OCW WP 069 / V1.0 / 4 NOV 2026

PATIENT GUIDE

Oral weight management medicines *phentermine, topiramate, metformin and others*

Five tablets and capsules sit on the weight programme alongside the weekly injections. Two are approved for weight, two are approved for something else, and one is compounded.

MEDICINES	APPROVED FOR WEIGHT	OFF LABEL	COMPOUNDED	SOURCES
Five, taken orally	Phentermine, Qsymia	Metformin, ondansetron	Low dose naltrexone	32 · PMID linked

§ 01

Overview

Weight that is affecting your health deserves treatment, and the American Gastroenterological Association puts that plainly: it recommends adding medicine to lifestyle change for adults with a body mass index of 30 or more, or 27 or more with a weight related complication, who have not had enough response from lifestyle change alone.[1] Most of the attention now goes to the weekly injections. This guide covers the medicines on our programme that come as a tablet or a capsule instead.

There are five of them, and they do not share a legal status. Phentermine is approved by the U.S. Food and Drug Administration for short term use in obesity, and phentermine combined with topiramate in an extended release capsule, sold as Qsymia, is approved for long term weight management.[3 5] Metformin is approved for type 2 diabetes only, so prescribing it for weight or for insulin resistance without diabetes is off label.[6] Low dose naltrexone is compounded by a pharmacy and is not FDA approved in any form.[10] Ondansetron is approved for the nausea of chemotherapy, radiotherapy and surgery, so using it for the nausea of a weight medicine is off label too.[8] A physician may prescribe off label, and we say so each time below. The weekly injections are covered in our semaglutide guide (OCW WP 023) and our tirzepatide guide (OCW WP 024), and the approved daily GLP 1 tablets in our oral GLP 1 tablets guide (OCW WP 053). Every source is listed at the end, with links.

9.8%	**Average weight reduction on the highest Qsymia dose.** In CONQUER, 2,487 adults with overweight or obesity and two or more weight related conditions took phentermine 15 mg with topiramate 92 mg or placebo for 56 weeks; weight fell 9.8 percent against 1.2 percent.[11]
6.7 kg	**Weight reduction on phentermine alone.** In a randomized, double blind trial of 68 Korean adults taking phentermine 37.5 mg daily with behavioural therapy, weight fell by 6.7 kg and waist size by 6.2 cm, both by more than placebo.[16]

0.56 BMI **What metformin does to weight in people without diabetes.** Pooling 49 randomized trials, metformin lowered body mass index by 0.56 points more than placebo, which the authors describe as a modest reduction.[22]

0 **Published trials of low dose naltrexone with weight as an outcome.** The controlled trials of it were run in fibromyalgia and in Crohn disease, and they measured pain and bowel inflammation.[25] [26]

§ 02

What these medicines are

Phentermine is a sympathomimetic amine, related chemically and pharmacologically to amphetamine, and the label calls drugs of its class anorectics.[3] Qsymia puts a lower dose of it together with topiramate, an older medicine for epilepsy and migraine prevention; topiramate is not a controlled substance, and the combination is, because of the phentermine in it.[5] Metformin is a biguanide, the first medicine most physicians reach for in type 2 diabetes, and ondansetron blocks serotonin type 3 receptors and prevents the nausea of chemotherapy, radiotherapy and surgery; neither has ever carried a weight indication.[6] [8]

Low dose naltrexone is a compounded capsule, usually 1.5 to 4.5 mg. Naltrexone itself is an FDA approved opioid blocker, licensed since 20 November 1984 and marketed as tablets of 25, 50 and 100 mg for alcohol dependence and for blocking the effects of opioids.[7] [10] Nothing in the 1.5 to 4.5 mg range has ever been approved, so a low dose capsule is prepared by a licensed pharmacy on a prescription written for one patient.[31] A separate approved medicine, Contrave, pairs naltrexone 8 mg with bupropion 90 mg in an extended release tablet for long term weight management; two tablets twice a day give 32 mg of naltrexone, roughly ten times a low dose capsule, so it is a different product with a different evidence base.[9]

THE FIVE ORAL MEDICINES, AND WHAT EACH ONE IS APPROVED TO DO

MEDICINE	WHAT IT IS	FORM	FDA STATUS
Phentermine	Sympathomimetic amine, related to amphetamine; Schedule IV[3]	37.5 mg tablet or capsule; 8 mg tablet (Lomaira)[4]	Approved as a short term adjunct in exogenous obesity[3]
Phentermine with topiramate (Qsymia)	Low dose phentermine plus topiramate, an antiepileptic drug; Schedule IV[5]	Extended release capsule, four strengths[5]	Approved for long term weight management in adults and in children aged 12 and older[5]
Metformin	Biguanide; lowers the glucose the liver releases[6]	500, 850 and 1000 mg tablets, taken with meals[6]	Approved for type 2 diabetes only; any weight use is off label[6]
Low dose naltrexone	Opioid receptor blocker at a fraction of the approved dose[7]	Compounded capsule, usually 1.5 to 4.5 mg[10]	Not FDA approved; the approved product is 50 mg for alcohol and opioid dependence[10]
Ondansetron	Serotonin type 3 receptor blocker[8]	4 mg and 8 mg tablets, including a form that dissolves on the tongue[8]	Approved for nausea from chemotherapy, radiotherapy and surgery; other use is off label[8]

