Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

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/m^2. 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.

Obesity (2019) **27**, 591-602. doi:10.1002/oby.22430

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

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Funding agencies: This work was supported by Patient-Centered Outcomes Research Institute (PCORI) as part of the Patient Outcomes Research to Advance Learning (PORTAL) project (PCORI CDRN 1306-04681).

Disclosure: The authors declared no conflicts of interest.

Author contributions: Study concept and design: KHL, DEA, and JA; acquisition, analysis, and interpretation of data: all authors; drafting of manuscript: KHL and HF; critical revision of manuscript: all authors; statistical analysis plan: HF, KHL, and DEA; graphical support: CK; supervision: KHL, DEA, and DRY.

Additional Supporting Information may be found in the online version of this article.

Received: 9 November 2018; **Accepted:** 9 January 2019; **Published online 22 March 2019. doi:10.1002/oby.22430**

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/m^2 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

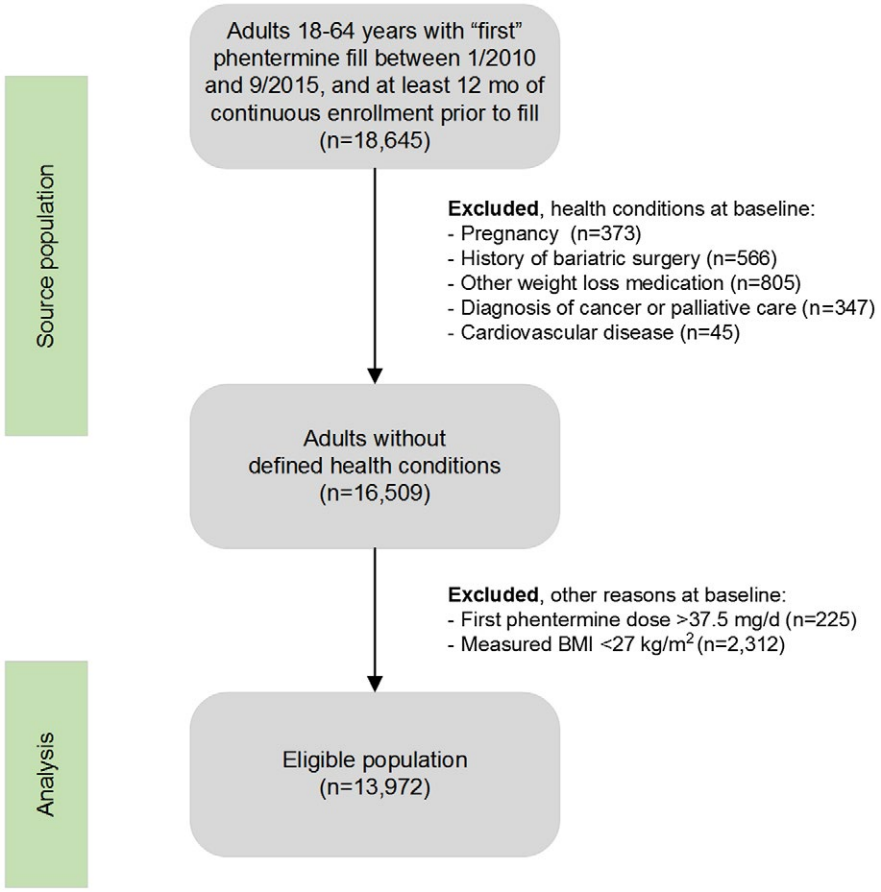

Figure 1 Flow diagram for identification of incident phentermine users eligible for cohort inclusion from electronic health records. [Colour figure can be viewed at wileyonlinelibrary.com]

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[a]

