) Fatigue experienced during the terminal stages of disease;

   (v) Depression experienced during the terminal stages of disease; or

   (vi) IntractableC*hronic pain, as defined in rule 4731-21-014731-11-01 of the Administrative Code.

(g) The treatment of binge eating disorder.
(3) Upon ascertaining or having reason to believe that the patient has a history of or shows a propensity for alcohol or drug abuse, or that the patient has consumed or disposed of any controlled substance other than in strict compliance with the treating physician's directions, the physician shall perform both of the following;

(a) Reappraise the desirability of continued utilization of schedule II controlled substance stimulants and shall document in the patient record the factors weighed in deciding to continue their use; and

(b) Actively monitor such patient for signs and symptoms of drug abuse and drug dependency.

(C) A violation of any provision of this rule, as determined by the board, shall constitute any or all of the following:

(1) "Failure to maintain minimal standards applicable to the selection or administration of drugs," as that clause is used in division (B)(2) of section 4731.22 of the Revised Code;

(2) "Selling, giving away, personally furnishing, prescribing, or administering drugs for other than legal and legitimate therapeutic purposes," as that clause is used in division (B)(3) of section 4731.22 of the Revised Code;

(3) "A departure from, or the failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances, whether or not actual injury to a patient is established," as that clause is used in division (B)(6) of section 4731.22 of the Revised Code.
Controlled substances: Utilization of short term anorexiants for weight reduction.

(A) A physician shall utilize a schedule III or IV controlled substance short term anorexiant for purposes of weight reduction only if it has an F.D.A. approved indication for this purpose and then only in accordance with all of the provisions of this rule.

(B) Before initiating treatment for weight reduction utilizing any schedule III or IV controlled substance short term anorexiant, the physician shall complete all of the following requirements:

1. The physician shall review the physician's own records of prior treatment or review the records of prior treatment by another treating physician, dietitian, or weight-loss program to determine the patient's past efforts to lose weight in a treatment program utilizing a regimen of weight reduction based on caloric restriction, nutritional counseling, intensive behavioral therapy, and exercise, without the utilization of controlled substances, and that the treatment has been ineffective.

2. The physician shall complete and document the findings of all of the following:

   (a) Obtain a thorough history;

   (b) Perform an appropriate physical examination of the patient;

   (c) Determine the patient's BMI;

   (d) Rule out the existence of any recognized contraindications to the use of the controlled substance to be utilized;

   (e) Assess and document the patient's freedom from signs of drug or alcohol abuse, and the presence or absence of contraindications and adverse side effects.

   (f) Access OARRS for the patient's prescription history during the preceding twelve month period and document in the patient's record the receipt and assessment of the report received; and

   (g) Develop and record in the patient record a treatment plan that includes, at a minimum, a diet and exercise program for weight loss.
(3) The physician shall not initiate treatment utilizing a controlled substance short term anorexiant upon ascertaining or having reason to believe any one or more of the following:

(a) The patient has a history of or shows a propensity for alcohol or drug abuse, or has made any false or misleading statement to the physician related to the patient's use of drugs or alcohol;

(b) The patient has consumed or disposed of any controlled substance other than in strict compliance with the treating physician's directions;

(c) The physician knows or should know the patient is pregnant;

(d) The patient has a BMI of less than thirty, unless the patient has a BMI of at least twenty seven with comorbid factors;

(e) The review of the physician's own records of prior treatment or review of records of prior treatment provided by another physician, dietician, or weight-loss program indicate that the patient made less than a substantial good faith effort to lose weight in a treatment program utilizing a regimen of weight reduction based on caloric restriction, nutritional counseling, intensive behavioral therapy, and exercise without the utilization of controlled substances.

(C) A physician may utilize a schedule III or IV controlled substance short term anorexiant, that bears appropriate F.D.A. approved labeling for weight loss, in the treatment of obesity as an adjunct, in a regimen of weight reduction based on caloric restriction, provided that:

(1) The physician shall personally meet face-to-face with the patient, at a minimum, every thirty days when controlled substances are being utilized for weight reduction, and shall record in the patient record information demonstrating the patient's continuing efforts to lose weight, the patient's dedication to the treatment program and response to treatment, and the presence or absence of contraindications, adverse effects, and indicators of possible substance abuse that would necessitate cessation of treatment utilizing controlled substances.

(2) The controlled substance short term anorexiant is prescribed strictly in accordance with the F.D.A. approved labeling. If the F.D.A. approved labeling of the controlled substance short term anorexiant being utilized for weight loss states that it is indicated for use for "a few weeks," the total course of treatment using that controlled substance shall not exceed twelve
weeks. That time period includes any interruption in treatment that may be permitted under paragraph (C)(3) of this rule.

(3) A physician shall not initiate a course of treatment utilizing a controlled substance short term anorexiant for purposes of weight reduction if the patient has received any controlled substance for purposes of weight reduction within the past six months. However, the physician may resume utilizing a controlled substance short term anorexiant following an interruption of treatment of more than seven days if the interruption resulted from one or more of the following:

(a) Illness of or injury to the patient justifying a temporary cessation of treatment; or

(b) Unavailability of the physician; or

(c) Unavailability of the patient, if the patient has notified the physician of the cause of the patient's unavailability.

(4) After initiating treatment, the physician may elect to switch to a different controlled substance short term anorexiant for weight loss based on sound medical judgment, but the total course of treatment for any short term anorexiant combination of controlled substances each of which is indicated for "a few weeks" shall not exceed twelve weeks.

(5) The physician shall not initiate or shall discontinue utilizing all controlled substance short term anorexiants for purposes of weight reduction immediately upon ascertaining or having reason to believe:

(a) That the patient has a history of or shows a propensity for alcohol or drug abuse, or has made any false or misleading statement to the physician relating to the patient's use of drugs or alcohol;

(b) That the patient has consumed or disposed of any controlled substance other than in strict compliance with the treating physician's directions;

(c) That the patient has failed to lose weight while under treatment with a controlled substance or controlled substances over a period of thirty days during the current course of treatment, which determination shall be made by weighing the patient at least every thirtieth day, except that a patient who has never before received treatment for obesity utilizing
any controlled substance who fails to lose weight during the first thirty
days of the first such treatment attempt may be treated for an additional
thirty days;

(d) That the patient has repeatedly failed to comply with the physician's
treatment recommendations; or

(e) That the physician knows or should know the patient is pregnant.

(D) A violation of any provision of this rule, as determined by the board, shall constitute
the following:

(1) "Failure to maintain minimal standards applicable to the selection or
administration of drugs," as that clause is used in division (B)(2) of section
4731.22 of the Revised Code;

(2) "Selling, giving away, personally furnishing, prescribing, or administering
drugs for other than legal and legitimate therapeutic purposes," as that clause
is used in division (B)(3) of section 4731.22 of the Revised Code; and

(3) "A departure from, or the failure to conform to, minimal standards of care of
similar practitioners under the same or similar circumstances, whether or not
actual injury to a patient is established," as that clause is used in division
(B)(6) of section 4731.22 of the Revised Code.
Controlled substances: utilization for chronic weight management.

(A) A physician shall determine whether to utilize a controlled substance anorexiant for purposes of chronic weight management as an adjunct to a reduced calorie diet and increased physical activity. The determination shall be made in compliance with the provisions of this rule.

(1) Before initiating treatment utilizing any controlled substance anorexiant, the physician shall complete all of the following requirements:

(a) Obtain a thorough history;

(b) Perform a physical examination of the patient;

(c) Determine the patient's BMI;

(d) Review the patient's attempts to lose weight in the past for indications that the patient has made a substantial good faith effort to lose weight in a regimen for weight reduction based on caloric restriction, nutritional counseling, intensive behavioral therapy, and exercise without the utilization of controlled substance anorexiants. The review shall include available records from the physician's own prior treatment of the patient, prior treatment provided by another physician, prior participation in a weight-loss program, or prior treatment by a dietitian;

(e) Rule out the existence of any recognized contraindications to the use of the controlled substance anorexiant to be utilized;

(f) Assess and document the patient's freedom from signs of drug or alcohol abuse;

(g) Access OARRS and document in the patient's record the receipt and assessment of the information received; and

(h) Develop and record in the patient record a treatment plan that includes, at a minimum, a diet and exercise program for weight loss.

(2) The physician shall not initiate treatment utilizing a controlled substance anorexiant upon ascertaining or having reason to believe any one or more of the following:
(a) The patient has a history of, or shows a propensity for, alcohol or drug abuse, or has made any false or misleading statement to the physician or physician assistant relating to the patient's use of drugs or alcohol;

(b) The patient has consumed or disposed of any controlled substance other than in strict compliance with the treating physician’s directions; or

(c) The physician knows or should know the patient is pregnant.

(3) The physician shall not initiate treatment utilizing a controlled substance anorexiant if any of the following conditions exist:

(a) The patient has an initial BMI of less than thirty, unless the patient has an initial BMI of at least twenty seven with comorbid factors.

(b) The review of the patient's attempts to lose weight in the past indicates that the patient has not made a substantial good faith effort to lose weight in a regimen for weight reduction based on caloric restriction, nutritional counseling, intensive behavioral therapy, and exercise without the utilization of controlled substance anorexiants. The review shall include available records from the physician's own prior treatment of the patient, prior treatment provided by another physician, prior participation in a weight-loss program, or prior treatment by a dietitian.

(4) The physician shall prescribe the controlled substance anorexiant strictly in accordance with the F.D.A. approved labeling;

(5) Throughout the course of treatment with any controlled substance anorexiant the physician shall comply with rule 4731-11-11 of the Administrative Code and the physician assistant shall comply with rule 4730-2-10 of the Administrative Code.

(B) A physician shall provide treatment utilizing a controlled substance anorexiant for weight management in compliance with paragraph (A) of this rule and the following:

(1) The physician shall meet face-to-face with the patient for the initial visit and at least every thirty days during the first three months of treatment. If the F.D.A. approved labeling for the controlled substance anorexiant requires induction of treatment at one dose and an increase to a higher dose after a stated period of less than thirty days, the physician may give the patient a prescription for
the higher dose at the initial visit and the first thirty day period then starts from the date the prescription for the higher dose may be filled.

(2) Following the initial visit and two follow-up visits, the treatment may be continued under one of the following means:

(a) The physician may authorize refills for the controlled substance anorexiant up to five times within six months after the initial prescription date;

(b) The treatment may be provided by a physician assistant in compliance with this rule, the supervisory plan or policies of the healthcare facility and the physician assistant formulary adopted by the board.

(3) When treatment for chronic weight management is provided by a physician assistant, the following requirements apply:

(a) The supervising physician shall personally review the medical records of each patient to whom the physician assistant has prescribed a controlled substance anorexiant following each visit; and

(b) A physician assistant shall not initiate utilization of a different controlled substance anorexiant, but may recommend such change for the supervising physician's initiation.

(4) A physician shall discontinue utilizing any controlled substance anorexiant immediately upon ascertaining or having reason to believe:

(a) That the patient has repeatedly failed to comply with the physician's treatment recommendations; or

(b) That the patient is pregnant.

(C) A violation of any provision of this rule, as determined by the board, shall constitute the following as applicable:

(1) For a physician:

(a) "Failure to maintain minimal standards applicable to the selection or administration of drugs," as that clause is used in division (B)(2) of
section 4731.22 of the Revised Code;

(b) "Selling, giving away, personally furnishing, prescribing, or administering drugs for other than legal and legitimate therapeutic purposes," as that clause is used in division (B)(3) of section 4731.22 of the Revised Code; and

(c) "A departure from, or the failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances, whether or not actual injury to a patient is established," as that clause is used in division (B)(6) of section 4731.22 of the Revised Code.

(2) For a physician assistant:

(a) "A departure from, or failure to conform to, minimal standards of care of similar physician assistants under the same or similar circumstances, regardless of whether actual injury to a patient is established," as that clause is used in division (B)(19) of section 4730.25 of the Revised Code;

(b) "Failure to comply with the requirements of this chapter, Chapter 4731. of the Revised Code, or any rules adopted by the board," as that clause is used in division (B)(2) of section 4730.25 of the Revised Code; and

(c) "Violating or attempting to violate, directly or indirectly, or assisting in or abetting the violation of, or conspiring to violate, any provision of this chapter, Chapter 4731. of the Revised Code, or the rules adopted by the board," as that clause is used in division (B)(3) of section 4730.25 of the Revised Code.
Research utilizing controlled substances.

The provisions of this chapter of the Administrative Code shall not apply to or in any way prohibit research conducted under the auspices of an accredited medical school, or research which meets both of the following conditions:

(A) The U.S. food and drug administration has approved an investigational new drug ("IND") application for the research or has notified the researchers that the proposed study is exempt from the "IND" regulations; and

(B) The research is conducted in conformance with the approval granted by either of the following:

(1) An institutional review board of a hospital or medical center accredited by the "Joint Commission," "Healthcare Facilities Accreditation Program" or other accrediting body approved by the board; or

(2) An institutional review board accredited by the association for the accreditation of human research protection programs.
4731-11-11 Standards and procedures for review of "Ohio Automated Rx Reporting System" (OARRS).

(A) For purposes of this rule:

(1) "Delegate" means an authorized representative who is registered with the Ohio board of pharmacy to obtain an OARRS report on behalf of a physician;

(2) "OARRS" means the "Ohio Automated Rx Reporting System" drug database established and maintained pursuant to section 4729.75 of the Revised Code.

(3) "OARRS report" means a report of information related to a specified patient generated by the drug database established and maintained pursuant to section 4729.75 of the Revised Code.

(4) "Personally furnish" means the distribution of drugs by a prescriber to the prescriber's patients for use outside the prescriber's practice setting.

(5) "Reported drugs" means all the drugs listed in rule 4729-37-02 of the Administrative Code that are required to be reported to the drug database established and maintained pursuant to section 4729.75 of the Revised Code, including controlled substances in schedules II, III, IV, and V.

(B) Standards of care:

(1) The accepted and prevailing minimal standards of care require that when prescribing or personally furnishing a reported drug, a physician shall take into account all of the following:

(a) The potential for abuse of the reported drug;

(b) The possibility that use of the reported drug may lead to dependence;

(c) The possibility the patient will obtain the reported drug for a nontherapeutic use or distribute it to other persons; and

(d) The potential existence of an illicit market for the reported drug.