§ 03

How they work

Phentermine works on appetite. The Qsymia label states that its effect on weight is likely mediated by the release of catecholamines in the hypothalamus, which reduces appetite and food intake, and that the exact mechanism is not known.[5] The phentermine label goes further and says it has not been established that appetite suppression is the primary action of drugs of this class, since other effects in the brain, or metabolic effects, may be involved.[3] Topiramate is the less obvious half

of the combination. Its effect on weight is not known either; the label lists the candidates, which include raising the activity of the neurotransmitter gamma aminobutyrate, changing the behaviour of voltage gated ion channels, blocking one family of excitatory glutamate receptors, and inhibiting carbonic anhydrase. [5] That last one explains several of the things topiramate does elsewhere in the body, including the drift towards metabolic acidosis, the kidney stones and the low potassium that the label asks us to watch for with blood tests. [5]



Both halves of Qsymia act on appetite, and neither one burns fat. The Qsymia label attributes the effect of phentermine to the release of catecholamines in the hypothalamus, and says the mechanism of topiramate on weight is not known, though it may involve gamma aminobutyrate, ion channels, glutamate receptors and carbonic anhydrase.[5] The other three medicines in this guide do not act on this chain: metformin lowers the glucose the liver releases and improves insulin sensitivity, naltrexone blocks opioid receptors, and ondansetron blocks serotonin type 3 receptors in the vomiting reflex. [6] [7] [8]

Metformin does something different. It lowers the glucose the liver releases, reduces how much glucose the gut absorbs, and improves how well your tissues respond to insulin, all without raising insulin secretion.[6] Weight reduction follows that work rather than being its purpose, so the label carries a diabetes indication and not a weight one. [6]

Naltrexone at 50 mg is a pure opioid antagonist that blocks the effects of opioids, completely and reversibly, for around 24 hours.[7] The reasoning behind the much smaller doses is separate. A review of the idea proposes that brief, partial blockade of opioid receptors acts on microglia, the immune cells of the central nervous system, and dampens inflammation there, an effect said to be specific to low doses; the same review calls the use of low dose naltrexone for chronic conditions highly experimental, with small trials and few replications. [23] No published work connects that idea to body weight. Ondansetron does not touch appetite or metabolism at all: serotonin type 3 receptors sit on the vagal nerve endings in the gut and in the chemoreceptor trigger zone of the brainstem, and blocking them interrupts the signal that sets off vomiting. [8]

KEY POINT

These five medicines are not five versions of the same thing. Two act on appetite and were tested for weight in year long trials.[5] [11] One lowers blood sugar and lowers weight a little as it does so. [22] One rests on a mechanism studied in pain and bowel inflammation rather than in weight. [23] One treats nausea so that another treatment can continue. [8]

§ 04

What the research shows

The weight evidence is uneven, because the five medicines arrived by different routes. Qsymia has a programme of year long randomized trials behind its approval; phentermine alone was approved in 1959, long before modern trial requirements; metformin has been tested for weight many times in people without diabetes; and low dose naltrexone and ondansetron have no weight trials at all.

What the evidence supports

Qsymia lowers weight substantially, and the effect holds for two years. In CONQUER, among 2,487 adults with a body mass index of 27 to 45 and two or more weight related conditions, weight fell by 7.8 percent on 7.5 mg with 46 mg and by 9.8 percent on 15 mg with 92 mg, against 1.2 percent on placebo; at least 5 percent of body weight was lost by 62 and 70 percent of those two groups against 21 percent on placebo.[11] In EQUIP, in adults with a body mass index of 35 or more, the figures were 5.1 and 10.9 percent against 1.6 percent. [12] SEQUEL continued CONQUER to 108 weeks in 676 people, and the weight reduction was still 9.3 and 10.5 percent against 1.8 percent, with fewer adverse events in the second year than the first. [13] Pooling the randomized trials, the average weight loss against placebo was 7.73 kg overall, and 3.55, 7.27 and 8.25 kg for the three main doses. [14] Among the 475 participants who had prediabetes or the metabolic syndrome at the start, two years of treatment lowered the annual rate of new type 2 diabetes by 70.5 and 78.7 percent on the two higher doses. [15]

Phentermine on its own works, and the longer people take it the more they lose. The randomized evidence is one trial: 68 relatively healthy Korean adults with a body mass index of 25 or more took 37.5 mg daily or placebo with behavioural therapy, and weight fell by 6.7 kg and waist circumference by 6.2 cm, significantly more than placebo, with no significant change in blood pressure.[16] A cohort of 13,972 adults starting phentermine between 2010 and 2015 then found that those who took it continuously for more than 12 months had lost 7.4 percent more weight at two years than those who took it for three months or less, with cardiovascular events or death rare and no difference between the duration groups. [17] That study watched practice rather than assigning treatment, so it cannot settle cause.