	On-label users		Off-label users			
	Short-term referent (*n* = 6,764)	Short-term intermittent (*n* = 2,938)	Medium-term continuous (*n* = 1,703)	Medium-term intermittent (*n* = 2,423)	Long-term continuous (*n* = 144)	Total (*N* = 13,972)
Sex[b]						
Female	5,611 (83.1%)	2,523 (85.8%)	1,402 (82.3%)	2,047 (84.3%)	116 (80.6%)	11,699 (83.7%)
Race/ethnicity[c]						
Non-Hispanic white	3,007 (44.5%)	1,093 (37.2%)	894 (52.5%)	1,181 (48.6%)	80 (55.6%)	6,255 (44.8%)
Non-Hispanic black	1,370 (20.3%)	786 (26.7%)	253 (14.9%)	446 (18.4%)	19 (13.2%)	2,874 (20.6%)
Hispanic	1,749 (25.9%)	764 (26.0%)	367 (21.6%)	564 (23.2%)	27 (18.8%)	3,471 (24.8%)
Asian	305 (4.5%)	137 (4.7%)	101 (5.9%)	107 (4.4%)	12 (8.3%)	662 (4.7%)
Other	324 (4.8%)	162 (5.5%)	88 (5.2%)	130 (5.4%)	6 (4.2%)	710 (5.1%)
Age (y)[c]	43.7 (10.9)	42.3 (10.6)	44.3 (10.4)	43.7 (10.5)	46.5 (10.0)	43.5 (10.7)
BMI (kg/m^2)[c]						
Mean (SD)	38.0 (7.5)	37.0 (6.9)	38.4 (7.0)	37.6 (6.8)	37.5 (7.1)	37.8 (7.2)
27-29.9	687 (10.2%)	381 (13%)	118 (6.9%)	234 (9.6%)	14 (9.7%)	1,434 (10.3%)
30-34.9	1,977 (29.3%)	979 (33.3%)	477 (28%)	738 (30.4%)	45 (31.3%)	4,216 (30.2%)
35-39.9	1,890 (28.0%)	773 (26.3%)	519 (30.5%)	735 (30.3%)	46 (31.9%)	3,963 (28.4%)
40-49.9	1,733 (25.7%)	673 (22.9%)	472 (27.7%)	593 (24.4%)	30 (20.8%)	3,501 (25.1%)
≥50.0	468 (6.9%)	136 (4.6%)	117 (6.9%)	128 (5.3%)	9 (6.3%)	858 (6.1%)
Hypertension diagnosis[d]	1,443 (21.4%)	578 (19.6%)	357 (21%)	476 (19.6%)	35 (24.3%)	2,889 (20.7%)
Diabetes diagnosis[c,d]	824 (12.2%)	299 (10.2%)	224 (13.2%)	253 (10.4%)	24 (16.7%)	1,624 (11.6%)
Smoking status[c,e]						
Never users	4,211 (62.3%)	1,870 (63.6%)	1,035 (60.8%)	1,469 (60.5%)	69 (47.9%)	8,654 (61.9%)
Ever users	2,298 (34%)	944 (32.1%)	612 (35.9%)	849 (35%)	65 (45.1%)	4,768 (34.1%)
Missing/unknown	246 (3.6%)	128 (4.4%)	56 (3.3%)	110 (4.5%)	10 (6.9%)	550 (3.9%)
Area families below poverty level[f]						
Missing[e,g]	234 (3.5%)	146 (5%)	56 (3.3%)	93 (3.8%)	9 (6.3%)	538 (3.9%)
<5%	1,568 (23.2%)	686 (23.3%)	445 (26%)	612 (25.2%)	38 (26.4%)	3,349 (24%)
5-<10%	1,779 (26.3%)	769 (26.1%)	448 (26.2%)	656 (27%)	37 (25.7%)	3,682 (26.4%)
10-<20%	1,812 (26.8%)	798 (27.1%)	443 (25.9%)	629 (25.9%)	35 (24.3%)	3,717 (26.6%)
≥20%	1,362 (20.2%)	543 (18.5%)	318 (18.6%)	438 (18%)	25 (17.4%)	2,686 (19.2%)
Follow-up duration (y)[c]	1.6 (1.1)	2.2 (0.9)	1.6 (1.0)	2.4 (0.8)	2.3 (0.8)	1.9 (1.0)
Median percent of follow-up on phentermine	9%	16%	33%	42%	75%	19%
Daily phentermine dose[c]						
<37.5 mg	3,688 (54.6%)	1,528 (51.9%)	1,120 (65.8%)	1,526 (62.9%)	89 (61.8%)	7,951 (56.9%)
37.5 mg	3,053 (45.2%)	1,404 (47.7%)	580 (34.1%)	892 (36.7%)	53 (36.8%)	5,982 (42.8%)
Missing[g]	14 (0.2%)	10 (0.3%)	3 (0.2%)	10 (0.4%)	2 (1.4%)	39 (0.3%)

Data given as *n* (%) for categorical variables and mean (SD) for continuous variables.
[a]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).
[b]$P = 0.004$ for χ^2 test.
[c]$P < 0.001$ for difference across groups using χ^2 test for categorical and Kruskal-Wallis test for continuous variables.
[d]Defined as one relevant inpatient or two outpatient *International Classification of Diseases, Ninth Revision* codes in year prior to index phentermine prescription.
[e]Tobacco "ever users" includes current and historical smokers.
[f]Using geographic information systems measures mapping to 2010 census block group socioeconomic status data, categories go from highest to lowest SES vertically.
[g]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[a]