(2) In considering whether a prescription for or the personally furnishing of a reported drug is appropriate for the patient, the physician shall use sound clinical judgment and obtain and review an OARRS report consistent with the provisions of this rule.
(C) A physician shall obtain and review an OARRS report to help determine if it is appropriate to prescribe or personally furnish an opioid analgesic, benzodiazepine, or reported drug to a patient as provided in this paragraph and paragraph (F) of this rule:

(1) A physician shall obtain and review an OARRS report before prescribing or personally furnishing an opiate analgesic or benzodiazepine to a patient, unless an exception listed in paragraph (G) of this rule is applicable.

(2) A physician shall obtain and review an OARRS report when a patient's course of treatment with a reported drug other than an opioid analgesic or benzodiazepine has lasted more than ninety days, unless an exception listed in paragraph (G) of this rule is applicable.

(3) A physician shall obtain and review an OARRS report when any of the following red flags pertain to the patient:

   (a) Selling prescription drugs;

   (b) Forging or altering a prescription;

   (c) Stealing or borrowing reported drugs;

   (d) Increasing the dosage of reported drugs in amounts that exceed the prescribed amount;

   (e) Suffering an overdose, intentional or unintentional;

   (f) Having a drug screen result that is inconsistent with the treatment plan or refusing to participate in a drug screen;

   (g) Having been arrested, convicted, or received diversion or intervention in lieu of conviction for a drug related offense while under the physician's care;

   (h) Receiving reported drugs from multiple prescribers, without clinical basis;

   (i) Traveling with a group of other patients to the physician's office where all or most of the patients request controlled substance prescriptions;
(j) Traveling an extended distance or from out of state to the physician's office;

(k) Having a family member, friend, law enforcement officer, or health care professional express concern related to the patient's use of illegal or reported drugs;

(l) A known history of chemical abuse or dependency;

(m) Appearing impaired or overly sedated during an office visit or exam;

(n) Requesting reported drugs by street name, color, or identifying marks;

(o) Frequently requesting early refills of reported drugs;

(p) Frequently losing prescriptions for reported drugs;

(q) A history of illegal drug use;

(r) Sharing reported drugs with another person; or

(s) Recurring visits to non-coordinated sites of care, such as emergency departments, urgent care facilities, or walk-in clinics to obtain reported drugs.

(D) A physician who decides to utilize an opioid analgesic, benzodiazepine, or other reported drug in any of the circumstances within paragraphs (C)(2) and (C)(3) of this rule, shall take the following steps prior to issuing a prescription for or personally furnishing the opioid analgesic, benzodiazepine, or other reported drug:

(1) Review and document in the patient record the reasons why the physician believes or has reason to believe that the patient may be abusing or diverting drugs;

(2) Review and document in the patient's record the patient's progress toward treatment objectives over the course of treatment;

(3) Review and document in the patient record the functional status of the patient, including activities for daily living, adverse effects, analgesia, and aberrant behavior over the course of treatment;
(4) Consider using a patient treatment agreement including more frequent and periodic reviews of OARRS reports and that may also include more frequent office visits, different treatment options, drug screens, use of one pharmacy, use of one provider for the prescription or personally furnishing of reported drugs, and consequences for non-compliance with the terms of the agreement. The patient treatment agreement shall be maintained as part of the patient record; and

(5) Consider consulting with or referring the patient to a substance abuse specialist.

(E) Frequency for follow-up OARRS reports:

(1) For a patient whose treatment with an opioid analgesic or benzodiazepine lasts more than ninety days, a physician shall obtain and review and OARRS report for the patient at least every ninety days during the course of treatment, unless an exception listed in paragraph (G) of this rule is applicable.

(2) For a patient who is treated with a reported drug other than an opioid analgesic or benzodiazepine for a period lasting more than ninety days, the physician shall obtain and review and OARRS report for the patient at least annually following the initial OARRS report obtained and reviewed pursuant to paragraph (C)(2) of this rule until the course of treatment utilizing the reported drug has ended, unless an exception in paragraph (G) of this rule is applicable.

(F) When a physician or their delegate requests an OARRS report in compliance with this rule, a physician shall document receipt and review of the OARRS report in the patient record, as follows:

(1) Initial reports requested shall cover at least the twelve months immediately preceding the date of the request:

(2) Subsequent reports requested shall, at a minimum, cover the period from the date of the last report to present;

(3) If the physician practices primarily in a county of this state that adjoins another state, the physician or their delegate shall also request a report of any information available in the drug database that pertains to prescriptions issued or drugs furnished to the patient in the state adjoining that county; and

(4) If an OARRS report regarding the patient is not available, the physician shall
document in the patient's record the reason that the report is not available and any efforts made in follow-up to obtain the requested information.

(G) A physician shall not be required to review and assess an OARRS report when prescribing or personally furnishing an opioid analgesic, benzodiazepine, or other reported drug under the following circumstances, unless a physician believes or has reason to believe that a patient may be abusing or diverting reported drugs:

1. The reported drug is prescribed or personally furnished to a hospice patient in a hospice care program as those terms are defined in section 3712.01 of the Revised Code, or any other patient diagnosed as terminally ill;

2. The reported drug is prescribed for administration in a hospital, nursing home, or residential care facility;

3. The reported drug is prescribed or personally furnished in an amount indicated for a period not to exceed seven days;

4. The reported drug is prescribed or personally furnished for the treatment of cancer or another condition associated with cancer; and

5. The reported drug is prescribed or personally furnished to treat acute pain resulting from a surgical or other invasive procedure or a delivery.
Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort

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Objective: The aim of this work was to study weight loss and risk of cardiovascular disease (CVD) or death associated with longer-term phentermine use.

Methods: Using electronic health record data, 13,972 adults were identified with a first phentermine fill in 2010 to 2015, creating exposure categories according to a patient’s duration of use (referent: ≤ 3 months). Multivariable linear models were used to compare percent weight loss across categories at 6, 12, and 24 months, and Cox proportional hazards models were used to compare risk of composite CVD or death, up to 3 years after starting phentermine.

Results: The cohort was 84% female and 45% white, with a mean (SD) baseline age 43.5 (10.7) years and BMI of 37.8 (7.2) kg/m2. In multivariable models, longer-term users of phentermine experienced more weight loss; patients using continuously for > 12 months lost 7.4% more than the referent group at 24 months (P < 0.001). The composite CVD or death outcome was rare (0.3%, 41 events), with no significant difference in hazard ratios between groups.

Conclusions: Greater weight loss without increased risk of incident CVD or death was observed in patients using phentermine monotherapy for longer than 3 months. Despite the limitations of the observational design, this study supports the effectiveness and safety of longer-term phentermine use for low-risk individuals.

Introduction

Lifestyle interventions remain the cornerstone of treatment for patients with obesity, typically yielding a peak weight loss of 5% to 10% after 6 months (1). However, up to one-third of patients do not respond to such programs (2,3), and weight regain is common following intervention cessation (4,5). Pharmacotherapy can increase the proportion of individuals who respond to lifestyle interventions as well as the duration and magnitude of response (6). Clinically significant durable weight loss has been demonstrated in placebo-controlled trials of antiobesity medications (7-14), but broader use of medications remains limited because of concerns about cost, efficacy, and adverse events (15).

The most commonly used weight-loss medication in the United States is phentermine (16,17), a sympathomimetic amine that acts by inhibiting appetite and that was originally approved for weight loss in 1959 (18,19). Most studies examining phentermine monotherapy have limited treatment duration to less than 12 weeks (20), aligning with a package insert that recommends that the medication be used as “a short-term adjunct (a few weeks)” to lifestyle-based programs (21). Concerns about longer-term phentermine use include increased risk...
of cardiovascular disease (CVD) (6,17) and potential for addiction (22).

Weight-loss treatment approaches are evolving to favor long-term therapy, aligning with the new chronic disease model of obesity. Newer antiobesity medications have, accordingly, been approved by the Food and Drug Administration (FDA) for long-term use (i.e., more than 12 months) (20). If phentermine monotherapy, which is widely available and low cost, was found to be safe and effective for long-term use, the impact for obesity treatment could be significant.

Using data from electronic health records (EHRs), we studied whether adults prescribed phentermine for longer than 12 weeks experienced differential weight loss, change in blood pressure (BP) or heart rate (HR), or increased risk of incident CVD or death compared with adults prescribed phentermine in an on-label short-term episode. Our primary hypothesis was that longer-term users would experience greater weight loss without increased risk of CVD or death.

Methods

Study design, health care systems, and data sources

The data sources for this retrospective cohort study were EHRs abstracted from the Patient Outcomes Research to Advance Learning (PORTAL) cohort, a collaborative data effort across several integrated health insurance and care-delivery systems in the United States as part of the National Patient-Centered Clinical Research Network (PCORnet) initiative (23,24). Data elements included membership status, demographics, vital signs, health care use, laboratory values, and pharmacy dispensing. This cohort included data from Kaiser Permanente (Southern California, Colorado, Northwest, Washington state, Hawaii, and Mid-Atlantic States [Maryland, Virginia, District of Columbia]) and from Denver Health and HealthPartners (Minnesota). The study was approved by the Kaiser Permanente Southern California Institutional Review Board, with other sites ceding primary review.

Study population

We identified adult health plan members 18 to 64 years old with a “first” phentermine fill (dose ≤ 37.5 mg/d) between January 1, 2010, and September 30, 2015. To find likely incident users, we limited selection to patients with at least 12 months of continuous baseline enrollment, during which there were no prior phentermine prescriptions (25). We chose the study end date to coincide with the International Classification of Diseases, Ninth Revision to Tenth Revision transition, after which changes in diagnosis coding could have led to systematic differences in detection of outcomes and covariates.

We required patients to have BMI ≥ 27 kg/m² within 3 months prior to their first phentermine fill. We excluded those with history of bariatric surgery or cancer diagnosis (other than nonmelanoma skin cancer). We also excluded anyone with baseline year evidence of pregnancy, use of other weight-loss medications, palliative care encounters, or diagnosis and/or procedure codes for any cardiovascular outcomes of interest, including myocardial infarction, stroke, angina, coronary artery bypass grafting, or carotid artery procedures (Figure 1). Weight, BP, and HR analyses were limited to individuals with at least one relevant measurement before and after initiating phentermine.

Exposure

Our exposure of interest was a patient’s pattern of phentermine use in follow-up, characterized based on duration and persistence of use. For each individual, we first created episodes of phentermine use and mapped them across follow-up time (26-28). See Supporting Information Figure S1 for details on how episodes were created.

Individuals with one phentermine treatment episode lasting ≤ 112 days and no subsequent use during follow-up were treated as our referent or “short-term” use group, reflecting FDA-approved use of the medication. This episode duration (≤ 112 days) was based on multiplying the on-label duration of 90 days by a factor of 1.25 to account for days in the episode when a patient was between fills (28). Patients with a single phentermine treatment episode lasting > 112 and up to 365 days, but with no subsequent treatment episodes, were labeled “medium-term continuous” users. Patients with a single continuous episode lasting > 365 days were labeled “long-term continuous” users.

In clinical practice, patients often take phentermine intermittently over time. To separately capture these individuals and allow for follow-up beyond the first treatment episode, we created two additional groups. Persons with two or more separate treatment episodes in which each episode exceeded 112 days were termed “short-term intermittent” users. Those with two or more episodes in which at least one episode exceeded 112 days were termed “medium-term intermittent” users.

We treated phentermine use as a time-varying exposure. A patient’s inclusion in a particular exposure category was dependent on his or her exposure pattern up to the time point of interest, meaning that patients could change exposure categories over time. For example, at the 6-month mark, we could not yet classify anyone as being in the long-term continuous group because less than a year of phentermine exposure had elapsed. Therefore, these individuals were included in our medium-term continuous group for 6-month analyses, only separating out as a distinct group after 12 months of continuous exposure to phentermine.

Outcomes

Our outcome for drug effectiveness was percent change in weight from baseline, measured at 6, 12, and 24 months after initial phentermine dispensing. We abstracted all weights recorded in the outpatient setting. We selected baseline weight (kilograms) as the nearest measure on or within 90 days prior to the index date. Because we were working with clinical data, follow-up did not occur precisely at 6, 12, or 24 months for most individuals. We accepted weights for each follow-up point based on a variable window that enlarged as follow-up time progressed. For our 6-month outcome, we accepted the nearest weight measure within –30 to + 90 days; at 12 months, we accepted the nearest weight measure within –90 to + 90 days; and at 24 months, we accepted the nearest weight measure within –180 to + 180 days.

We examined changes in systolic BP (SBP), diastolic BP (DBP) (mmHg), and HR (beats per minute [bpm]) from baseline as intermediate outcomes for cardiovascular risk because of the sympathomimetic effect of phentermine. We derived change in HR, SBP, and DBP from outpatient measures, selecting the nearest measure per window per patient for analysis. Additional rules used for cleaning vital sign data are available in Supporting Information Table S1.

Our distal outcome measure for cardiovascular risk was a composite measure of incident myocardial infarction, stroke, angina, coronary artery
bypass grafting, carotid artery intervention, or death. We abstracted all relevant International Classification of Diseases, Ninth Revision diagnosis or procedure and Current Procedural Terminology procedure codes (Supporting Information Table S2) and used a previously published method to assign incident events (29). Information about date of death came from a combination of EHR, administrative, and state mortality databases (30).

Covariates
All models included EHR-derived covariates for sex, race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other), age group (18-34, 35-49, 50-64), baseline BMI category (27-29.9, 30-34.9, 35-39.9, 40-49.9, or ≥50), hypertension, diabetes, smoking status, health care system, calendar year of phentermine initiation, and average daily dose category of phentermine (37.5 mg/d or <37.5 mg/d). BP and HR models were adjusted for baseline tertile of each measure.

We used demographic information from geographic information systems to create a covariate for area-level measure of poverty (percent of households in census block below poverty level: <5%, 5% to <10%, 10% to <20% or ≥20%) (31). We assigned the rare patients missing phentermine dose (n = 39) or poverty (n = 538) the modal values for their region.

Statistical analysis
We built separate multivariable linear models at 6, 12, and 24 months of follow-up to examine the outcomes of percent change in weight and change in SBP, DBP, and HR. In weight analyses, we limited inclusion in the referent group to patients with at least one refill because patients with a single refill were likely intolerant to phentermine. Their inclusion would have biased weight loss results in favor of longer-term users.

We used Cox proportional hazards models with phentermine treated as a time-varying covariate to examine the composite outcome of incident CVD or death in a time-to-event fashion up to 3 years after the index date. Patients achieving any one of the submeasures composing our composite outcome were considered to have the outcome at that time.