Metformin lowers weight modestly and holds it for years. In the Diabetes Prevention Program, 3,234 adults with raised blood sugar were randomized to metformin 850 mg twice daily, placebo or an intensive lifestyle programme, and metformin cut the rate of new diabetes by 31 percent over a mean of 2.8 years, against 58 percent for the lifestyle programme.[19] Weight fell by 2.06 percent on metformin against 0.02 percent on placebo during the trial, and stayed lower through seven to eight more years of open label follow up, 2.0 against 0.2 percent, in proportion to how reliably people kept taking it. [20] Among those who had lost at least 5 percent in the first year, the metformin group held the most weight off between years 6 and 15, a mean of 6.2 percent below their starting weight. [21]

What is not yet known

Metformin's weight effect in people without diabetes is small. Pooling 49 randomized trials in adults with a body mass index of 25 or more, metformin lowered body mass index by 0.56 points more than placebo across doses from 500 to 2,550 mg a day, with no difference by dose or duration, and no difference at all between metformin and lifestyle modification; orlistat outperformed it, and the authors graded the trials as low quality.[22]

Low dose naltrexone has never been tested for weight, and its two best known trials were in fibromyalgia. A crossover trial in 31 women found daily pain reduced by 28.8 percent on 4.5 mg against 18.0 percent on placebo, with better mood but no change in fatigue or sleep, and the authors described the evidence as preliminary and asked for parallel group trials.[24] One was then run: 99 women took 6 mg or placebo for 12 weeks, pain fell by 1.3 points on an 11 point scale against 0.9 points on placebo, and the difference of 0.34 points was not statistically significant. [25] In Crohn disease, a Cochrane review found two randomized trials with 46 participants between them; remission at 12 weeks was reached by 30 percent on low dose naltrexone against 18 percent on placebo, which was not significant, while a partial response and an endoscopic response did favour it, and the reviewers rated the evidence low in quality and said no firm conclusion was possible. [26]

Ondansetron has no published trial for the nausea of a weight medicine; its own trials were run in chemotherapy, radiotherapy and surgery.[8] It is prescribed because it is a well characterised antinausea medicine and nausea that stops you eating or drinking normally is worth treating, but nobody has measured how well it does that job here. No trial has compared any medicine in this guide head to head with a GLP 1 medicine either. The AGA guideline suggests phentermine with topiramate extended release for long term management on moderate certainty evidence, and phentermine on its own on low certainty evidence, which is the guideline's way of saying the two rest on very different amounts of data. [1]

THE MAIN HUMAN EVIDENCE These studies were run separately and cannot be compared with each other unless the study itself made the comparison.

STUDY	N	DESIGN	MAIN FINDING
CONQUER 2011 [11]	2,487	Randomized, double blind, placebo controlled, 56 weeks, BMI 27 to 45 with two or more comorbidities	Weight fell 7.8 and 9.8 percent on the two doses against 1.2 percent
SEQUEL 2012 [13]	676	Double blind extension of CONQUER to 108 weeks	Weight still 9.3 and 10.5 percent below baseline against 1.8 percent
Kim 2006 [16]	68	Randomized, double blind, placebo controlled, phentermine 37.5 mg daily	Weight fell 6.7 kg and waist 6.2 cm, more than placebo
Lewis 2019 [17]	13,972	Observational health record cohort, phentermine alone	7.4 percent more weight lost at 2 years with use beyond 12 months; no difference in cardiovascular events or deaths by duration
DPPOS 2019 [21]	1,066	15 year follow up of those who lost 5 percent in year one	6.2 percent below baseline in years 6 to 15 on metformin against 2.8 percent on placebo
Haber 2024 [22]	49 trials	Systematic review and meta analysis, adults without diabetes, BMI 25 or more	BMI 0.56 points lower than placebo; no difference against lifestyle change
FINAL 2024 [25]	99	Randomized, double blind, parallel group, naltrexone 6 mg for 12 weeks, fibromyalgia	No significant difference from placebo in pain, 0.34 points
Cochrane 2018 [26]	46	Systematic review, 2 randomized trials of naltrexone 4.5 mg, Crohn disease	Remission 30 against 18 percent, not significant; evidence quality low

SUMMARY

Qsymia has the strongest weight evidence of the five, with two years of randomized data and a clear dose response, and phentermine alone has a much thinner evidence base that still points the same way. [13] [16] Metformin lowers weight by a small amount and keeps it off for years in the people who keep taking it, which suits a different purpose from the one most patients come in asking about. [21] [22] Low dose naltrexone has no weight evidence, and its pain trials have gone from encouraging in a small crossover study to flat in a larger one. [24] [25] Ondansetron is on the programme to make another treatment tolerable; it does nothing to weight itself. [8]

§ 05

How they are taken

Every dose below comes from a current FDA label, except for low dose naltrexone, where no label exists and the only numbers available are the doses used in published trials of other conditions. Your physician sets your own dose and will tell you which of these schedules you are following.