	6 months		12 months		24 months	
	Parameter estimate (95% CI)	*n* (% of enrolled with weight data available)[b]	Parameter estimate (95% CI)	*n* (% of enrolled with weight data available)[b]	Parameter estimate (95% CI)	*n* (% of enrolled with weight data available)[b]
Intercept[c]	–2.68 (–3.28 to –2.08)[d,e]		–1.38 (–2.08 to –0.67)[f]		–0.16 (–1.07 to 0.75)	
Short-term[c]	Referent	2,555 (66%)	Referent	2,074 (78%)	Referent	1,323 (90%)
Short-term intermittent[c]	–1.75 (–2.13 to –1.37)[d,g]	1,450 (73%)	–1.36 (–1.80 to –0.93)[g]	1,743 (82%)	–0.26 (–0.83 to 0.32)[g]	1,545 (92%)
Medium-term continuous[c]	–5.07 (–5.40 to –4.73)[d,g]	2,352 (74%)	–4.66 (–5.13 to –4.19)[g]	1,371 (78%)	–1.71 (–2.46 to –0.96)[g]	613 (89%)
Medium-term intermittent[c]	–4.22 (–5.11 to –3.33)[d,g]	179 (78%)	–5.63 (–6.13 to –5.13)[g]	1,178 (86%)	–3.48 (–4.07 to –2.88)[g]	1,368 (93%)
Long-term continuous[c]	n/a		n/a		–7.36 (–8.96 to –5.76)[g]	98 (89%)

[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/m^2, 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,

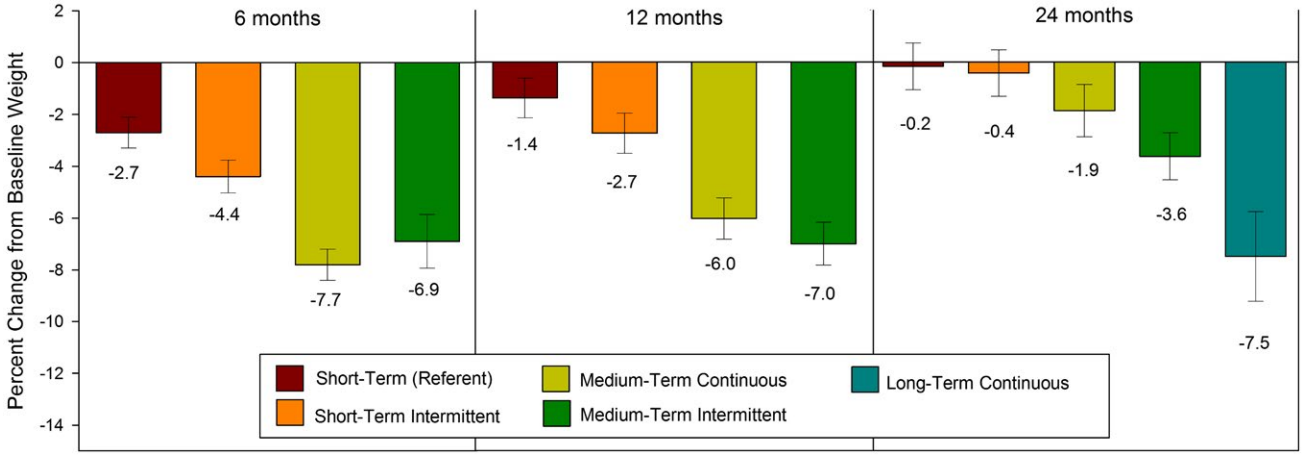

Figure 2 Estimated percent weight loss at 6 months and 1 and 2 years after phentermine initiation; results from multivariable linear models. Estimates at each time point are from separate multivariable linear models, and *n* (%) by group over follow-up is presented in Table 2. Note that because real 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 3 Difference in percent weight loss over follow-up: results from multivariable linear models using time-varying exposure among early phentermine responders[a]