Patients were not included in multivariable linear models if any of the following occurred before a time point of interest: health insurance plan disenrollment, >18 months since any clinical care or encounters...
### TABLE 1 Characteristics of phentermine users according to final exposure categorization

<table>
<thead>
<tr>
<th></th>
<th>On-label users</th>
<th>Off-label users</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-term referent (n = 6,764)</td>
<td>Short-term intermittent (n = 2,938)</td>
<td>Medium-term continuous (n = 1,703)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5,611 (83.1%)</td>
<td>2,523 (85.8%)</td>
<td>1,402 (82.3%)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>3,007 (44.5%)</td>
<td>1,093 (37.2%)</td>
<td>894 (52.5%)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>1,370 (20.3%)</td>
<td>786 (26.7%)</td>
<td>253 (14.9%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1,749 (25.9%)</td>
<td>764 (26.0%)</td>
<td>367 (21.6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>305 (4.5%)</td>
<td>137 (4.7%)</td>
<td>101 (5.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>324 (4.8%)</td>
<td>162 (5.5%)</td>
<td>88 (5.2%)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>43.7 (10.9)</td>
<td>42.3 (10.6)</td>
<td>44.3 (10.4)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>38.0 (7.5)</td>
<td>37.0 (6.9)</td>
<td>38.4 (7.0)</td>
</tr>
<tr>
<td>27-29.9</td>
<td>687 (10.2%)</td>
<td>381 (13%)</td>
<td>118 (6.9%)</td>
</tr>
<tr>
<td>30-34.9</td>
<td>1,977 (29.3%)</td>
<td>979 (33.3%)</td>
<td>477 (28%)</td>
</tr>
<tr>
<td>35-39.9</td>
<td>1,890 (28.0%)</td>
<td>773 (26.3%)</td>
<td>519 (30.5%)</td>
</tr>
<tr>
<td>40-49.9</td>
<td>1,733 (25.7%)</td>
<td>673 (22.9%)</td>
<td>472 (27.7%)</td>
</tr>
<tr>
<td>≥50.0</td>
<td>468 (6.9%)</td>
<td>136 (4.6%)</td>
<td>117 (6.9%)</td>
</tr>
<tr>
<td><strong>Hypertension diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4,211 (62.3%)</td>
<td>1,870 (63.6%)</td>
<td>1,035 (60.8%)</td>
</tr>
<tr>
<td>Ever</td>
<td>2,298 (34%)</td>
<td>944 (32.1%)</td>
<td>612 (35.9%)</td>
</tr>
<tr>
<td>Missing/unknown</td>
<td>246 (3.6%)</td>
<td>128 (4.4%)</td>
<td>56 (3.3%)</td>
</tr>
<tr>
<td><strong>Area families below poverty level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>234 (3.5%)</td>
<td>146 (5%)</td>
<td>56 (3.3%)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>1,568 (23.2%)</td>
<td>686 (23.3%)</td>
<td>445 (26%)</td>
</tr>
<tr>
<td>5–&lt;10%</td>
<td>1,779 (26.3%)</td>
<td>769 (26.1%)</td>
<td>448 (26.2%)</td>
</tr>
<tr>
<td>10–&lt;20%</td>
<td>1,812 (26.8%)</td>
<td>798 (27.1%)</td>
<td>443 (25.9%)</td>
</tr>
<tr>
<td>≥20%</td>
<td>1,362 (20.2%)</td>
<td>543 (18.5%)</td>
<td>318 (18.6%)</td>
</tr>
<tr>
<td><strong>Follow-up duration (y)</strong></td>
<td>1.6 (1.1)</td>
<td>2.2 (0.9)</td>
<td>1.6 (1.0)</td>
</tr>
<tr>
<td><strong>Median percent of follow-up on phentermine</strong></td>
<td>9%</td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Daily phentermine dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37.5 mg</td>
<td>3,688 (54.6%)</td>
<td>1,528 (51.9%)</td>
<td>1,120 (65.8%)</td>
</tr>
<tr>
<td>37.5 mg</td>
<td>3,053 (45.2%)</td>
<td>1,404 (47.7%)</td>
<td>580 (34.1%)</td>
</tr>
<tr>
<td>Missing</td>
<td>14 (0.2%)</td>
<td>10 (0.3%)</td>
<td>3 (0.2%)</td>
</tr>
</tbody>
</table>

Data given as n (%) for categorical variables and mean (SD) for continuous variables.

*On-label short-term users (referent) had a single phentermine use episode ≤ 112 days. Short-term intermittent users rotated on and off phentermine but never remained on the drug for longer than 112 days. Off-label user groups defined as follows: medium-term continuous users had a single phentermine treatment episode lasting > 112 but ≤ 365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days. Note that “n” in each column corresponds to final exposure assignment at end of follow-up. Because of the time-varying nature of the exposure, relative size of groups and distribution of characteristics may differ between time points in early follow-up (e.g., at 6 and 12 months).

*Missing includes current and historical smokers.

*Using geographic information systems measures mapping to 2010 census block group socioeconomic status data, categories go from highest to lowest SES vertically.

*For analyses, patients missing either the area-level poverty measure or daily phentermine dose had these values set to modal value for patients in their region. A sensitivity analysis was conducted excluding these patients entirely from analyses and results did not change.
TABLE 2 Difference in percent weight loss over follow-up: results from multivariable linear models using time-varying exposure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter estimate (95% CI)</td>
<td>n (% of enrolled with weight data available)</td>
<td>Parameter estimate (95% CI)</td>
</tr>
<tr>
<td>Intercept</td>
<td>$-2.68 \ (\text{-3.28 to -2.08})^{d,e}$</td>
<td>2,555 (66%)</td>
<td>Referent 2,074 (78%)</td>
</tr>
<tr>
<td>Short-term</td>
<td>Referent</td>
<td>1,450 (73%)</td>
<td>$-1.36 \ (\text{-1.80 to -0.93})^{f}$</td>
</tr>
<tr>
<td>Short-term intermittent</td>
<td>$-1.75 \ (\text{-2.13 to -1.37})^{d,g}$</td>
<td>2,352 (74%)</td>
<td>$-4.66 \ (\text{-5.13 to -4.19})^{g}$</td>
</tr>
<tr>
<td>Medium-term continuous</td>
<td>$-5.07 \ (\text{-5.40 to -4.73})^{d,g}$</td>
<td>179 (78%)</td>
<td>$-5.63 \ (\text{-6.13 to -5.13})^{g}$</td>
</tr>
<tr>
<td>Medium-term intermittent</td>
<td>$-4.22 \ (\text{-5.11 to -3.33})^{d,g}$</td>
<td>179 (78%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Long-term continuous</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

---

*a Separate models built for each time point, all adjusted for gender, race and ethnicity, smoking, diabetes, hypertension, baseline BMI, average medication strength, year of original prescription, and site.

*b n (%) by exposure category within each time point references those with a weight measure versus total number assigned to that exposure category at that time point.

*c Short-term users (referent) had a single phentermine use episode ≤112 days; short-term intermittent users rotated on and off phentermine but never remained on the drug for longer than 112 days. Off-label user groups were defined as follows: medium-term continuous users had a single phentermine treatment episode lasting >112 but ≤365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days.

*d Parameter estimates for intercept approximate percent weight loss of referent group when all covariates are set to their referent value, and parameter estimates for comparison groups should be interpreted as difference in percent weight loss compared with referent group.

*e $P < 0.0001$ for comparing intercept to zero.

*f $P < 0.001$ for comparing intercept to zero.

*g $P < 0.0001$ for comparing percent weight loss in comparison groups to referent group.

n/a, not applicable.
in their health system, incident pregnancies, bariatric procedures, prescription of any weight-loss medication besides phentermine, prescription for phentermine ≥ 37.5 mg/d, CVD outcome (e.g., myocardial infarction), or death. Patients were censored at these times in the Cox model.

**Sensitivity analyses**

Unmeasured patient characteristics or differential response to phentermine could predict greater medication persistence and more weight loss. Therefore, we conducted two sensitivity analyses to assess whether patients who used phentermine for longer did so because the medication was working better for them. In the first sensitivity analysis, we treated phentermine use over follow-up as a fixed exposure, allowing patients to populate their final exposure categories artificially early. We then conducted weight-loss analysis using these fixed exposure categories, beginning at 3 months, when phentermine duration should have been relatively equal between categories.

Second, we conducted a separate “responders-only” sensitivity analysis. In this analysis, we limited inclusion in the cohort to patients who achieved ≥ 3% weight loss by 3 months. Our goal with this analysis was to reduce the potential impact of phentermine nonresponders on lower weight loss in the referent group. The responder analysis was also conducted in two ways, treating phentermine as both time varying and fixed.

To test the sensitivity of our weight findings to varying acceptable time windows for follow-up measures, we reran models using acceptable windows of −/+/90 days, +90 days, −/+60 days, +60 days, −30/+90 days, and −30/+60 days at each time point (6, 12, and 24 months).

To examine whether a higher-risk subgroup of patients might be more likely to experience adverse effects, we repeated HR and BP analyses on the subset of individuals with baseline hypertension diagnoses.

**Results**

**Study population**

We identified 13,972 incident phentermine users (Figure 1). Most were women (84%), and the mean (SD) baseline age was 43.5 (10.7) years; just under half (45%) were non-Hispanic white (Table 1). Baseline BMI was 37.8 (7.2) kg/m², 21% carried a diagnosis of hypertension at baseline, and 12% had a diagnosis of diabetes. Phentermine use groups differed by baseline characteristics, with on-label users slightly more likely to be minorities, younger, not diabetic, and never smokers compared with off-label groups. Off-label groups included a higher proportion of patients taking a lower daily dose of phentermine.

**Weight loss**

At 6, 12, and 24 months after phentermine initiation, weight loss was greater among off-label and intermittent short-term users than our referent short-term single episode users (Table 2). The mean weight change for short-term single episode (referent) phentermine use can be approximated by examining the intercept values for models at each time point (Table 2, Figure 2). By 6 months after drug initiation (or ~3 months after discontinuing phentermine), short-term users averaged 2.7% (95% CI: 2.1%-3.3%) total weight loss. By 12 months, their weight loss was 1.4% (95% CI: 0.7%-2.1%), and by 24 months, the weight change in this group was not different from zero.

The magnitude of difference in weight loss between comparison groups and the referent group varied with duration of follow-up (Table 2, Figure 2). At 6 months, short-term intermittent users lost 1.8% (95% CI: 1.4%-2.1%) additional body weight relative to short-term single episode (referent) users, while medium-term continuous users lost 5.1% (95% CI: 4.7%-5.4%) more. At 12 months, the medium-term intermittent group lost 5.6% (95% CI: 5.1%-6.1%) more weight than short-term single episode users. At 24 months after phentermine initiation,
TABLE 3 Difference in percent weight loss over follow-up: results from multivariable linear models using time-varying exposure among early phentermine responders

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter estimate (95% CI)</strong></td>
<td><strong>n (% of enrolled with weight data available)</strong></td>
<td><strong>Parameter estimate (95% CI)</strong></td>
<td><strong>n (% of enrolled with weight data available)</strong></td>
</tr>
<tr>
<td>Intercept&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.26 (−7.09 to −5.43)&lt;sup&gt;q,a&lt;/sup&gt;</td>
<td>767 (70%)</td>
<td>−4.07 (−5.20 to −2.94)&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>Short-term&lt;sup&gt;e&lt;/sup&gt; Referent</td>
<td>−1.54 (−2.12 to −0.97)&lt;sup&gt;q,a&lt;/sup&gt;</td>
<td>565 (78%)</td>
<td>−1.75 (−2.49 to −1.02)&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>Medium-term continuous&lt;sup&gt;e&lt;/sup&gt;</td>
<td>−3.35 (−3.82 to −2.88)&lt;sup&gt;q,a&lt;/sup&gt;</td>
<td>1,574 (78%)</td>
<td>−3.64 (−4.33 to −2.95)&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>Medium-term intermittent&lt;sup&gt;e&lt;/sup&gt;</td>
<td>−2.25 (−3.34 to −1.15)&lt;sup&gt;q,a&lt;/sup&gt;</td>
<td>103 (82%)</td>
<td>−4.21 (−4.93 to −3.48)&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>Long-term continuous&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n/a</td>
<td>n/a</td>
<td>−7.68 (−10.02 to −5.34)&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Separate models built for each time point, all adjusted for gender, race and ethnicity, smoking, diabetes, hypertension, baseline BMI, average medication strength, year of original prescription, and site. Models include only patients who had documented weight loss of ≥3% by 3 months after starting phentermine.

<sup>b</sup>n (%), by exposure category within each time point references those with a weight measure versus total number assigned to that exposure category at that time point.

<sup>c</sup>Short-term users (referent) had a single phentermine use episode ≤112 days; short-term intermittent users rotated on and off phentermine but never remained on drug for longer than 112 days. Off-label user groups were defined as follows: medium-term continuous users had a single phentermine treatment episode lasting >112 but ≤365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days.

<sup>d</sup>Parameter estimates for intercept approximate percent weight loss of referent group when all covariates are set to their referent value, and parameter estimates for comparison groups should be interpreted as difference in percent weight loss compared with referent group.

<sup>e</sup>P < 0.0001 for comparing intercept to zero.

<sup>f</sup>P < 0.001 for comparing intercept to zero.

<sup>g</sup>P < 0.0001 for comparing percent weight loss in comparison groups with referent group.

<sup>h</sup>n/a, not applicable.
long-term continuous (>12 months) users lost 7.4% (95% CI: 5.8%-9.0%) more weight than short-term single episode users.

When we examined weight change at 3 months using final assigned exposure categories rather than time-varying exposure, individuals in the off-label and intermittent use categories already had greater weight loss than those in the referent group (Supporting Information Table S3). In these models, short-term users had lost 3.5% (95% CI: 3.1%-4.0%) body weight at 3 months, with additional weight loss by group as follows: short-term intermittent, 0.4% (95% CI: 0.1%-0.7%); medium-term continuous, 2.6% (95% CI: 2.3%-2.9%); medium-term intermittent, 3.0% (95% CI: 2.7%-3.3%); and long-term continuous, 3.4% (95% CI: 2.6%-4.3%). Referent and between-group patterns for weight loss at 6, 12, and 24 months showed slightly greater early weight loss among responders, referent group weight loss was greater than in our main analysis (Table 3) but with greater overall weight loss between groups showed slightly greater early weight loss among comparison groups compared with the referent group; however, between-group differences at this early time point were attenuated (Supporting Information Table S4).