Phentermine

The usual adult dose of the 37.5 mg tablet is one tablet a day, taken before breakfast or one to two hours after it; half a tablet, 18.75 mg, is enough for some people, and in some cases half a tablet twice a day suits better. Late evening doses are avoided because of insomnia, and the dose is limited to 15 mg a day in severe kidney impairment. [3] The 8 mg Lomaira tablet is taken three times a day, half an hour before meals, and it is scored so that half a tablet can be given. [4] The label describes a

few weeks of treatment and adds that tolerance to the appetite effect usually develops within a few weeks, at which point the drug should be stopped rather than increased. [3] Prescriptions that run longer are off label, which a physician may do; the AGA guideline suggests phentermine for long term management while grading the certainty of that evidence as low. [1] [17]

Qsymia

One capsule is taken each morning, with or without food, and evening doses are avoided because of insomnia.[5] The label asks for a negative pregnancy test before the first capsule and once a month during treatment, and for blood tests of bicarbonate, creatinine and potassium before starting and from time to time afterwards, with glucose added for anyone taking medicine for type 2 diabetes. [5]

QSYMIA: STARTING, INCREASING AND STOPPING From the FDA prescribing information.[5]

STEP	ONCE DAILY DOSE
First 14 days	3.75 mg phentermine with 23 mg topiramate
Then for 12 weeks	7.5 mg with 46 mg
At 12 weeks, if less than 3 percent of starting weight has gone	11.25 mg with 69 mg for 14 days, then 15 mg with 92 mg
After 12 weeks on the highest dose	Continue if at least 5 percent of starting weight has gone; stop if it has not
Stopping the highest dose	Take it every other day for at least a week first, to avoid provoking a seizure

The dose is capped at 7.5 mg with 46 mg in moderate or severe kidney impairment and in moderate liver impairment, and Qsymia is avoided in severe liver impairment and in end stage kidney disease on dialysis.[5] Because of the risk to a pregnancy, Qsymia reaches patients only through certified pharmacies under a federal Risk Evaluation and Mitigation Strategy, so your prescription may be filled somewhere other than your usual pharmacy. [5]

Metformin

Treatment starts at 500 mg twice a day or 850 mg once a day with meals, and rises by 500 mg a week or 850 mg every two weeks to a maximum of 2,550 mg a day in divided doses; above 2,000 mg a day, three doses with meals are often easier on the stomach.[6] Taking it with food is part of the instruction. Kidney function is measured before starting and at intervals afterwards: metformin is contraindicated below an estimated filtration rate of 30, and the label advises against starting it between 30 and 45. [6] It is held before an imaging scan with contrast dye in several situations and restarted 48 hours later once kidney function has been rechecked. [6]

Low dose naltrexone

No regulator has set a dose, because no low dose product has been approved, so your physician sets both the dose and the schedule.[10] The published trials used 4.5 mg once a day in the evening for fibromyalgia and for Crohn disease, and 6 mg once a day in the larger fibromyalgia trial, which are doses from studies of other conditions rather than doses established for weight. [24] [25] [26] One practical point matters more than the number: naltrexone blocks opioid painkillers, so anyone taking an opioid, or likely to need one, needs to tell us before starting. [7]

Ondansetron

The label doses belong to the situations the medicine was approved for: 8 mg before moderately emetogenic chemotherapy with a second dose eight hours later, a single 24 mg dose before highly emetogenic chemotherapy, 8 mg one to two hours before radiotherapy to the abdomen, and 16 mg an hour before anaesthesia. With severe liver impairment the total should

not exceed 8 mg a day.[8] Prescribing it for the nausea of a weight medicine is off label, so the dose and the timing are set by your physician, and it is written to be used when you need it rather than every day.

§ 06

What to expect

The first weeks. On Qsymia the starting dose is deliberately small, so the first fortnight is about tolerating the medicine rather than losing weight.[5] On phentermine the effect on appetite is usually noticeable within days, together with the things that come with a stimulant: a dry mouth, a little trouble sleeping if the dose is late, and sometimes a faster pulse.[3] On metformin the first two weeks are the hardest on the bowel, so the dose climbs slowly and is taken with meals.[6]

The first three months. Qsymia has its checkpoints written into the label. At 12 weeks on 7.5 mg with 46 mg, 3 percent of starting weight should be gone, or the dose goes up; after 12 weeks on the highest dose, 5 percent should be gone, or the medicine is stopped because further treatment is unlikely to achieve meaningful weight loss.[5] Those are the label's own numbers, and we will use them with you. Phentermine's label points the other way, noting that tolerance to the appetite effect usually appears within a few weeks.[3]

Over a year and beyond. The trial results that matter were measured at 56 and 108 weeks, so the timescale for a weight medicine is a year or two rather than a month.[11][13] With metformin the effect was small from the start and was held for a decade by the people who kept taking it.[20][21] With any of them the benefit lasts while the medicine is taken. Large weight loss also takes some lean tissue along with the fat, and a joint advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association and The Obesity Society recommends resistance training and an adequate, protein focused diet for everyone on a weight medicine.[27]