	6 months		12 months		24 months	
	Parameter estimate (95% CI)	*n* (% of enrolled with weight data available)[b]	Parameter estimate (95% CI)	*n* (% of enrolled with weight data available)[b]	Parameter estimate (95% CI)	*n* (% of enrolled with weight data available)[b]
Intercept[c]	−6.26 (−7.09 to −5.43)[d,e]		−4.07 (−5.20 to −2.94)[e]		−3.01 (−4.53 to −1.48)[f]	
Short-term[c]	Referent	767 (70%)	Referent	604 (82%)	Referent	364 (94%)
Short-term intermittent[c]	−1.54 (−2.12 to −0.97)[d,g]	565 (78%)	−1.75 (−2.49 to −1.02)[g]	604 (84%)	−0.07 (−1.16 to 1.02)[g]	495 (93%)
Medium-term continuous[c]	−3.35 (−3.82 to −2.88)[d,g]	1,574 (78%)	−3.64 (−4.33 to −2.95)[g]	848 (80%)	−0.54 (−1.71 to 0.64)[g]	364 (89%)
Medium-term intermittent[c]	−2.25 (−3.34 to −1.15)[d,g]	103 (82%)	−4.21 (−4.93 to −3.48)[g]	744 (90%)	−2.47 (−3.49 to −1.46)[g]	788 (94%)
Long-term continuous[c]	n/a		n/a		−7.68 (−10.02 to −5.34)[g]	52 (91%)

[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. Models include only patients who had documented weight loss of ≥3% by 3 months after starting phentermine.
[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 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 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 in this sensitivity analysis using fixed phentermine use groups were otherwise similar to our main findings.

Our responders-only analysis for weight loss included 4,340 individuals who experienced ≥3% weight loss by 3 months, representing 62% of the 7,043 patients who had weight data available at that time point. In multivariable models treating phentermine as a time-varying exposure among responders, referent group weight loss was greater than in our main analyses, as follows: 6.3% (95% CI: 5.4%-7.1%) at 6 months, 4.1% (95% CI: 2.9%-5.2%) at 12 months, and 3.0% (95% CI: 1.5%-4.5%) at 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 month) 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.

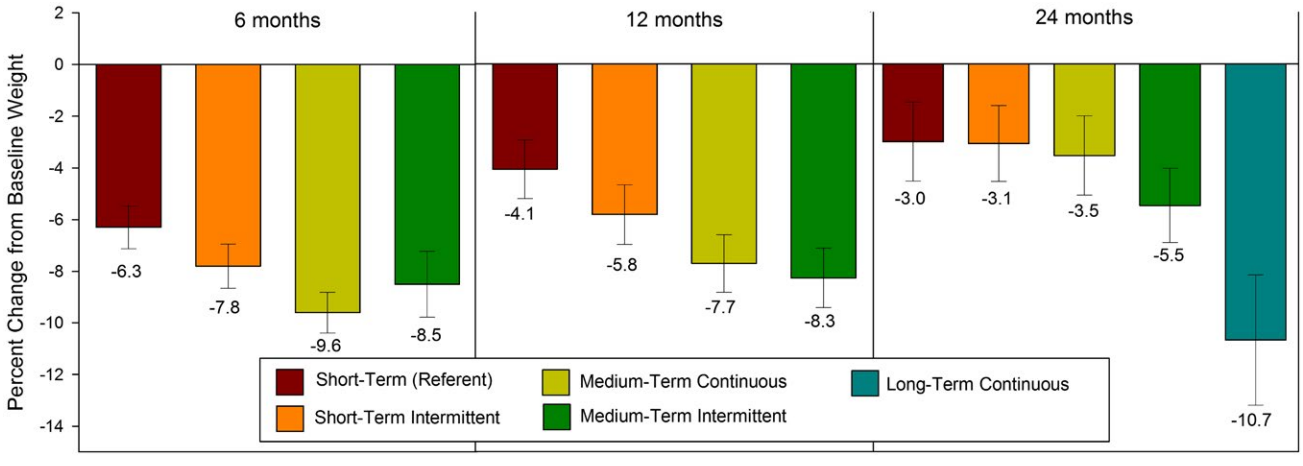

Figure 3 Estimated percent weight loss at 6 months and 1 and 2 years after phentermine initiation among responders; results from multivariable linear models. Models include only phentermine responders, patients who had lost ≥3% body weight by 3 months after initiating medication. Estimates at each time 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[a]