Varying the time window for acceptable EHR weight measures did not appreciably change referent or between-group results compared with our main analysis despite a large amount of variability in missingness that occurred as a result of requiring narrower or wider time windows around each point (Supporting Information Table S5). Related to missingness, the reader will note that the number of patients in each exposure category varies over follow-up. In part, this is due to the time-varying nature of our exposure; however, additional reasons for missingness are summarized in Supporting Information Table S6.

**Changes in BP and HR**

At baseline, mean (SD) HR was 79 (12) bpm, and mean (SD) BP was 122 (12)/74 (9). Patients in the short-term single episode (referent) group had no significant change in HR at 6, 12, or 24 months (Table 4). The greatest relative HR increase among medium-term continuous users was at 6 months and was 1.6 (95% CI: 1.0-2.2) bpm higher than the referent group; among medium-term intermittent users, at 12 months, it was 1.1 (95% CI: 0.3-1.9) bpm higher than the referent group. Comparison group changes in HR did not differ from the referent group at 24 months.

SBP in the referent group was stable at 6 and 12 months, but at 24 months, it had increased by 1.8 (0.5-3.2) mmHg, relative to baseline. There was no between-group difference in SBP change at 6 months; however, the comparison groups on the whole had slightly lower BP than the referent group at 12 and 24 months, again with variability in magnitude of difference by group. For example, at 24 months, patients in the long-term continuous user group experienced SBP Δ=−3.3 (−0.8 to −5.9) mmHg relative to the on-label users.

DBP in the referent (short-term) group was stable relative to baseline at 6, 12, and 24 months, and there were no significant between-group differences in DBP over follow-up.

---

**Figure 3** Estimated percent weight loss at 6 months and 1 and 2 years after phentermine initiation among responders; results from multivariable linear models. Models include only phentermine responders, patients who had lost ≥3% body weight by 3 months after initiating medication. Estimates at each time point are from separate multivariable linear models, and n (%) by group over follow-up is presented in Table 2. Note that because real clinical follow-up does not occur at exact 6-month intervals, weights were drawn from an acceptable time window of outpatient visits around each time point of interest, as outlined in Methods. Estimates for the referent group (on-label continuous) were based on the y-intercept of multivariable models in the case in which all covariates are set to referent. Estimates for comparison groups were generated by summing the intercept weight loss and the additional change in weight by group at each time point. Error bars represent 95% CI for each estimate.
### TABLE 4 Change in heart rate (HR) and blood pressure (BP) over follow-up: results from multivariable linear models using time-varying exposure

#### Heart rate results

<table>
<thead>
<tr>
<th>Exposure Category</th>
<th>Parameter estimate ΔHR (bpm) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔHR (bpm) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔHR (bpm) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intersect</td>
<td>1.01 (−0.13 to 2.16)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n/a</td>
<td>0.64 (−0.51 to 1.80)</td>
<td>n/a</td>
<td>0.55 (−0.77 to 1.86)</td>
<td>n/a</td>
</tr>
<tr>
<td>Short-term</td>
<td>0.81 (0.08 to 1.53)&lt;sup&gt;de&lt;/sup&gt;</td>
<td>4,268 (68%)</td>
<td>0.27 (−0.43 to 0.96)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1,439 (79%)</td>
<td>0.27 (−0.84 to 1.38)&lt;sup&gt;de&lt;/sup&gt;</td>
<td>3,672 (79%)</td>
</tr>
<tr>
<td>Short-term intermittent</td>
<td>1.61 (0.99 to 2.24)&lt;sup&gt;de&lt;/sup&gt;</td>
<td>2,363 (75%)</td>
<td>1.16 (0.40 to 1.92)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1,362 (79%)</td>
<td>1.16 (0.40 to 1.92)&lt;sup&gt;de&lt;/sup&gt;</td>
<td>3,672 (79%)</td>
</tr>
<tr>
<td>Long-term continuous</td>
<td>−0.77 (−2.57 to 1.04)&lt;sup&gt;de&lt;/sup&gt;</td>
<td>181 (80%)</td>
<td>1.09 (0.28 to 1.90)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1,184 (88%)</td>
<td>1.09 (0.28 to 1.90)&lt;sup&gt;de&lt;/sup&gt;</td>
<td>3,672 (79%)</td>
</tr>
</tbody>
</table>

#### Blood pressure results

<table>
<thead>
<tr>
<th>Exposure Category</th>
<th>Parameter estimate ΔSBP (mmHg) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔDBP (mmHg) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
<th>Parameter estimate ΔSBP (mmHg) (95% CI)</th>
<th>n (%) enrolled with VS data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intersect</td>
<td>−0.99 (−2.13 to 0.14)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n/a</td>
<td>−0.19 (−1.37 to 0.99)</td>
<td>n/a</td>
<td>−0.19 (−1.18 to 0.99)</td>
<td>n/a</td>
</tr>
<tr>
<td>Short-term</td>
<td>−0.33 (−1.18 to 0.52)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Referent 4,377 (68%)</td>
<td>−0.57 (−1.44 to 0.29)</td>
<td>Referent 3,742 (79%)</td>
<td>−0.57 (−1.44 to 0.29)</td>
<td>Referent 3,742 (79%)</td>
</tr>
<tr>
<td>Short-term intermittent</td>
<td>−0.78 (−1.49 to 0.06)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1,468 (75%)</td>
<td>−0.41 (−1.11 to 0.30)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1,759 (83%)</td>
<td>−0.41 (−1.11 to 0.30)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1,759 (83%)</td>
</tr>
<tr>
<td>Medium-term</td>
<td>0.08 (−0.46 to 0.61)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2,402 (76%)</td>
<td>−0.21 (−0.31 to 0.73)</td>
<td>1,395 (80%)</td>
<td>−0.21 (−0.31 to 0.73)</td>
<td>1,395 (80%)</td>
</tr>
<tr>
<td>Medium-term intermittent</td>
<td>−0.5 (−1.12 to 0.12)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2,363 (75%)</td>
<td>−1.11 (−1.88 to 0.33)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1,362 (79%)</td>
<td>−1.11 (−1.88 to 0.33)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1,362 (79%)</td>
</tr>
<tr>
<td>Long-term continuous</td>
<td>−0.36 (−0.11 to 0.82)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>183 (80%)</td>
<td>−0.39 (−0.95 to 0.18)</td>
<td>1,200 (88%)</td>
<td>−0.39 (−0.95 to 0.18)</td>
<td>1,200 (88%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Separate models built for each time point, all adjusted for gender, race and ethnicity, smoking, diabetes, hypertension, baseline HR or BP tertile, average medication strength, year of original prescription, and site.<br>
<sup>b</sup>n (%) by exposure category within each time point references those with a HR measure versus total number assigned to that exposure category at that time point.<br>
<sup>c</sup>Short-term users (referent) had a single phentermine use episode ≤112 days; short-term intermittent users rotated on and off phentermine but never remained on the drug for longer than 112 days. Off-label user groups were defined as follows: medium-term continuous users had a single phentermine treatment episode lasting >112 but ≤365 days; medium-term intermittent users had multiple treatment episodes in which at least one exceeded 112 days; and long-term continuous users had a single episode lasting >365 days.<br>
<sup>d</sup>Parameter estimates for intercept approximate change from baseline in BP or HR of referent group when all covariates are set to their referent value, and parameter estimates for comparison groups should be interpreted as difference in BP or HR compared with referent group.<br>
<sup>e</sup>P < 0.0001 for comparing HR and BP change in comparison groups with referent group.<br>
<sup>f</sup>P = 0.005 for comparing HR change in comparison groups with referent group.<br>
<sup>g</sup>P = 0.008 for comparing HR change in comparison groups with referent group.<br>
<sup>h</sup>P = 0.02 for comparing SBP change in comparison groups with referent group.<br>
<sup>i</sup>P = 0.03 for comparing SBP change in comparison groups with referent group.<br>
<sup>j</sup>P = 0.03 for comparing SBP change in comparison groups with referent group.<br>
<sup>k</sup>VS, vital signs; n/a, not applicable.
TABLE 5 Results from multivariable Cox modelsa: hazard ratio for composite outcome of incident myocardial infarction, stroke, CVD intervention, or death up to 3 years after phentermine initiation

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>CIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term (referent)</td>
<td>Reference</td>
</tr>
<tr>
<td>Short-term intermittent</td>
<td>0.74</td>
</tr>
<tr>
<td>Medium-term intermittent</td>
<td>0.50</td>
</tr>
<tr>
<td>Medium &amp; long-term continuous combinedc</td>
<td>1.58</td>
</tr>
</tbody>
</table>

aModels include phentermine exposure as time-varying covariate as well as gender, race and ethnicity, smoking, diabetes, hypertension, baseline BMI, average medication strength, year of original prescription, and site.
bP = 0.30 for examining differences between groups.
cThere were no events in long-term continuous subgroup; therefore, to allow this group to contribute person-time to the models, it was grouped with the medium-term continuous exposure category.

Among patients with baseline hypertension, BP increased more over time than in our main cohort (Supporting Information Table S7), but there were no 6- or 12-month differences by phentermine exposure category. By 24 months, SBP in longer-term phentermine use groups for hypertensive patients was lower than among short-term hypertensive users. Between-group comparisons for ΔHR among patients with hypertension were similar to our main analysis.

Incident CVD or death

Up to 3 years after the index date, incidence of composite adverse outcomes was low. Forty-one people out of 13,972 (0.3%) experienced an event (for group-specific event rates, see Supporting Information Table S8). Because there were no qualifying CVD or death events in the long-term continuous user group, these individuals were grouped with the medium-term continuous users for analysis. Multivariable Cox regression models treating phentermine use as a time-varying covariate found no significant difference in risk of incident CVD or death between groups (Table 5).

Discussion

In this large cohort study, a longer duration of phentermine use was associated with clinically significant greater weight loss up to 2 years after initiating medication, with no observed increase in risk for incident cardiovascular events or death over 3 years of follow-up. Discontinuation of phentermine consistently resulted in weight regain.

There are few prior studies examining long-term use of phentermine, particularly as monotherapy for obesity (6,20,22,32). However, in 2012, a new brand-named drug, Phentermine/Topiramate-CR, earned FDA approval for long-term (≥12 months) use as a weight-loss medication. Randomized trial data from patients taking this medication for 24 months showed sustained 9% to 11% weight loss without increased cardiovascular risk (33,34). While these findings suggested possible safety and effectiveness of using phentermine monotherapy for longer than 12 weeks, Phentermine/Topiramate-CR has a lower daily phentermine dose than is typical of monotherapy, necessitating additional studies on this topic to inform clinical care.

Experts now recognize obesity as a chronic disease, best treated with comprehensive intensive lifestyle intervention and long-term follow-up, using tools such as pharmacotherapy and bariatric surgery to supplement lifestyle change as needed (35). There is a need for longer-term effective, safe, and affordable pharmacotherapy that can be used as an adjunct to lifestyle change advice. Longer-term use of phentermine in the United States indeed appears to be a pervasive practice (36); 30% of our cohort was made up of individuals with at least one phentermine episode lasting >12 weeks.

Our findings show that patients prescribed phentermine for ≤3 months, as is currently directed by labeling, did not experience durable clinically significant weight loss. In contrast, patients using phentermine off-label for longer periods generally experienced greater weight loss that was sustained so long as they remained on medication. For example, medium-term users (those on phentermine for up to 12 months) averaged significantly greater weight loss than the referent group at 12 months but had regained nearly 70% by 24 months.

Findings from our analysis of phentermine responders, patients with at least 3% weight loss by 3 months after medication initiation, underscore the importance of not continuing to prescribe a medication to patients who do not appear to experience clinical benefit (Figure 2, Figure 3). Patients who responded early across all groups reached clinically significant levels of weight loss (≥5% on average) by 6 months and generally had more durable weight loss. This finding aligns with similar observations from the literature on diet-induced weight loss, in which early response tends to predict greater overall weight-loss success (2,37).

We observed a slight increase in average HR among phentermine users that normalized after discontinuation. This finding is consistent with the drug’s mechanism of action, and the magnitude of increase is similar to prior studies of phentermine-containing medications (33). The relative decrease in SBP associated with longer-term phentermine use, despite the sympathomimetic effect of the drug, may be attributable to greater weight loss, resulting in a net-lowering effect. We observed this relative BP lowering even among patients with baseline hypertension. We cannot exclude the occurrence of rare hypertensive events resulting in emergency department visits because our analyses relied on outpatient information.

Importantly, we did not observe an increase in risk of CVD or death related to the duration of phentermine use up to 3 years after initiating medication. Additional study of these rare outcomes is needed, including research with a larger higher-risk population of long-term users and greater duration of follow-up. Our overall low rate of the composite outcome (0.3% of all patients experienced an event) may be related to the patient population in this study: 85% were women, and we excluded individuals with prevalent CVD. However, our findings are consistent with those from placebo-controlled trials of Phentermine/Topiramate-CR, in which 7 of 2,581 (0.3%) of active drug patients experienced a similar composite outcome (34) and provide some reassurance about the relative safety of phentermine prescribing in low-risk individuals.

Our study has several important limitations. First, we cannot interpret the relationship between duration of phentermine use and percent weight loss as causal. Our referent group likely includes patients who discontinued phentermine because of ineffectiveness, and, conversely,
our comparison groups contained people who remained on medication precisely because it was effective for them. Our sensitivity analyses support this suspicion; differences in weight loss favored longer-term users even at the 3-month mark when phentermine duration was approximately equal between groups. We tried to mitigate this bias by limiting our weight analyses to patients with at least one refill and by conducting a responders-only analysis; however, the possibility for residual confounding and/or reverse causality remains.

Duration of follow-up differed between exposure categories and was systematically greater for longer-term phentermine users. This could have led to an ascertainment bias between categories, but it is not clear in which direction our results would be biased.

We did not address provider- or health-system–level variables, and it is possible that these factors differed systematically between groups in a way that favored longer-term phentermine users. For example, if physicians willing to prescribe phentermine for longer durations are more likely to be obesity specialists (36), or if this pattern of prescribing is more likely to be associated with participation in a comprehensive weight-management program, such differences could confound the relationship between phentermine use duration and weight loss.

Our data should be interpreted with regard to dispensing of phentermine and may not fully indicate whether patients reliably took the medication. Similarly, we did not specifically study appropriate dosing for longer-term use of this medication. However, we did not examine coadministered medications that could have led to weight loss or gain or changing BP or HR as a side effect (e.g., topiramate, metoprolol). We did censor for incident use of any FDA-approved weight-loss medications in follow-up.