DURING TREATMENT

- Tell us about blurred vision or eye pain on Qsymia without waiting, because acute short sightedness with raised eye pressure usually appears within the first month and reverses when the medicine is stopped promptly.[5]
- Do not stop the highest Qsymia dose suddenly. It is tapered over at least a week, because abrupt withdrawal of topiramate has provoked seizures in people with no history of them. Drink enough, particularly in hot weather and during hard exercise, because topiramate reduces sweating in some people and raises the chance of a kidney stone.[5]
- On metformin, report feeling unusually weak, achy, breathless or drowsy, or new abdominal pain, and stop the tablets if you cannot keep fluids down.[6]
- Tell any clinician treating you that you take naltrexone, because it blocks opioid painkillers and because sensitivity to opioids rises again after it is stopped.[7]

§ 07

Safety

Of the five, metformin is the one with a boxed warning, and Qsymia is the one with the longest list of things to monitor. The phentermine label carries no boxed warning but a long list of contraindications, and both naltrexone and ondansetron have specific risks that are easy to miss because the medicines are so familiar.[3][5][7][8]

METFORMIN CARRIES A BOXED WARNING FOR LACTIC ACIDOSIS

Cases reported after marketing have resulted in death, low body temperature, low blood pressure and slow heart rhythms that do not respond to treatment. The onset is often subtle, with nothing more specific than feeling unwell, aching muscles, breathlessness, drowsiness and abdominal pain. The risk factors named on the label are reduced kidney function, certain other medicines, including carbonic anhydrase inhibitors such as topiramate, being 65 or older, having a scan with contrast dye, surgery, states of low oxygen such as acute heart failure, drinking heavily, liver impairment and mitochondrial disease. If it is suspected, metformin is stopped at once and treated in hospital.[6] Topiramate being named in that list is why we are careful about metformin and Qsymia together.[5]

Phentermine and Qsymia

The side effects of Qsymia are mostly those of topiramate, and they are dose related. Pins and needles, a dry mouth, constipation, an altered sense of taste, insomnia and dizziness are the ones that occurred in at least 5 percent of adults and at least half again as often as on placebo, and a meta analysis of the randomized trials found the same pattern in terms of odds.[5] [14]

QSYMIA SIDE EFFECTS REPORTED BY AT LEAST 2 PERCENT OF ADULTS Percent of adults in the one year placebo controlled trials, from the FDA prescribing information.[5]

SIDE EFFECT	PLACEBO (N=1,561)	3.75 WITH 23 MG (N=240)	7.5 WITH 46 MG (N=498)	15 WITH 92 MG (N=1,580)
Pins and needles	2%	4%	14%	20%
Dry mouth	3%	7%	14%	19%
Constipation	6%	8%	15%	16%
Altered taste	1%	1%	7%	9%
Insomnia	5%	5%	6%	9%
Dizziness	3%	3%	7%	9%
Depression	2%	3%	3%	4%
Trouble concentrating	1%	0%	2%	4%

- **Harm to a pregnancy.** Qsymia is contraindicated in pregnancy, and so is phentermine, because losing weight offers a pregnant woman no benefit and may harm the fetus.[3] A fetus exposed to topiramate in the first trimester has a raised risk of major birth defects, cleft lip and cleft palate among them, and of being small for its gestational age. In the North American registry, oral clefts affected 1.4 percent of topiramate exposed infants against 0.3 percent of infants exposed to a comparison antiepileptic drug and 0.11 percent of infants whose mothers had neither epilepsy nor antiepileptic treatment, against a United States background rate of 0.17 percent; the relative risk was 12.5. Being small for gestational age affected 19.7 percent of exposed newborns against 5.4 percent of unexposed.[5]
- **Mood, suicidal thinking and concentration.** Antiepileptic drugs including topiramate roughly double the risk of suicidal thoughts or behaviour, an adjusted relative risk of 1.8, which worked out as 0.43 percent of 27,863 treated patients against 0.24 percent of 16,029 on placebo, or about one extra case for every 530 people treated. Qsymia is avoided after a suicide attempt or with active suicidal thinking and stopped if such thoughts appear. It can also affect concentration, memory and finding the right word, more so when the dose rises quickly, so take care with driving and machinery until you know how it affects you.[5]

- **Heart rate, valves and lung pressure.** Over eight weeks of ambulatory monitoring, Qsymia raised the 24 hour average heart rate by 3.6 beats per minute against placebo, and a rise of more than 10 beats per minute at some point was recorded in 56 percent of those on the highest dose against 42 percent on placebo.[5] Phentermine's label lists palpitation, fast heart rate and raised blood pressure among its adverse reactions, asks for caution even in mild hypertension, and contraindicates the drug outright in anyone with a history of cardiovascular disease. Rare cases of primary pulmonary hypertension and of leaking heart valves have been reported with phentermine alone, mostly from the era when it was combined with fenfluramine, and it is stopped for new breathlessness, chest pain on exertion, fainting or swollen ankles. [3]
- **Blood chemistry, kidneys, eyes and growth.** Topiramate inhibits carbonic anhydrase, which pushes blood bicarbonate and potassium down, raises the chance of a kidney stone, and can raise creatinine; hence the blood tests before and during treatment. Acute short sightedness with secondary angle closure glaucoma has been reported, usually within a month of starting, and it needs the medicine stopped as quickly as possible. Qsymia is approved from the age of 12, with height monitored, since treated adolescents gained 1.3 to 1.4 cm a year less height than those on placebo over 56 weeks; phentermine alone is not recommended at or under 16.[5] [3]
- **Abuse and stopping.** Phentermine is related to the amphetamines, and the label asks that the risk of abuse be assessed before it is prescribed and that no more than necessary be dispensed at a time; abrupt cessation after prolonged high doses brings extreme fatigue and low mood.[3]