		Heart rate results					
		6 months		12 months		24 months	
		Parameter estimate ΔHR (bpm) (95% CI)	*n* (%) enrolled with VS data[b]	Parameter estimate ΔHR (bpm) (95% CI)	*n* (%) enrolled with VS data[b]	Parameter estimate ΔHR (bpm) (95% CI)	*n* (%) enrolled with VS data[b]
Intercept[c]		1.01 (−0.13 to 2.16)[d]	n/a	0.64 (−0.51 to 1.80)	n/a	0.55 (−0.77 to 1.86)	n/a
Short-term[c]		Ref	4,268 (68%)	Ref	3,672 (79%)	Ref	2,534 (91%)
Short-term intermittent[c]		0.81 (0.08 to 1.53)[d,e]	1,439 (74%)	0.27 (−0.43 to 0.96)[f]	1,723 (83%)	0.13 (−0.65 to 0.91)	1,533 (93%)
Medium-term continuous[c]		1.61 (0.99 to 2.24)[d,e]	2,353 (75%)	1.16 (0.40 to 1.92)[f]	1,362 (79%)	−0.19 (−1.28 to 0.90)	610 (90%)
Medium-term intermittent[c]		−0.77 (−2.57 to 1.04)[d,e]	181 (80%)	1.09 (0.28 to 1.90)[f]	1,184 (88%)	0.67 (−0.14 to 1.49)	1,360 (95%)
Long-term continuous[c]		n/a		n/a		2.64 (0.15 to 5.14)	96 (90%)
		Blood pressure results					
		Parameter estimate (95% CI)	*n* (%) enrolled with VS data[b]	Parameter estimate (95% CI)	*n* (%) enrolled with VS data[b]	Parameter estimate (95% CI)	*n* (%) enrolled with VS data[b]
Intercept[c]	ΔSBP (mmHg)	−0.99 (−2.13 to 0.14)[d]	n/a	−0.19 (−1.37 to 0.99)	n/a	1.83 (0.48 to 3.19)[g]	n/a
	ΔDBP (mmHg)	−0.33 (−1.18 to 0.52)[d]		−0.57 (−1.44 to 0.29)		0 (−0.98 to 0.98)	
Short-term[c]	ΔSBP (mmHg)	Referent	4,377 (68%)	Referent	3,742 (79%)	Referent	2,592 (92%)
	ΔDBP (mmHg)						
Short-term intermittent[c]	ΔSBP (mmHg)	−0.78 (−1.49 to −0.06)[d]	1,468 (75%)	−0.41 (−1.11 to 0.30)[h]	1,759 (83%)	0.2 (−0.60 to 1.00)[i]	1,560 (94%)
	ΔDBP (mmHg)	0.08 (−0.46 to 0.61)[d]		0.21 (−0.31 to 0.73)		0.4 (−0.18 to 0.98)	
Medium-term continuous[c]	ΔSBP (mmHg)	−0.5 (−1.12 to 0.12)[d]	2,402 (76%)	−1.11 (−1.88 to −0.33)[h]	1,395 (80%)	−0.94 (−2.05 to 0.17)[i]	622 (90%)
	ΔDBP (mmHg)	0.36 (−0.11 to 0.82)[d]		−0.39 (−0.95 to 0.18)		−0.12 (−0.93 to 0.69)	
Medium-term intermittent[c]	ΔSBP (mmHg)	−1.18 (−2.98 to 0.61)[d]	183 (80%)	−0.92 (−1.74 to −0.09)[h]	1,200 (88%)	−0.41 (−1.25 to 0.43)[i]	1,383 (95%)
	ΔDBP (mmHg)	−0.81 (−2.16 to 0.53)[d]		−0.19 (−0.79 to 0.41)		0.12 (−0.49 to 0.73)	
Long-term continuous[c]	ΔSBP (mmHg)	n/a		n/a		−3.31 (−5.85 to −0.76)[i]	99 (91%)
	ΔDBP (mmHg)					−0.69 (−2.54 to 1.16)	

[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]$P = 0.005$ for comparing HR change in comparison groups with referent group.
[g]$P = 0.008$ for comparing intercept to zero.
[h]$P = 0.02$ for comparing SBP change in comparison groups with referent group.
[i]$P = 0.03$ for comparing SBP change in comparison groups with referent group.
VS, vital signs; n/a, not applicable.

TABLE 5 Results from multivariable Cox models[a]: hazard ratio for composite outcome of incident myocardial infarction, stroke, CVD intervention, or death up to 3 years after phentermine initiation

	Hazard ratio	CI[b]
Short-term (referent)	Reference	
Short-term intermittent	0.74	0.29-1.91
Medium-term intermittent	0.50	0.14-1.74
Medium & long-term continuous combined[c]	1.58	0.69-3.63

[a]Models 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.
[b]$P = 0.30$ for examining differences between groups.
[c]There 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, 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.O

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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