As with any EHR-based study, there was loss to follow-up in our cohort over time, with missingness possibly not at random. We did find that a large portion of the missingness (e.g., 32% at 24 months) was due to patients prescribed phentermine in later years reaching the end of the study period (September 30, 2015), which is unlikely to be a source of bias. On a related note, the number of patients in our “long-term continuous” use group was quite small relative to the other groups; therefore, additional study with a larger group of patients using phentermine for ≥12 months would help to bolster our findings.

Finally, we did not attempt to characterize other possible adverse outcomes of phentermine use such as anxiety, sleep disturbance, or addiction. A clinical trial with regular standardized outcome assessments at predetermined intervals would be important to accurately describe the risk of such events.

**Conclusion**

Recommendations to limit phentermine use to less than 3 months do not align with current concepts of pharmacological treatment for patients with obesity. Our results show that longer-term phentermine users experienced greater weight loss without apparent increases in cardiovascular risk. Given the chronicity of obesity and the paucity of good long-term treatment options for this condition, these data provide reinsurance that longer-term phentermine monotherapy is a reasonable treatment option in low-risk individuals. Still, there is a need for randomized controlled trials to definitively establish the safety and effectiveness of protracted phentermine monotherapy.

**Acknowledgments**

We thank Dr. Sengwee Toh of the Department of Population Medicine at Harvard Pilgrim Healthcare Institute/Harvard Medical School for providing his input and expertise on pharmacoepidemiologic methods for this paper. Additionally, we thank the analysts in each PORTAL region for their time and effort in extracting the EHR data used in this study.

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**References**


MEMORANDUM

TO:    Mark Bechtel, M.D., President
       Members, State Medical Board of Ohio

FROM:  Kimberly C. Anderson, Chief Legal Counsel

RE:    Initial Circulation of Rules

DATE:  December 30, 2020 (UPDATED 1/7/21)

Several sets of rules are due for their five-year rule review in 2021. Technical changes have been proposed, including some required by recent legislation.

4731-11-08 Prescribing to Self and Family: Proposed no change;

4731-14-01 Pronouncement of Death: Edits to reflect statutory changes;

4731-23-01 Definitions: Proposed no change;

4731-23-02 Delegation of Medical Tasks Changes needed for sections dealing with DODD statutes which have been repealed. I have reached out to DODD for comments;

4731-23-03 Delegation of Medical Tasks: Prohibitions Proposed no change;

4731-23-04 Violations Proposed no change;

4731-26-01 Definitions Updated to add and delete license types to reflect statutory changes; updated language change to “license” from “certificate”; 

4731-26-02 Prohibitions Updated statutory authority and amplifying statutes;

4731-26-03 Violations; Miscellaneous Updated to add and delete license types to reflect statutory changes; updated statutory authority and amplifying statutes

Requested action: Approve rules for initial circulation to interested parties.
4731-11-08. Utilizing controlled substances for self and family members

(A) Accepted and prevailing standards of care presuppose a professional relationship between a patient and physician when the physician is utilizing controlled substances. By definition, a physician may never have such a relationship with himself or herself. Thus, a physician may not self-prescribe or self-administer controlled substances. This paragraph does not prohibit a physician from obtaining a schedule V controlled substance for personal use in conformance with state and federal laws, in the same manner that a non-physician may obtain a schedule V controlled substance.

(B) Accepted and prevailing standards of care require that a physician maintain detached professional judgment when utilizing controlled substances in the treatment of family members. A physician shall utilize controlled substances when treating a family member only in an emergency situation which shall be documented in the patient's record.

(C) For purposes of this rule, "family member" means a spouse, parent, child, sibling or other individual in relation to whom a physician's personal or emotional involvement may render that physician unable to exercise detached professional judgment in reaching diagnostic or therapeutic decisions.

Cite as Ohio Admin. Code 4731-11-08

History. Five Year Review (FYR) Dates: 08/17/2016 and 08/17/2021
Promulgated Under: 119.03
Statutory Authority: 4731.05
Rule Amplifies: 4731.22
Prior Effective Dates: 11/11/98, 3/15/01, 9/30/08

Prior History: (Effective: 09/30/2008
R.C. 119.032 review dates: 06/06/2008 and 09/30/2013
Promulgated Under: 119.03
Statutory Authority: 4731.05, 4731.052
Rule Amplifies: 4731.22, 4731.052
Prior Effective Dates: 11/11/98; 3/15/01 )
4731-14-01 Pronouncement of death.

(A) Only an individual holding one of the following current certificates or licenses may pronounce a person dead:

1. A certificate to practice medicine and surgery or osteopathic medicine and surgery issued under section 4731.14 or 4731.29 of the Revised Code;
2. A training certificate issued under section 4731.291 of the Revised Code;
3. A clinical research faculty certificate issued under section 4731.293 of the Revised Code;
4. A special activities certificate issued under section 4731.294 of the Revised Code;
5. A certificate of authority to practice as a certified nurse practitioner or clinical nurse specialist issued under section 4731.297 of the Revised Code;
6. A license to practice as a registered nurse issued under section 4723.09 of the Revised Code, when the holder acts in compliance with section 4723.36 of the Revised Code.
7. A license to practice as a physician assistant issued under section 4730.12 of the Revised Code, when the holder acts in compliance with section 4730.202 of the Revised Code;
8. A certificate of conceded eminence issued under section 4731.297 of the Revised Code;
9. A certificate to practice podiatric medicine and surgery issued under section 4731.56, 4731.57, or 4731.571 of the Revised Code.

(B) A physician holding a current certificate to practice medicine or surgery or osteopathic medicine and surgery issued under section 4731.14 or 4731.29 of the Revised Code may pronounce a person dead without personally examining the body of the deceased only if a competent observer has recited the facts of the deceased’s present medical condition to the physician and the physician is satisfied that death has occurred.

(C) For purposes of this rule a competent observer shall mean one of the following:

1. A licensed practical nurse holding a current license issued under Chapter 4723. of the Revised Code;
2. An EMT-Basic holding a current certificate issued under section 4765.30 of the Revised Code;
3. An EMT-intermediate holding a current certificate issued under section 4765.30 of the Revised Code;
4. A EMT-paramedic holding a current certificate issued under section 4765.30 of the Revised Code;
5. A chiropractor holding a current certificate issued under Chapter 4734. of the Revised Code;
6. An individual authorized to pronounce a person dead under paragraph (A) of this rule;
(7) A coroner's investigator as referenced in section 313.05 of the Revised Code.

Replaces: 4731-14-01
Definitions.

As used in Chapter 4731-23 of the Administrative Code:

(A) "Administer" means the direct application of a drug, whether by injection, inhalation, ingestion, or any other means to a person.

(B) "Delegate" means to transfer authority for the performance of a medical task to an unlicensed person.

(C) "On-site supervision" means that the physical presence of the physician is required in the same location (e.g., the physician's office suite) as the unlicensed person to whom the medical task has been delegated while the medical task is being performed. "On-site supervision" does not require the physician's presence in the same room.

(D) "Physician" means an individual authorized by Chapter 4731. of the Revised Code to practice medicine and surgery, osteopathic medicine and surgery, or podiatric medicine and surgery.

(E) "Task" includes, but is not limited to, a routine medical service not requiring the special skills of a licensed provider.

(F) "Unlicensed person" means an individual who is not licensed or otherwise specifically authorized by the Revised Code to perform the delegated medical task.

(G) "Drug" means the same as in division (E) of section 4729.01 of the Revised Code.

Effective: 11/30/2016
Five Year Review (FYR) Dates: 08/16/2016 and 11/30/2021
Promulgated Under: 119.03
Statutory Authority: 4731.05, 4731.053
Rule Ammplies: 4731.053, 4731.22, 4731.34
Prior Effective Dates: 9/30/01
4731-23-02 Delegation of medical tasks.

(A) A physician shall not delegate the performance of a medical task unless that physician has complied with all of the requirements of this chapter of the Administrative Code and the delegation otherwise conforms to minimal standards of care of similar physicians under the same or similar circumstances.

(B) Prior to a physician's delegation of the performance of a medical task, that physician shall determine each of the following:

(1) That the task is within that physician's authority;

(2) That the task is indicated for the patient;

(3) The appropriate level of supervision;

(4) That no law prohibits the delegation;

(5) That the person to whom the task will be delegated is competent to perform that task; and,

(6) That the task itself is one that should be appropriately delegated when considering the following factors:

(a) That the task can be performed without requiring the exercise of judgment based on medical knowledge;

(b) That results of the task are reasonably predictable;

(c) That the task can safely be performed according to exact, unchanging directions;

(d) That the task can be performed without a need for complex observations or critical decisions;

(e) That the task can be performed without repeated medical assessments; and,

(f) That the task, if performed improperly, would not present life threatening consequences or the danger of immediate and serious harm to the patient.

(C) When a physician delegates the administration of drugs, that physician shall provide on-site supervision, except in the following situations:

(1) When the physician has transferred responsibility for the on-site supervision of the unlicensed person who is administering the drug to another physician and that physician has knowingly accepted that responsibility on a patient-by-patient basis; or

(2) In the routine administration of a topical drug, such as a medicated shampoo.

(3) When delegation occurs pursuant to section 5126.36 of the Revised Code within the programs and services offered by a county board of developmental disabilities. Statute is repealed. Check with DODD.
(4) When delegation occurs pursuant to section 5123.42 of the Revised Code. Is statute still applicable? Check with DODD.

(5) When written policies and procedures have been adopted for the distribution of drugs by an unlicensed person to individuals incarcerated in state correctional institutions as defined in division (A) of section 2796.01 of the Revised Code, other correctional facilities including county and municipal jails, workhouses, minimum security jails, halfway houses, community residential centers, regional jails and multi-county jails, or any other detention facility as defined in division (F) of section 2921.01 of the Revised Code.

(D) This chapter of the Administrative Code shall not apply if the rules contained herein:

(1) Prevent an individual from engaging in an activity performed for a handicapped child as a service needed to meet the educational needs of the child, as identified in the individualized education program developed for the child under Chapter 3323. of the Revised Code;

(2) Prevent delegation from occurring pursuant to section 5126.36 of the Revised Code within the programs and services offered by a county board of developmental disabilities; Statute is repealed. Check with DODD.

(3) Conflict with any provision of the Revised Code that specifically authorizes an individual to perform a particular task;

(4) Conflict with any rule adopted pursuant to the Revised Code that is in effect on the effective date of this section, as long as the rule remains in effect, specifically authorizing an individual to perform a particular task;

(5) Prohibit a perfusionist from administering drugs intravenously while practicing as a perfusionist.

Effective: 11/30/2016
Five Year Review (FYR) Dates: 08/16/2016 and 11/30/2021
Promulgated Under: 119.03
Statutory Authority: 4731.05, 4731.053
Rule Amplifies: 4731.22, 4731.053, 4731.34
Prior Effective Dates: 9/30/01, 5/31/02
4731-23-03 Delegation of medical tasks; Prohibitions.

(A) A physician shall not delegate the practice of medicine as defined in section 4731.34 of the Revised Code unless specifically authorized to do so in the Revised Code or by an administrative rule adopted pursuant to the Revised Code and which became effective prior to April 10, 2001. Nothing in this chapter of the Administrative Code shall prohibit the performance of emergency medical tasks.

(B) A physician shall not delegate a task to an unlicensed person if the task is beyond that person's competence. In a hospital, as defined in section 3727.01 of the Revised Code, or an ambulatory care center affiliated with the hospital (if the center meets the same credentialing, quality assurance, and utilization review standards as the hospital) wherein unlicensed persons are employed or otherwise authorized by the governing authority of the institution to perform specific medical tasks, one factor the physician shall take into account is the policies by which the employer or the governing authority of the institution seeks to ensure that competent persons will be performing the delegated tasks.

(C) A physician shall not delegate a medical task that is not within the authority of that physician or is beyond the physician's training, expertise, or normal course of practice.

(D) A physician shall not transfer his or her responsibility for supervising an unlicensed person in the performance of a delegated medical task, except to another physician who has knowingly accepted that responsibility.

(E) A physician shall not authorize or permit an unlicensed person to whom a medical task is delegated to delegate the performance of that task to another person.

(F) Except as provided in divisions (D)(4) to (D)(8) of section 4731.053 of the Revised Code, a physician shall not delegate to an unlicensed person the administration of anesthesia, controlled substances, or drugs administered intravenously.

(G) The supervising physician retains responsibility for the manner in which the delegated task is carried out.

Five Year Review (FYG) Dates: 08/17/2016 and 08/17/2021
Promulgated Under: 119.03
Statutory Authority: 4731.05, 4731.053
Rule Amplifies: 4731.22, 4731.34
Prior Effective Dates: 9/30/01, 5/31/02
4731-23-04 Violations.

(A) A violation of any provision of any rule in this chapter of the Administrative Code, as determined by the board, shall constitute "a departure from, or the failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances, whether or not actual injury to a patient is established," as that clause is used in division (B)(6) of section 4731.22 of the Revised Code.

(B) A violation of any provision of any rule in this chapter of the Administrative Code that pertains to the administration of drugs, as determined by the board, shall constitute "failure to maintain minimal standards applicable to the selection or administration of drugs," as that clause is used in division (B)(2) of section 4731.22 of the Revised Code.

Five Year Review (FYR) Dates: 08/17/2016 and 08/17/2021
Promulgated Under: 119.03
Statutory Authority: 4731.05, 4731.053
Rule Amplifies: 4731.22, 4731.34
Prior Effective Dates: 9/30/01
4731-26-01 Definitions.

For purposes of Chapter 4731-26 of the Administrative Code:

(A) "Licensee" means any of the following:

1) An individual holding a license certificate to practice as a physician assistant under Chapter 4730. of the Revised Code;

2) An individual holding a license certificate to practice medicine and surgery, osteopathic medicine and surgery, or podiatric medicine and surgery under Chapter 4731. of the Revised Code;

3) An individual holding a license certificate to practice a limited branch of medicine under Chapter 4731. of the Revised Code;

4) An individual holding a license to practice dietetics under Chapter 4759 of the Revised Code

5) An individual holding a license certificate of registration as an anesthesiologist assistant under Chapter 4760. of the Revised Code;

6) An individual holding a license or limited permit to practice respiratory care under Chapter 4761 of the Revised Code

7) An individual holding a license certificate to practice as an acupuncturist or an oriental medicine practitioner under Chapter 4762. of the Revised Code;

8) An individual holding a license certificate to practice as a radiologist assistant under Chapter 4774. of the Revised Code; or

9) An individual holding a license to practice as a genetic counselor under Chapter 4778. of the Revised Code.