Metformin, naltrexone and ondansetron

Metformin's common side effects are digestive and they settle. In the trial behind the label, diarrhea affected 53 percent on metformin against 12 percent on placebo, nausea or vomiting 26 against 8 percent, and 6 percent of patients stopped because of diarrhea; over 29 weeks vitamin B12 fell from a normal level to below normal in about 7 percent, so the label asks for blood counts once a year and a B12 level every two to three years.[6] In the Diabetes Prevention Program, digestive symptoms were more common than on placebo and became less frequent over time, and no new safety problem appeared across more than a decade. [20]

Naltrexone's risks come from what it blocks and from the liver. It is contraindicated in anyone taking opioid painkillers, anyone dependent on opioids including those on methadone or buprenorphine, and anyone in opioid withdrawal, and starting it in those situations precipitates withdrawal; tolerance to opioids also falls while it is taken, so a dose that was once tolerated can become dangerous after the medicine stops.[7] Cases of hepatitis and significant liver dysfunction have been reported, and drug levels rise about fivefold in compensated cirrhosis and tenfold in decompensated cirrhosis. [7] In an open label safety study of about 570 people with alcohol dependence taking the full 50 mg dose, new side effects were nausea in 10 percent, headache in 7 percent, and dizziness, nervousness, fatigue, insomnia, vomiting, anxiety and sleepiness each in 2 to 4 percent. [7] Those figures come from a dose ten or more times larger than a compounded capsule, and no safety study of the low dose exists outside the small trials in pain and bowel disease, where side effects were no more frequent than on placebo. [25] [26]

Ondansetron prolongs the QT interval, the time the heart takes to recharge between beats, and cases of a dangerous rhythm called torsade de pointes have been reported after marketing. The label asks that it be avoided in congenital long QT syndrome and that an electrocardiogram be used to monitor anyone with low potassium or magnesium, heart failure, a slow heart rhythm, or other medicines that prolong the QT interval. The size of the effect depends on dose and route: in 58 healthy volunteers given single intravenous doses, the QT interval lengthened by 19.5 milliseconds after 32 mg but by 5.6 milliseconds after 8 mg, which the label describes as not clinically relevant.[8] Serotonin syndrome has been reported, mostly alongside other serotonin raising medicines such as antidepressants and tramadol, and some cases were fatal. In its own chemotherapy trials headache affected 24 percent against 13 percent on placebo and malaise or fatigue 13 against 2 percent. [8]

TELL YOUR PHYSICIAN BEFORE STARTING IF ANY OF THESE APPLY

- You are pregnant, might be, or are planning a pregnancy, or you are breastfeeding. Phentermine and Qsymia are both contraindicated in pregnancy, and Qsymia requires a negative pregnancy test before it starts and monthly afterwards.[3 5]
- You have heart disease of any kind, including coronary disease, a past stroke, an abnormal rhythm, heart failure or blood pressure that is not controlled, which rule out phentermine entirely.[3]
- You have glaucoma or any other eye condition, an overactive thyroid, a history of drug abuse or an agitated state, or you take a monoamine oxidase inhibitor or stopped one less than 14 days ago.[3 5]
- You have had depression, suicidal thoughts, an eating disorder, kidney stones, or a seizure, or you take another medicine that inhibits carbonic anhydrase.[5]
- You have reduced kidney function or liver disease, or you drink heavily, which all matter for metformin and change the maximum dose of Qsymia.[6]
- You take an opioid painkiller or any opioid medicine, or you are in treatment for opioid dependence, which rules out naltrexone at any dose.[7]
- You have been told you have long QT syndrome, or you take medicines that affect heart rhythm, which matters for ondansetron.[8]
- You have surgery, sedation or a scan with contrast dye coming up. Please bring a full list of your medicines and supplements.[6]

Qsymia has 108 weeks of randomized data behind it, phentermine alone has no published randomized trial longer than a few months, metformin has more than a decade of follow up from the Diabetes Prevention Program, and low dose naltrexone has nothing longer than 12 weeks.[13 16 20 25] This guide is scheduled for review as new evidence is published.

§ 08

Is this right for you

Obesity is a chronic condition, and the point of treating it is the health that comes with the weight: blood pressure, blood sugar, lipids, sleep, joints and the risk of diabetes. The AGA recommends medicine added to lifestyle change for adults with a body mass index of 30 or more, or 27 or more with a weight related complication, who have not had enough response from lifestyle change alone, and it treats that as long term treatment rather than a course.[1] Where a medicine you already take is contributing to your weight, the Endocrine Society guideline asks that prescribing take weight into account and choose alternatives with better weight profiles where they exist.[2]

Before we begin

- [ ] A review of your medical history, family history, every current medication and supplement, and any history of heart disease, depression, kidney stones, seizures, eating disorders or opioid use[3 5 7]
- [ ] Weight, waist measurement, blood pressure and heart rate, so we have a clear starting point and know what the medicine is doing to your pulse[5]
- [ ] Baseline bloodwork of the kind the labels ask for, which for Qsymia means bicarbonate, creatinine and potassium, and for metformin means kidney function[5 6]
- [ ] A written note of your goals, for weight, health and how you want to feel, so we can judge progress together

Finding the cause comes first. Thyroid disease, poorly controlled diabetes, sleep apnea, depression and several common prescriptions all push weight up, and treating them helps the weight as well as the person. If a pregnancy is possible, contraception is part of the plan for Qsymia, and the label asks for a negative pregnancy test before the first capsule and every month afterwards.[5]

Reviewing your progress

Qsymia brings its own schedule: weight is assessed after 12 weeks on the middle dose and again after 12 weeks on the highest, and treatment stops if 5 percent of starting weight has not gone.[5] Phentermine's label asks for the drug to be stopped rather than increased when its effect on appetite fades.[3] For the medicines without a weight indication there is no label checkpoint, so we will agree one with you in advance and reassess against your documented starting point. You are welcome to stop at any time.

> QUESTIONS TO ASK YOUR PHYSICIAN
>
> Which of these medicines would you choose for someone in my situation, and would an injection serve me better? Is this prescription within the FDA label or off label, and why that choice? What would make you stop it? Do any of my current medicines interact with it, and does any of them need changing first? What blood tests will we do, and how often? How much protein should I eat, and how will we protect my muscle? What happens when I stop?

We are glad to answer all of these.

§ 09

Regulatory status

Phentermine. Approved in the United States since 1959, phentermine is indicated, in the label's own words, as a short term adjunct of a few weeks in a regimen of weight reduction based on exercise, behavioural modification and caloric restriction, in the management of exogenous obesity, for patients with an initial body mass index of 30 or more, or 27 or more in the presence of other risk factors such as controlled high blood pressure, diabetes or raised cholesterol. The same section adds that the limited usefulness of drugs of this class should be measured against the risks of using them, and it is a Schedule IV controlled substance, so federal rules govern how it is prescribed and dispensed.[3] Treatment that continues past a few weeks goes beyond the label, which a physician may do, and the AGA guideline does suggest phentermine for long term use while grading the certainty of that evidence as low.[1] The 8 mg Lomaira tablet was approved on 12 September 2016 and carries the same indication.[4] [10]

Phentermine with topiramate extended release. Qsymia was approved on 17 July 2012 and is indicated, with a reduced calorie diet and increased physical activity, to reduce excess body weight and maintain weight reduction long term in adults and children aged 12 and older with obesity, and in adults with overweight and at least one weight related condition.[5] [10] Its label states two limitations: the effect on cardiovascular illness and death has not been established, and neither has its safety or effectiveness alongside other weight loss products, whether prescription, over the counter or herbal. Because topiramate can harm a fetus, Qsymia is available only through a limited programme under a Risk Evaluation and Mitigation Strategy, and only certified pharmacies may distribute it. It is a Schedule IV controlled substance by virtue of its phentermine content, and it is approved as a drug, not as a biologic.[5]

Metformin and ondansetron. Metformin, approved since 1995, is indicated as an adjunct to diet and exercise to improve blood sugar control in adults and children aged 10 and older with type 2 diabetes mellitus, and that is the whole of its indication; there is no approved use for weight, prediabetes, insulin resistance or polycystic ovary syndrome, so prescribing it for any of those is off label, and its label carries the boxed warning for lactic acidosis.[6] Ondansetron, approved since 1991 and not a controlled substance, is indicated for preventing the nausea and vomiting of chemotherapy, of radiotherapy to the abdomen or total body irradiation, and of surgery; nausea from any other cause, including nausea from a weight medicine, is

outside the label. [8] [10] A physician may prescribe off label where the evidence and the patient's situation support it, and for metformin outside diabetes that published evidence is substantial even though the FDA has not reviewed it for those uses. [19] [22]

Naltrexone. Naltrexone hydrochloride tablets were approved on 20 November 1984 and are indicated for the treatment of alcohol dependence and for blocking the effects of opioids given from outside the body; the label adds that naltrexone has not been shown to provide any therapeutic benefit except as part of a plan of management for those addictions, and the labelled dose is 50 mg once a day.[7] No FDA approved product exists at 1.5 to 4.5 mg, so a low dose capsule is a compounded medicine: it is not FDA approved, the agency does not review its safety, effectiveness or quality before it is dispensed, and it is prepared by a state licensed pharmacy or physician against a prescription for one named patient under section 503A of the federal law, or by an outsourcing facility registered with the FDA under section 503B. [10] [30] [31] Naltrexone is not a peptide, so the federal enforcement discretion policy for compounded peptides published on 30 October 2026 has no application to it. [29] Naltrexone with bupropion, sold as Contrave and approved on 10 September 2014 for long term weight management, delivers 32 mg of naltrexone a day alongside 360 mg of bupropion, so its label should not be read across to a low dose capsule. [9]