(B) "Health care services" means examination, consultation, health care, treatment, or other services provided by a licensee under the legal authority conferred by a license, certificate, permit or registration issued by the board.

(C) "Patient" means a person for whom the licensee has provided health care services, whether provided by mutual consent or implied consent, or provided without consent pursuant to a court order. Once a licensee-patient relationship is established, a person remains a patient until the relationship is terminated. Patient includes any of the following:

1) A person who is receiving or has received health care services from the licensee without termination of the licensee-patient relationship; or

2) A person who meets the criteria of a key third party, as that term is defined in paragraph (D) of this rule.

(D) "Key third party" means an individual closely involved in the patient's decision-making regarding health care services, including but not limited to, the patient's spouse or partner, parents, child, sibling, or guardian. For purposes of this chapter, an individual's status as a key
third party ceases upon the termination of the licensee-patient relationship or upon termination of the individual's relationship with the patient.

(E) "Chaperone" means a third person who, with the patient's consent, is present during a medical examination.

(F) "Former patient" means one of the following:

1. A person for whom the licensee has not rendered health care services since the licensee-patient relationship was terminated; or

2. A person who has otherwise been admitted, discharged, or referred to another licensee for care subsequent to receipt of health care services by a licensee in an emergency setting or on an episodic basis, and such action has been recorded in the person's medical record or chart.

(G) "Intimate examination" means an examination of the pelvic area, genitals, rectum, breast, or prostate.

(H) "Sexual misconduct" means conduct that exploits the licensee-patient relationship in a sexual way, whether verbal or physical, and may include the expression of thoughts, feelings, or gestures that are sexual or that reasonably may be construed by a patient as sexual. Sexual misconduct includes sexual impropriety, sexual contact, or sexual interaction as follows:

1. "Sexual impropriety" means conduct by the licensee that is seductive, sexually suggestive, disrespectful of patient privacy, or sexually demeaning to a patient, including but not limited to, the following:

   a. Neglecting to employ disrobing or draping practices respecting the patient's privacy;

   b. Subjecting a patient to an intimate examination in the presence of a third party, other than a chaperone, without the patient's consent or in the event such consent has been withdrawn;

   c. Making comments that are not clinically relevant about or to the patient, including but not limited to, making sexual comments about a patient's body or underclothing, making sexualized or sexually demeaning comments to a patient, criticizing the patient's sexual orientation, or making comments about potential sexual performance;

   d. Soliciting a date or romantic relationship with a patient;

   e. Participation by the licensee in conversation regarding the sexual problems, sexual preferences, or sexual fantasies of the licensee;

   f. Requesting details of the patient's sexual history, sexual problems, sexual preferences, or sexual fantasies when not clinically indicated for the type of health care services; and

   g. Failing to offer the patient the opportunity to have a third person or chaperone in the examining room during an intimate examination and/or failing to provide a third person or chaperone in the examining room during an intimate examination upon the request of the patient.

2. "Sexual contact" includes, but is not limited to, the following:
(a) Touching a breast or any body part that has sexual connotation for the licensee or patient, for any purpose other than appropriate health care services, or where the patient has refused or has withdrawn consent; and

(b) Examining or touching of the patient's genitals without the use of gloves.

(3) "Sexual interaction" means conduct between a licensee and patient, whether or not initiated by, consented to, or participated in by a patient, that is sexual or may be reasonably interpreted as sexual, including but not limited to, the following:

(a) Sexual intercourse, genital to genital contact;

(b) Oral to genital contact;

(c) Oral to anal contact, genital to anal contact;

(d) Kissing in a romantic or sexual manner;

(e) Encouraging the patient to masturbate in the presence of the licensee or masturbation by the licensee while the patient is present;

(f) Offering to provide health care services, such as drugs, in exchange for sexual favors; and

(g) Performing an intimate examination without clinical justification.

(h) Conduct that is sexually demeaning to a patient or which demonstrates a lack of respect for the patient's privacy.

(4) Conduct described in paragraphs (H)(1)(a), (H)(1)(b), (H)(1)(g), and (H)(2)(b) of this rule does not constitute sexual misconduct when all of the following criteria are met:

(a) The conduct occurred during the rendering of health care services in an emergency setting;

(b) The health care services rendered were clinically necessary;

(c) The patient was unconscious or otherwise unable to consent to health care services; and

(d) The patient's clinical condition required immediate action and the licensee's violation of the provisions of paragraph (H)(1)(a), (H)(1)(b), (H)(1)(g), or (H)(2)(b) of this rule, as applicable, was due to circumstances not within the licensee's control.

(I) "Emergency setting" means an emergency department.

(J) "Board" means the state medical board of Ohio.

(K) "Conduct" includes, but is not limited to the following:

(1) Behaviors, gestures, or expressions, whether verbal or physical; or

(2) The creation, receipt, exchange, saving, or sending of images or communications, whether verbal or written, via a telecommunications device.
Effective: 6/30/2016
Five Year Review (FYR) Dates: 03/15/2016 and 06/30/2021
Promulgated Under: 119.03
Statutory Authority: 4730.07, 4731.05, 4759.05, 4760.19, 4761.03, 4762.19, 4774.11, 4778.12
Rule Amplifies: 4730.25, 4731.22, 4759.07, 4760.13, 4761.09, 4762.13, 4774.13, 4778.14
Prior Effective Dates: 11/30/06, 11/30/10
**4731-26-02 Prohibitions.**

Sexual misconduct, as that term is defined in paragraph (H) of rule 4731-26-01 of the Administrative Code, between a licensee and a patient is never diagnostic or therapeutic.

(A) A licensee shall not engage in sexual misconduct with a patient or key third party, as that term is defined in paragraph (C) of rule 4731-26-01 of the Administrative Code.

(B) Conduct included within the definition of sexual misconduct occurring between a licensee and a former patient constitutes sexual misconduct and is prohibited if it meets any of the following criteria:

1. The conduct occurred within ninety days after the licensee-patient relationship was terminated;

2. The conduct occurred between a psychiatrist and a person to whom the psychiatrist formerly provided psychiatric or mental health services, and the conduct is in violation of the code of ethics of the "American Psychiatric Association"; or

3. The board determines that the conduct constitutes sexual misconduct upon consideration of the following factors:
   (a) The duration of the licensee-patient relationship;
   (b) The nature of the health care services provided;
   (c) The lapse of time since the licensee-patient relationship ended;
   (d) The extent to which the former patient confided personal or private information to the licensee;
   (e) The degree of emotional dependence that the former patient has or had on the licensee; and
   (f) The extent to which the licensee used or exploited the trust, knowledge, emotions, or influence derived from the previous licensee-patient relationship.

Replaces: 4731-26-02
4731-26-03 Violations, miscellaneous.

(A) Except as provided in paragraph (C) of this rule, a violation of rule 4731-26-02 of the Administrative Code, as determined by the board, shall constitute the following:

(1) For a physician, massage therapist, or cosmetic therapist, "a departure from, or the failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances, whether or not actual injury to a patient is established," as that clause is used in division (B)(6) of section 4731.22 of the Revised Code.

(2) For a physician assistant, "a departure from, or failure to conform to, minimal standards of care of similar physician assistants under the same or similar circumstances, regardless of whether actual injury to a patient is established," as that clause is used in division (B)(19) of section 4730.25 of the Revised Code.

(3) For a dietitian, "a departure from, or failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances, whether or not actual injury to a patient is established," as that clause is used in division (A)(11) of section 4759.07 of the Revised Code.

(4) For an anesthesiologist assistant, "a departure from, or failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances whether or not actual injury to the patient is established," as that clause is used in division (B)(4) of section 4760.13 of the Revised Code.

(5) For a respiratory care professional or limited permit holder, "a departure from, or a failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances whether or not actual injury to a patient is established," as that clause is used in division (A)(10) of section 4761.09 of the Revised Code.

(6) For an acupuncturist or oriental medicine practitioner, "a departure from, or failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances whether or not actual injury to the patient is established," as that clause is used in division (B)(4) of section 4762.13 of the Revised Code.

(7) For a radiologist assistant, "a departure from, or failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances whether or not actual injury to the patient is established," as that clause is used in division (B)(4) of section 4774.13 of the Revised Code.

(8) For a genetic counselor, "a departure from, or failure to conform to, minimal standards of care of similar practitioners under the same or similar circumstances whether or not actual injury to the patient is established," as that clause is used in division (B)(4) of section 4778.14 of the Revised Code.

(B) Where the alleged conduct does not in itself constitute sexual misconduct, as defined in paragraph (H) of rule 4731-26-01 of the Administrative Code, the board may consider expert testimony or other evidence in making its determination as to whether the conduct of the licensee constitutes sexual misconduct.
(C) Nothing in this rule shall limit the board’s authority to investigate and take action under section 4730.25, 4731.22, 4759.07, 4760.13, 4761.09, 4762.13, 4774.13 or 4778.14 of the Revised Code.

Effective: 6/30/2016
Five Year Review (FYR) Dates: 03/15/2016 and 06/30/2021
Promulgated Under: 119.03
Statutory Authority: 4730.07, 4731.05, 4759.05, 4760.19, 4761.03, 4762.19, 4774.11, 4778.12
Rule Amplifies: 4730.25, 4731.22, 4759.07, 4760.13, 4761.09, 4762.13, 4774.13, 4778.14
Prior Effective Dates: 11/30/06, 11/30/10
MEMORANDUM

TO: Mark Bechtel, M.D., President
Members, State Medical Board of Ohio

FROM: Kimberly C. Anderson, Chief Legal Counsel

RE: CME Rules

DATE: December 30, 2020; Updated January 5, 2021

Sixteen rules were filed in the package related to physician continuing medical education. The public hearing was held on December 4, 2020, and the Hearing Examiner’s report is attached. The JCARR meeting was held on December 7, 2020. No comments were received. JCARR jurisdiction was scheduled to end on January 3, 2021.

HB 442 was recently adopted by the General Assembly. It will become effective 90 days after signature by Governor DeWine, likely in early April.

Section 4745.04(C)(2) is being amended to increase the number of CME credits which may be earned through providing volunteer health care services. Currently up to three credits may be earned and the new legislation permits physicians to earn up to ten hours. The legislation also adds language regarding the calculation so that physicians may earn continuing medical education at the rate of one credit hour for every five hours spent providing healthcare services as a volunteer. A copy of the relevant portion of the legislation is attached.

In addition, the continuing medical education requirement for holders of a clinical research faculty license has been eliminated.

These changes will require an amendment to rules 4731-10-02(A)(6), (F) and 4731-10-08(D). I have placed these rules in TBR status so that they may be refiled with the amendments.

The following amendments are recommended:

4731-10-02  Requisite Hours of Continuing Medical Education for License Renewal or Reinstatement

(A)(6) Pursuant to section 4745.04 of the Revised Code, providing health care services in Ohio, as a volunteer, to indigent and uninsured persons, up to a maximum of three hours per registration period.

(F) During a clinical research registration period, every holder of a clinical research faculty
certificate shall be required to complete seventy-five hours of CME pursuant to the requirements of section 4731.293 of the Revised Code. Such hours must meet the criteria established in paragraph (A)(1) of this rule. If a holder of a clinical research faculty certificate has not completed the requisite hours of CME, a holder is not eligible for certificate renewal until such time as the requisite hours have been completed. Any CME undertaken after the end of a clinical research registration period and utilized for purposes of renewing a suspended certificate cannot also be utilized to meet the CME requirement of the current clinical research registration period.

4731-10-08 Evidence of Continuing Medical Education

(D) Licensees seeking to receive credit pursuant to paragraph (A)(36) of rule 4731-10-02 of the Administrative Code shall maintain a log of their qualifying activities. The log shall indicate the dates the health care services were provided, the number of hours spent providing health care services on those dates, and the location where the health care services were provided.

Requested motion: I move to amend rules 4731-10-02 and 4731-10-08 as set forth in the December 30, 2020 memorandum from Ms. Anderson and to adopt the rules in this package at a later date.
Pursuant to Section 119.03, Ohio Revised Code, a public hearing was held on December 4, 2020, to hear comments concerning proposed changes to the administrative rules of the State Medical Board of Ohio (“Board”). R. Gregory Porter, Hearing Examiner, presided.

**PURPOSE OF THE HEARING**

The following changes are proposed:

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<td>Requisite Hours of Continuing Medical Education for License Renewal or Reinstatement</td>
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PROCEDURAL MATTERS

1. The record was held open until 5:00 p.m. on December 4, 2020, for the purpose of receiving written comments concerning the proposed changes to the Ohio Administrative Code. No comments were received.

2. The hearing examiner marked Exhibits 1, 2, and 3 post hearing.

3. Due to the ongoing Covid-19 emergency, the hearing was conducted via videoconferencing software.

TESTIMONY HEARD

Kimberly Anderson, Chief Legal Counsel for the Board

EXHIBITS EXAMINED

Exhibit 1: Copy of the rules originally filed in Package 189167 with JCARR, Secretary of State, and the Legislative Services Commission via the Electronic Rule-Filing System on October 30, 2020 and a copy of the confirmation of filing. Also included are copies of the confirmation of the revised filings on November 3 and November 24, 2020.

Exhibit 2: Copy of the Notice of Public Hearing for the rules in Package 189167 showing it was filed on October 30, 2020. Also attached are the revised Notices of Public Hearing showing that it was filed November 3, 2020 and November 24, 2020.

Exhibit 3: Copies of the address portion of e-mails sent to persons and organizations pursuant to their standing request to be notified when the Medical Board proposes rules.

SUMMARY OF EVIDENCE

1. Kimberly Anderson, Chief Legal Counsel for the Board, identified Exhibits 1 through 3. She further testified with respect to the notice that the Board provided to the public and interested parties regarding the proposed rule changes, and with respect to other procedural matters. (Hearing Transcript at 6-8)

2. No comments were received concerning the proposed changes to the Board’s administrative rules.
CONCLUSION

The requirements of Chapter 119, Ohio Revised Code, have been satisfied. The Board may proceed to take action regarding the proposed rescission of rules 4731-10-01, 4731-10-02, 4731-10-03, 4731-10-04, 4731-10-05, 4731-10-06, 4731-10-07, 4731-10-08, 4731-10-09, 4731-10-10, and 4731-10-11; and the proposed adoption of new rules 4731-10-01, 4731-10-02, 4731-10-03, 4731-10-04, and 4731-10-08.