Athletes. Phentermine appears in section S6 of the World Anti Doping Agency Prohibited List in force from 1 January 2026, among the stimulants prohibited in competition, and it sits in the non specified part of that class, which is the stricter category. It is not prohibited out of competition, but a tested athlete taking it needs either to stop it well before competition or to hold a therapeutic use exemption. Topiramate, metformin, naltrexone and ondansetron are not named anywhere in the 2026 List, so none of them is prohibited; bupropion, which is in Contrave rather than in any medicine in this guide, sits in the 2026 Monitoring Program and is not a prohibited substance. The List is reissued each year, so any athlete who is tested should confirm the current rules with their own anti doping organisation each season.[28]

If you would like details about the preparation used in your treatment, please ask.

§ 10

Common questions

Which of these are actually approved for weight loss?

Two. Phentermine is approved as a short term adjunct in the management of exogenous obesity, and Qsymia, which combines phentermine with topiramate, is approved for long term weight management in adults and in children aged 12 and older.[3] [5] Metformin is approved only for type 2 diabetes, ondansetron only for the nausea of chemotherapy, radiotherapy and surgery, and low dose naltrexone is not approved at all. [6] [8] [10]

If phentermine is only approved for a few weeks, why do people take it for months?

The label describes a few weeks of use and warns that tolerance to the appetite effect usually develops within a few weeks.[3] Practice has moved on: the AGA guideline suggests phentermine for long term management, grading the certainty of the evidence as low, and a cohort of 13,972 adults found more weight lost with use beyond 12 months and no rise in cardiovascular events or death, in a design that cannot establish cause. [1] [17] Treatment past a few weeks is off label, and your physician will say so when prescribing it.

Is phentermine addictive?

It is a Schedule IV controlled substance, related to amphetamine, and its label asks that the risk of abuse be assessed before prescribing and that the least amount feasible be dispensed at a time.[3] Against that, a study that interrupted treatment in 269 patients, including 117 who had taken phentermine for between about one and 21 years, found no abuse or psychological dependence and no amphetamine like withdrawal apart from a return of hunger. [18] A history of drug abuse is still a contraindication on the label.

Will metformin make me lose weight?

A little, and slowly. Pooling 49 randomized trials in adults without diabetes, metformin lowered body mass index by 0.56 points more than placebo and did no better than lifestyle change on its own.[22] What it does well is hold a small loss for years and lower the risk of developing diabetes, by 31 percent over about three years in the Diabetes Prevention Program.[19] [21]

Does low dose naltrexone help with weight?

No published trial has measured that. The controlled trials were run in fibromyalgia and in Crohn disease: a crossover trial in 31 women found more pain relief than placebo, a later trial in 99 women found no significant difference, and a Cochrane review of two small Crohn trials in 46 people found the evidence too imprecise for any firm conclusion.[24] [25] [26] Contrave, which contains naltrexone at roughly ten times the dose along with bupropion, is approved for weight management, and its results belong to that product.[9]

Can I take these alongside a weekly injection or another weight medicine?

That needs a direct conversation, because the labels are cautious about it. Qsymia's label states that its safety and effectiveness in combination with other weight loss products, prescription, over the counter or herbal, have not been established, and phentermine's label does not recommend combining it with other weight loss drugs at all.[3] [5] We watch metformin with Qsymia particularly closely, because the metformin boxed warning names carbonic anhydrase inhibitors such as topiramate among the risk factors for lactic acidosis.[6]

Will any of these show up in sport drug testing?

Phentermine will. It is listed among the stimulants prohibited in competition on the World Anti Doping Agency's 2026 Prohibited List, in the non specified part of that class, so a tested athlete needs to stop it in good time before competition or hold a therapeutic use exemption. Topiramate, metformin, naltrexone and ondansetron are not named in the 2026 List and are not prohibited.[28]

Where is a compounded medicine made, and who oversees it?

Federal law sets out two kinds of compounding. Under section 503A, a state licensed pharmacy or physician prepares a medicine for one patient against that patient's own prescription, and the state board of pharmacy carries the day to day oversight while the FDA inspects for cause and on surveillance.[30] Under section 503B, an outsourcing facility registers with the FDA, works to federal manufacturing quality standards, reports adverse events and the products it makes to the agency, and is inspected by the FDA on a risk based schedule; it may also supply a clinic directly rather than for one named patient.[31] We use both kinds, and which one prepares your medicine depends on the preparation.

Is a compounded medicine the same as an FDA approved one?

No, and the difference matters. A compounded preparation is not FDA approved, and the agency does not check its safety, effectiveness or quality before it is sold, which is why an approved product is the first choice whenever one fits your situation.[30] What a prescription from a licensed pharmacy or a registered outsourcing facility does give you is a named prescriber, a facility answerable to a state board or to the FDA, ingredients that meet federal requirements, and a route for reporting a problem. A capsule bought online and labelled for research use only has none of that: the FDA treats those products as unapproved new drugs when they are meant for people, and has written to the companies selling them.[32] Please do not use one.

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