R. Gregory Porter
Hearing Examiner
registered sanitary environmental health specialist shall use the title "registered sanitary" "registered environmental health specialist" or the abbreviation "R.S." "R.E.H.S." after the person's name, or represent self as a registered sanitary environmental health specialist. Whoever violates this section is guilty of a misdemeanor of the fourth degree.

Sec. 4745.04. (A) As used in this section:

(1) "Indigent and uninsured person" and "volunteer" have the same meanings as in section 2305.234 of the Revised Code.

(2) "Licensing agency that licenses health care professionals" means all of the following:

(a) The state dental board established under Chapter 4715. of the Revised Code;

(b) The board of nursing established under Chapter 4723. of the Revised Code;

(c) The state vision professionals board established under Chapter 4725. of the Revised Code;

(d) The state board of pharmacy established under Chapter 4729. of the Revised Code;

(e) The state medical board established under Chapter 4731. of the Revised Code;

(f) The state board of psychology established under Chapter 4732. of the Revised Code;

(g) The state chiropractic board established under Chapter 4734. of the Revised Code;

(h) The Ohio occupational therapy, physical therapy, and athletic trainers board established under Chapter 4755. of the
Revised Code;

(i) The counselor, social worker, and marriage and family therapist board established under Chapter 4757. of the Revised Code;

(j) The chemical dependency professionals board established under Chapter 4758. of the Revised Code;

(k) The state board of emergency medical services established under Chapter 4765. of the Revised Code;

(l) The state speech and hearing professionals board established under Chapter 4744. of the Revised Code;

(m) Any other licensing agency that considers its licensees to be health care professionals.

(B) Notwithstanding any provision of the Revised Code to the contrary, a licensing agency that licenses health care professionals shall apply toward the satisfaction of a portion of a licensee's continuing education requirement the provision of health care services if all of the following apply:

(1) The licensing agency that licenses health care professionals requires a licensee to complete continuing education as a condition of having a license renewed by the agency.

(2) The licensee provides the health care services to an indigent and uninsured person.

(3) The licensee provides the health care services as a volunteer.

(4) The licensee satisfies the requirements of section 2305.234 of the Revised Code to qualify for the immunity from

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liability granted under that section.

(5) The health care services provided are within the scope of authority of the licensee renewing the license.

(C)(1) Except as provided in division (C)(2) of this section, a licensing agency that licenses health care professionals shall permit a licensee to satisfy up to one-third of the licensee's continuing education requirement by providing health care services as a volunteer. A licensing agency that licenses health care professionals shall permit a licensee to earn continuing education credits at the rate of one credit hour for each sixty minutes spent providing health care services as a volunteer.

(2) In the case of a person holding a license to practice medicine and surgery, osteopathic medicine and surgery, or podiatric medicine and surgery, the state medical board shall permit the person to satisfy not more than three ten hours of the person's continuing education requirement by providing health care services as a volunteer. The board shall permit a licensee to earn continuing education credits at the rate of one credit hour for every five hours spent providing health care services as a volunteer.

(D) A licensing agency that licenses health care professionals shall adopt rules as necessary to implement this section. The rules shall be adopted in accordance with Chapter 119. of the Revised Code.

(E) Continuing education credit received under this section for providing health care services is not compensation or any other form of remuneration for purposes of section 2305.234 of the Revised Code and does not make the provider of
those services ineligible for the immunity from liability
granted under that section.

Sec. 4762.011. On and after the effective date of this
section, this chapter no longer applies to oriental medicine
practitioners.

Sec. 5107.541. A county department of job and family
services may contract with the chief administrator of a
nonpublic school or with any school district board of education
that has adopted a resolution under section 3319.089 of the
Revised Code to provide for a participant of the work experience
program who has a minor child enrolled in the nonpublic school
or a public school in the district to be assigned under the work
experience program to volunteer or work for compensation at the
school in which the child is enrolled. Unless it is not possible
or practical, a contract shall provide for a participant to
volunteer or work at the school as a classroom aide. If that is
impossible or impractical, the contract may provide for the
participant to volunteer to work in another position at the
school. A contract may provide for the nonpublic school or board
of education to receive funding to pay for coordinating,
training, and supervising participants volunteering or working
in schools.

Notwithstanding section 3319.088 of the Revised Code, a _A_
participant volunteering or working as a classroom aide under
this section is not required to obtain an educational aide-
permit or paraprofessional license. The participant shall not be
considered an employee of a political subdivision for purposes
of Chapter 2744. of the Revised Code and is not entitled to any
immunity or defense available under that chapter, the common law
of this state, or section 9.86 of the Revised Code.
Requisite hours of continuing medical education for license renewal or reinstatement.

(A) During a registration period, a licensee shall be required to complete fifty hours of CME. A licensee must complete a minimum of one hour of CME, approved by the board, on the topic of a licensee's duty to report misconduct under section 4731.224 of the Revised Code. The remainder shall be completed by participating in the following:

(1) Educational activities recognized by the American medical association as category 1 pursuant to its CME categorization system, and
   (a) Are certified for category 1 CME credit by the Ohio state medical association
   (b) Are certified for category 1 CME credit by an institution or organization accredited by the Ohio State Medical Association or the Accreditation Council for Continuing Medical Education; or
   (c) Have been awarded category 1 CME credit directly by the American medical association.

(2) Educational activities recognized by the American osteopathic association as category 1 pursuant to its CME categorization system, and
   (a) Are certified for category 1 CME credit by the Ohio osteopathic association
   (b) Are certified for category 1 CME credit by an institution or organization accredited by the Ohio osteopathic association or the American osteopathic association; or
   (c) Have been awarded category 1 CME credit directly by the American osteopathic association.

(3) Educational activities certified for category 1 CME credit by the Ohio foot and ankle medical association

(4) Educational activities certified for continuing education contact hours by a provider approved by the council on podiatric medical education

(5) Internships, residencies, or fellowships accredited by the accreditation council for graduate medical education, the American osteopathic association, or the council on podiatric medical education. Credit shall be earned at a rate of one hour of CME for each week of participation.
(6) Pursuant to section 4745.04 of the Revised Code, providing health care services in Ohio, as a volunteer, to indigent and uninsured persons, up to a maximum of three hours per registration period.

(B) If a licensee has not completed the requisite hours of CME, a licensee is not eligible for license renewal or license reinstatement until such time as the requisite hours have been completed. Any CME undertaken after the end of a registration period and utilized for purposes of renewing or reinstating a suspended license cannot also be utilized to meet the CME requirement of the current registration period.

(C) Licensees who are not working in the medical profession or who are retired from practice but wish to renew or reinstate their licenses shall meet the CME requirements of section 4731.282 of the Revised Code and this chapter of the Administrative Code.

(D) Licensees residing or practicing out of the state who wish to renew or reinstate their licenses must meet the CME requirements of section 4731.282 of the Revised Code and this chapter of the Administrative Code even though not currently residing or practicing in Ohio.

(E) During a volunteer registration period, every holder of a volunteer's certificate shall be required to complete one hundred fifty hours of CME pursuant to the requirements of section 4731.295 of the Revised Code. Seventy-five hours must meet the criteria established in paragraph (A)(1) of this rule. If a holder of a volunteer’s certificate has not completed the requisite hours of CME, a holder is not eligible for certificate renewal until such time as the requisite hours have been completed. Any CME undertaken after the end of a volunteer registration period and utilized for purposes of renewing a suspended certificate cannot also be utilized to meet the CME requirement of the current volunteer registration period.

(F) During a clinical research registration period, every holder of a clinical research faculty certificate shall be required to complete seventy-five hours of CME pursuant to the requirements of section 4731.293 of the Revised Code. Such hours must meet the criteria established in paragraph (A)(1) of this rule. If a holder of a clinical research faculty certificate has not completed the requisite hours of CME, a holder is not eligible for certificate renewal until such time as the requisite hours have been completed. Any CME undertaken after the end of a clinical research registration period and utilized for purposes of renewing a suspended certificate cannot also be utilized to meet the CME requirement of the current clinical research registration period.

(G) During a conceded eminence registration period, every holder of a certificate of conceded eminence shall be required to complete fifty hours of CME pursuant to the requirements of section 4731.297. Such hours must meet the criteria established in
paragraph (A)(1) of this rule. If a holder of a certificate of conceded eminence has not completed the requisite hours of CME, a holder is not eligible for certificate renewal until such time as the requisite hours have been completed. Any CME undertaken after the end of a conceded eminence registration period and utilized for purposes of renewing a suspended certificate cannot also be utilized to meet the CME requirement of the current conceded eminence registration period.
Replaces: 4731-10-02, 4731-10-05, 4731-10-07

Effective:

Five Year Review (FYR) Dates:

Certification

Date

Promulgated Under: 119.03
Statutory Authority: 4731.05, 4745.04
Rule Amplifies: 4731.282, 4731.291, 4731.293, 4731.295, 4731.297, 4745.04
Prior Effective Dates: 03/10/1998 (Emer.), 06/08/1998, 02/28/2003, 05/31/2018
Evidence of continuing medical education.

(A) Each licensee or certificate holder applying for license renewal or license reinstatement shall certify completion of the requisite hours of CME pursuant to the rules in this chapter.

(B) The board may select applications for verification that all CME requirements have been met. Licensees and certificate holders whose applications are selected shall submit additional documentation of compliance with CME requirements as the board may require. Failure to submit the additional documents shall constitute a violation of section 4731.282 of the Revised Code and section 4731.22 of the Revised Code.

(C) Licensees and certificate holders have a continuing obligation to maintain detailed records of CME hours completed. The licensee or certificate holder shall obtain verification of completion of CME activities. At a minimum, verification shall include a description of the CME activity, the date of attendance or completion, and the number of hours completed. Records of all CME undertaken shall be retained by the licensee or certificate holder for two years after the end of the CME period and shall be made available to the board upon request.

(D) Licensees seeking to receive credit pursuant to paragraph (A)(36) of rule 4731-10-02 of the Administrative Code shall maintain a log of their qualifying activities. The log shall indicate the dates the health care services were provided, the number of hours spent providing health care services on those dates, and the location where the health care services were provided.

(E) Notwithstanding the provisions of paragraph (C) of this rule, licensees and certificate holders shall not destroy or otherwise make unavailable written documentation of CME activity after the board has requested verification of CME pursuant to this rule or section 4731.22 of the Revised Code. Upon verification that all CME requirements have been met, the applicant or licensee or certificate holder may destroy the requested records.

(F) Nothing in this rule shall limit the board's authority to investigate and take action under section 4731.22 of the Revised Code.
Replaces: 4731-10-08

Effective:

Five Year Review (FYR) Dates:

Certification

Date

Promulgated Under: 119.03
Statutory Authority: 4745.04, 4731.282, 4731.05
Rule Amplifies: 4731.22, 4745.04, 4731.282
Prior Effective Dates: 05/16/1983, 10/31/1996, 03/10/1998 (Emer.),
06/08/1998, 02/28/2003, 05/31/2018
MEMORANDUM

TO: Dr. Bechtel, MD – Board President
    Board Members – State Medical Board of Ohio
    Stephanie Loucka, Executive Director of the State Medical Board of Ohio

FROM: Chelsea Wonski, Legislative Director

DATE: 1/13/2021

RE: Legislative Update

- Summary of lame duck
  - Senate Bill 310 is the capital appropriations bill. The language in the as passed version included amendments that waive supervision agreement requirements for physician assistants and advanced practice registered nurses allowing those individuals the ability to work with physicians other than those with which they hold a supervision agreement. Additionally, the bill allows retired medical professionals to practice temporarily without reinstatement of their license during the pandemic. The language included a provision that excludes those whose licenses had been previously suspended or revoked or were surrendered to avoid disciplinary action. These provisions will be effective until May 1, 2021 unless they are extended.

  - House Bill 263 places limits on the Boards ability to deny a license based on a prior criminal conviction. The new law requires the Board to create an inclusive list of criminal offenses that would prevent an applicant from becoming licensed. There are also new reporting requirements to the department of administrative services.

  - House Bill 442, which applies to certified public accounts, had an amendment added late in the legislative process which removes oriental medical practitioners and cosmetic therapists from under the regulatory authority of the Medical Board. The amendment also reduced the education hour requirements for massage therapists and increased the number of volunteer hours that may be applied as continuing education credit for physicians.

- Legislative outreach initiatives
MEMORANDUM

TO: Dr. Bechtel, MD – Board President
    Board Members – State Medical Board of Ohio
    Stephanie Loucka, Executive Director of the State Medical Board of Ohio

FROM: Nathan T. Smith, Senior Legal and Policy Counsel and Chelsea Wonski, Legislative Director

DATE: January 7, 2020

RE: Senate Bill 310 Implementation

Senate Bill 310 was passed and subsequently signed by Governor DeWine on December 29, 2020. Several uncodified sections respond to the COVID-19 pandemic and the resulting strain on the health care providers. There is an emergency clause attached to this bill making it effective immediately upon Governor DeWine’s signature until the May 1, 2021 end date stated in the legislation. This memo seeks to explain the impact of these uncodified sections and identify implementation issues.

I. Temporary Relaxation of Physician Assistant and Advanced Practice Nurse Supervision while practicing within a hospital or other health care facility

Physician Assistants:

- During the period beginning on December 29, 2020 and ending May 1, 2021, a physician assistant may practice under the direction, control, and supervision of a physician or podiatrist with whom the physician assistant has not entered into a supervision agreement.
  - The physician assistant may perform services authorized by a physician or podiatrist and by the hospital or other health care facility within which the physician assistant is practicing.

Impact:

For physician assistants that are employed by or under contract with a hospital or other health care facility, they may practice under the direction, control, and supervision of any physician or podiatrist in that setting regardless of whether they have a supervision agreement with that physician or podiatrist. Also, these PAs may perform services within their scope of practice, if authorized by the physician or podiatrist and the hospital or health care facility, regardless if those services are authorized in any existing supervision agreement to which they are a party.

For physicians and podiatrists practicing in a hospital or other health care facility, they may (1) supervise a PA (employed by or under contract with a hospital or other health care facility) that they do not have a supervision agreement with and (2) authorize that PA to perform services that are within their scope of practice if those services are also authorized by the hospital or health care facility.

For the Medical Board: Investigation and enforcement of certain statutory violations by physicians, podiatrists, and PAs related to supervising and practicing only within the confines of a supervision
agreement will have to be suspended for the four (4) month period that this uncodified law will be effective.

**Questions:**

(1) Who from the hospital or health care facility authorizes the services a PA is allowed to perform, and on what basis?

(2) How is this authorization recorded and communicated to supervising physicians, PAs, patients, and in the event of an adverse consequence to the Medical Board?

**Advanced Practice Nurses:**

There is also a section that provides similar relaxation of Advanced Practice Nurse Supervision under a standard care arrangement with a physician or podiatrist. The impact and questions related to this section are similar to those surrounding PAs, but are a Nursing Board issue.

II. **Temporary expansion of EMT scope of practice regarding administering COVID-19 tests**

- During the period beginning on December 29, 2020 and ending May 1, 2021, and notwithstanding any conflicting provision of the Revised Code, an emergency medical technician-basic, emergency medical technician-intermediate, and emergency medical technician-paramedic who has received proper training may administer a test for COVID-19 and collect and label test specimens.

III. **Temporary allowance of practice of a Licensed Practice Nurse at the direction of a Respiratory Care Professional**

- During the period beginning on December 29, 2020 and ending May 1, 2021, and notwithstanding any conflicting provision of the Revised Code, a licensed practical nurse may perform nursing care as identified in division (F) of section 4723.01 of the Revised Code at the direction of a respiratory care professional, and a respiratory care professional may provide that direction.

IV. **Temporary Licenses for inactive health professionals**

- A health care professional who meets both of the following conditions may practice during the period beginning on the effective date of this section and ending May 1, 2021:
  1. In the five-year period immediately preceding the effective date of this section, the professional held a license or certificate to practice issued by a licensing board.
  2. During the five-year period described in the language, the professional's license or certificate expired or became inactive, which may have occurred because the professional retired from practice.

- The health care professional shall be deemed to be practicing under a temporary license as if it were issued by the professional's respective licensing board and shall not be required to reactivate, restore, or renew the professional's prior license or certificate in order to practice under this section.

- The following health care professionals are eligible to practice under the provisions of HB 442:
  1. Licensed practical nurses, registered nurses, and advanced practice registered nurses;
2. Pharmacists;  
3. Physician assistants;  
4. Physicians, including podiatrists;  
5. Respiratory care professionals;  

- A health care professional who meets the previous conditions is not authorized to practice under this section if either of the following applies:
  1. The respective licensing board had revoked or suspended the professional's prior license or certificate.
  2. The professional surrendered the professional's prior license or certificate in an effort to avoid disciplinary or other adverse action.

Impact:
This legislation allows a physician, podiatrist, physician assistant, or respiratory care professional who meets the requirements to practice in Ohio on a temporary license until May 1, 2021 without having to reactivate, restore, or renew the medical professional’s prior license or certificate. The requirements are:
(1) The practitioner must have previously held a license with the State Medical Board of Ohio in the last 5 years (12/29/15 - 12/29/2020) and let that license expire during that time period to utilize this provision. The reason for the expiration of the license may be retirement but is not mandated.
(2) Practitioners who have had their license revoked or suspended or who had surrendered their license to avoid disciplinary or other adverse action are disqualified from utilizing this provision to practice temporarily in Ohio.

Questions:
(1) How will the Medical Board become aware of or track these expired practitioners practicing on a temporary license? There is no obligation to report to or register with the Medical Board imposed by this uncodified section.

(2) Is the practice of these expired practitioners practicing on a temporary license limited to a hospital or other health care facility who could achieve that reporting? The text of the uncodified section does not seem to limit it to that.

(3) If the Medical Board becomes aware of a practitioner practicing under this temporary license who is statutorily disqualified due to previous discipline by the State Medical Board, how can that practitioner be stopped from practicing? The uncodified section does not provide an enforcement mechanism. Could summary suspension be utilized?
MEMORANDUM

TO: Dr. Bechtel, MD – Board President  
   Board Members – State Medical Board of Ohio  
   Stephanie Loucka, Executive Director of the State Medical Board of Ohio

FROM: Chelsea Wonski, Legislative Director

DATE: January 7, 2020

RE: House Bill 442

Bill Number/ Sponsor(s): Rep. Bill Roemer (R-38) and Rep. Thomas West (D-49)

Date Introduced: 12/9/2019

Date of final passage: 12/22/2020

Effective Date: 3/22/2021

Summary:

- The original intent of the bill was to address concern regarding the experience and education requirements for certified public accountants
- The bill was amended in the Senate committee to include changes to the licensing authority of several state licensing boards
- Changes impacting the Medical Board include the following:
  - Eliminates the license for cosmetic therapists, currently under the purview of the Medical Board.
  - Allows the Medical Board the authority to recognize accrediting organizations for purposes of physician assistant education programs. Current law specifies that programs must be accredited by the Accreditation Review Commission on Education for the Physician Assistant.
  - Eliminates the license for oriental medicine practitioners.
  - Authorizes a physician to satisfy up to ten hours of the physician’s continuing education requirement by providing volunteer health care services. Currently, physicians may obtain three hours of CME for volunteer hours.
    - Additionally, the language sets the conversion rate for volunteer hours as one credit hour of continuing education for every five hours spent volunteering. The current ratio is 1:1.
  - Codifies in Ohio law a 600-hour education requirement to qualify for a license to practice massage therapy. Currently, massage therapists are required in OAC rule 4731-1-16 to complete 750 education hours to qualify for licensure.
Eliminates the following for clinical research faculty certificates: (1) qualification requirements other than proof of appointment to academic staff of medical school (MD, DO, DPM) and licensure in another state or country; (2) initial certificate and renewal fees; and (3) continuing medical education requirements.

Eliminates the qualification requirements other than proof of program acceptance and holding a current, unrestricted license to practice medicine in another country for visiting clinical professional development certificates and eliminates the associated fee.

Eliminates the fee for visiting podiatric faculty certificates.
MEMORANDUM

TO:         Dr. Bechtel, MD – Board President  
            Board Members – State Medical Board of Ohio  
            Stephanie Loucka, Executive Director of the State Medical Board of Ohio

FROM:       Chelsea Wonski, Legislative Director

DATE:       January 7, 2021

RE:         House Bill 263

Bill Number/ Sponsor(s): Rep Kyle Koehler (R- 79)

Date Introduced: 5/28/2019

Date of final passage: 12/22/2020

Effective Date: 3/31/2021

Summary:

**Establishment of List of Disqualifying Offenses (R.C. 9.79(B))**

- Within 180 days of the effective date of this section, each licensing authority shall establish and publish on its website a list of specific criminal offenses for which a conviction, judicial finding of guilt or plea of guilty may disqualify an individual from obtaining a license.

- The licensing authority must Identify each disqualifying offense by name or by the Revised Code section number and include only those criminal offenses that are directly related to the duties and responsibilities of the occupation.

- The licensing authority may include in the list an existing or former municipal ordinance or law of this or any other state or the United States that is substantially equivalent to any section or offense included in the adopted list.

**Restrictions on Use of Criminal Information in Making Licensing Decisions (R.C. 9.79(C)(1))**

- A licensing authority shall not refuse to issue an initial license to an individual based on any of the following:
  - Solely or in part on a conviction of, judicial finding of guilt of, or plea of guilty to an offense that is not included on the adopted list of disqualifying offenses.
A criminal charge that does not result in a conviction, judicial finding of guilt, or plea of guilty

A nonspecific qualification such as "moral turpitude" or lack of "moral character";

A disqualifying offense included on the adopted list of disqualifying offenses if consideration of that offense occurs after the time periods allowed in R.C. 9.79(D).

Use of Adopted List of Disqualifying Offenses in Making Licensing Decisions (R.C. 9.79 (C)(2) and (D))

- A licensing authority may take a conviction, judicial finding of guilt, or plea of guilty into consideration if the individual was convicted of, found guilty pursuant to a judicial finding of, or pleaded guilty to a disqualifying offense that is included in the adopted list. R.C. 9.79(C)(2).

Standard and Factors in Licensing Authority Consideration of a Disqualifying Offense (R.C. 9.79(D)(1)):

- In considering a conviction of, judicial finding of guilt of, or plea of guilty to a disqualifying offense in determining whether to refuse to issue an initial license, the licensing authority shall consider all of the following factors using a preponderance of the evidence standard to determine whether the conviction, judicial finding of guilt, or plea of guilty to the offense disqualifies the individual from receiving the license:
  
  - The nature and seriousness of the offense for which the individual was convicted, found guilty pursuant to a judicial finding, or pleaded guilty;
  
  - The passage of time since the individual committed the offense;
  
  - The relationship of the offense to the ability, capacity, and fitness required to perform the duties and discharge the responsibilities of the occupation;
  
  - Any evidence of mitigating rehabilitation or treatment undertaken by the individual, including whether the individual has been issued a certificate of qualification for employment (R.C. 2953.25) or a certificate of achievement and employability (R.C. 2961.22);
  
  - Whether the denial of a license is reasonably necessary to ensure public safety.

Time Limits on Use of Disqualifying Offenses (R.C. 9.79(D)(2)):

- A licensing authority may take a disqualifying offense into account only during the following time periods:
  
  - For a conviction of, judicial finding of guilt of, or plea of guilty to a disqualifying offense that is an offense of violence or a sexually oriented offense, any time.
  
  - For a conviction of, judicial finding of guilt of, or plea of guilty to a disqualifying offense that does not involve a breach of fiduciary duty and that is not an offense of violence or a sexually oriented offense, whichever of the following is later, provided the individual was not convicted of, found guilty pursuant to a judicial finding of, and did not enter a plea of guilty to any other offense during the applicable period:
    
    1. Five years from the date of conviction, judicial finding of guilt, or plea of guilty;
    
    2. Five years from the date of the release from incarceration;
    
    3. The time period specified in division (D)(3) of this section.
  
  - For a conviction of, judicial finding of guilt of, or plea of guilty to a disqualifying offense that involves a breach of fiduciary duty and that is not an offense of violence or a sexually oriented offense, whichever of the following is later, provided the individual was not convicted of, found guilty pursuant to a judicial finding of, and did not enter a plea of guilty to any other offense during the applicable period:
    
    1. Ten years from the date of conviction, judicial finding of guilt, or plea of guilty;
    
    2. Ten years from the date of the release from incarceration;
    
    3. The time period specified in division (D)(4) of this section.
Divisions (D)(3) and (D)(4) extend the time limits for which the licensing authority may take the offense into account when an individual is subject to community control, parole, or post-release control.

**Requirements for Notification by Licensing Authority Refusing to Issue an Initial License for Reason of Disqualifying Offense (R.C. 9.79(E))**

- If a licensing authority refuses to issue an initial license to an individual, the licensing authority shall notify the individual in writing of all the following:
  - The grounds and reasons for the refusal, including an explanation of the licensing authority's application of the factors in division (D) to the evidence the licensing authority used to reach the decision;
  - The individual's right to a hearing regarding the licensing authority's decision R.C. 119.06;
  - The earliest date the individual may reapply for a license;
  - Notice that evidence of rehabilitation may be considered on reapplication

**Burden of Proof in an Administrative Hearing (R.C. 9.79(F))**

In an administrative hearing or civil action reviewing a licensing authority's refusal to issue an initial license under this section, the licensing authority has the burden of proof on the question of whether the individual's conviction of, judicial finding of guilt of, or plea of guilty to an offense directly relates to the licensed occupation.

**Ability to Consider Licensure Discipline in Deciding Whether to Issue a License (R.C. 9.79(J))**

Nothing in this language prohibits a licensing authority from considering either of the following when making a determination of whether to issue a license to an individual: (1) Past disciplinary action taken by the licensing authority against the individual; (2) Past disciplinary action taken against the individual by an authority in another state that issues a license that is substantially similar to the license for which the individual applies.

**Relevant Miscellaneous provisions in R.C. 9.79:**

- A licensing authority that is authorized by law to limit or otherwise place restrictions on a license may do so to comply with the terms and conditions of a community control sanction, post-release control sanction, or an intervention plan established in accordance with section 2951.041 of the Revised Code (R.C. 9.79(G))
- Each licensing authority shall adopt any rules that it determines are necessary to implement this section (R.C. 9.79(H))
- Under R.C. 9.79(I)(2), the following relevant exclusion from the requirements of R.C. 9.79 applies: Any position for which federal law requires disqualification from licensure or employment based on a conviction of, judicial finding of guilt of, or plea of guilty to an offense.
- If a licensing authority issues a license to an individual after considering a conviction of, judicial finding of guilt of, or plea of guilty to an offense under division (D) of this section, the licensing authority shall not refuse to renew the individual's license based on that conviction, judicial finding of guilt, or plea of guilty. (R.C. 9.79(K))
Applying R.C. 9.79 to the Medical Board chapters of the Ohio Revised Code:

Consistent with the requirements and procedures for evaluating criminal convictions in R.C. 9.79, the new law does the following in Chapters 4730, 4731, 4759, 4760, 4761, 4762, 4774, and 4778 of the Ohio Revised Code:

1. Removes good moral character requirements
2. Removes Medical Board discretion in examining the criminal records check of an applicant in deciding whether to grant a license.
3. Adds provisions that state that the Medical Board shall not refuse to issue a license because of a conviction “unless the refusal is in accordance with section 9.79 of the Revised Code.”
4. Removes requirement of no criminal record to qualify for expedited licensure under R.C. 4731.299.

Annual Reporting requirements (R.C. 9.78(F))

- Requires a state licensing authority to provide an annual report to the director of administrative services including the following regarding each license type of the licensing authority:
  - The number of applications received for the license
  - The number of those applications that resulted in a license being granted
  - The number of those applications that resulted in a license being denied
  - A list of criminal offenses reported by individuals who were granted a license
  - A list of criminal offenses reported by individuals who were denied a license
  - A list of all requests by individuals who have been convicted of a criminal offense who have requested the licensing authority to determine whether the individual’s criminal conviction disqualifies the individual from obtaining a license that includes the following information:
    1. The number of requests for which the licensing authority determined that an individual’s criminal conviction disqualified the individual from obtaining a license and a list of those offenses
    2. The number of requests for which the licensing authority determined that an individual’s criminal conviction did not disqualify them from obtaining a license and a list of those offenses
      - For each disqualifying offense included on the list adopted R.C. 9.79(B), the number of individuals who were convicted of, found guilty pursuant to a judicial finding of, or pleaded guilty to that disqualifying offense who were issued a license and the number of individuals who were denied a license.
      - Any other information that the director may require
  - The first report is to be submitted to the director of administrative services by June 30, 2021 and must include the required information for January 1, 2016, to December 31, 2020, if available. Annual reports shall be submitted each year by the 30th day of June.