Weight Management Medications for Chronic Use Guidance for Treatment Selection January 2024

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT.

The respective Product Information for phentermine/topiramate (QSYMIA), orlistat (XENICAL, ALLI), naltrexone/bupropion (CONTRAVE), liraglutide (SAXENDA), semaglutide (WEGOVY), or tirzepatide (ZEPBOUND) should be consulted for detailed prescribing information.

Abbreviations: BMI = body mass index; BP = blood pressure; CFU = Criteria for Use; CIV = Schedule IV Controlled Substance; CKD = chronic kidney disease; CrCl = creatinine clearance; DC = discontinue; DM = diabetes mellitus; ESRD = end-stage renal disease; FDA = Food and Drug Administration; HR = heart rate; HTN = hypertension; MAOI = monoamine oxidase inhibitor; PA-F = Prior Authorization Facility level; REMS = Risk Evaluation and Mitigation Strategies; VANF = VA National Formulary; WMM = weight management medications

Use of Chronic Weight Management Medications

Basic Principles of Pharmacotherapy[1]

1. Pharmacotherapy with weight management medications should always be in conjunction with a comprehensive lifestyle intervention (i.e., clinically supported weight management program that targets all three aspects of weight management: behavioral, dietary, physical activity; in VA, this is the MOVE! Weight Management Program). See VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity at https://www.healthquality.va.gov/
2. Weight management medications can be initiated any time during participation in a comprehensive lifestyle intervention.
3. The optimal duration for use of a weight management medication and outcomes beyond 2 to 4 years have not been established. Weight management medications should be viewed as long-term therapy, as short-term use results in weight regain. Long-term use (> 1 year), while not always associated with additional weight loss, results in significantly less weight regain compared to lifestyle interventions alone.
4. When selecting a weight management medication, a number of factors must be considered including each drug's efficacy, side effects, cautions, warnings, the patient's comorbidities, and should be a shared decision between patient and provider.
5. If sufficient weight loss is not achieved within the first 6 months of pharmacotherapy or significant weight gain or regain after initial loss occurs, then the weight management medication should be discontinued (See individual prescribing information or section on Treatment Selection, Table 1 for details). A trial of a different weight management medication may be warranted provided the patient continues to adhere to comprehensive lifestyle intervention.

Pharmacotherapy's Place in Chronic Weight Management[1]

- The VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity suggests that weight management medications for long-term weight loss be offered to patients with a body mass index $\geq$ 30 kg/m^2 and to those with a BMI $\geq$ 27 kg/m^2 who also have obesity associated conditions, as an adjunct to comprehensive lifestyle intervention.

- Six weight management medications are FDA approved for chronic weight management. Phentermine/ topiramate and orlistat are available on VA National Formulary with Prior Authorization at the Facility level with Criteria for Use; liraglutide (SAXENDA),semaglutide (WEGOVY), and tirzepatide (ZEPBOUND) are available non-formulary with Criteria for Use. Naltrexone/bupropion is not available in VA.
- Common to all Criteria for Use of the chronic weight management medications are the following:
  - Exclusion Criteria
    - Pregnancy
    - Breastfeeding
    - Each weight management medication CFU has additional exclusion criteria pertaining to the drug's safety profile
  - Inclusion Criteria
    - Verifiable participation in a comprehensive lifestyle intervention that targets all three aspects of weight management (diet, physical activity, behavioral changes) (See Appendix A)
    - Patient's BMI is greater than or equal to 30 kg/m2 **OR** BMI is greater than or equal to 27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, dyslipidemia, metabolic syndrome, obstructive sleep apnea, osteoarthritis, metabolic dysfunction-associated steatotic liver disease)

Treatment Selection of a Weight Management Medication for Chronic Use

Considerations for Shared Decision-Making Regarding Pharmacotherapy for Weight Management[1,2]

- Review the patient's current treatment regimen for any medications with potential for weight gain and consider whether alternate therapy may be an option (see Appendix B).
- Discuss treatment expectations (see below and Tables 2 and 3), and importance of follow-up and adjustment of treatment plan as indicated:
  - Weight management medications offer the opportunity for increased weight reduction and should be used with continued comprehensive lifestyle intervention to provide optimal benefit.
  - Weight loss from clinical interventions, including with pharmacotherapy, will likely plateau around 6 to 9 months.
  - In clinical trials, high medication discontinuation rates (e.g., some over 30%) have been noted.
  - Weight is usually regained after the medication is discontinued.
  - Longer durations of treatment do not typically lead to greater weight loss, but instead help to prevent weight regain.
- In order to continue to receive prescriptions for a weight management medication, the patient is expected to achieve the respective initial weight loss goal, as well as demonstrate continued weight loss towards the patient's goal weight or maintenance of their desired goal weight (refer to Table 2 below).
  - Initial refill after 12 to 24 weeks: the patient continues to participate in MOVE! or acceptable non-VA comprehensive lifestyle intervention or has previously participated in or completed a comprehensive lifestyle intervention and has since received at least one follow-up visit with a clinician who is able to provide ongoing education and support to address elements of comprehensive lifestyle intervention.
  - Refills every 6 months: there are no specific requirements for documentation of continued participation in a comprehensive lifestyle intervention in order for the patient to obtain refills every 6 months for a weight management medication. However, maintenance of 67% initial weight loss or greater than 5% loss from baseline weight or continued weight loss is a reasonable goal for continued therapy. *Note: as continued participation in comprehensive lifestyle intervention is important for weight loss maintenance, this may be necessary in order for the patient to meet goals for weight loss maintenance or continued weight loss with chronic weight management medication.*

Table 1: Medication Initial Weight Loss Goals and Weight Maintenance

Medication for Chronic Weight Management	Initial Weight Loss Goals	Weight Maintenance
Phentermine/topiramate	If 3% weight loss not achieved at 12 weeks on 7.5 mg/46 mg, increase dose as per prescribing information. If 5% loss of baseline body weight not achieved at 12 weeks on 15 mg/92 mg, it is unlikely the patient will achieve a clinically meaningful reduction in weight with further treatment. Taper to discontinue.	Provide counseling on need for ongoing participation in a comprehensive lifestyle intervention in conjunction with medication use. Maintenance of 67% initial weight loss or greater than 5% loss from baseline weight or continued weight loss are reasonable goals for continued therapy.
Orlistat	3% weight loss at 12 weeks	
Naltrexone/bupropion (not available in VA)	5% weight loss by 12 weeks; per the prescribing information, discontinue if this goal is not achieved as it is unlikely that a clinically meaningful reduction in weight will be achieved and sustained with continued treatment.	
Liraglutide	4% weight loss at week 16; per the prescribing information, discontinue if this goal is not achieved as it is unlikely that a meaningful weight loss will be achieved and sustained with continued treatment.	
Semaglutide	5% weight loss after achieving dose titration to a maintenance dose of 2.4 mg (recommended) (approximately 20 weeks) or 1.7 mg once weekly. Per the prescribing information, if a dose is not tolerated during titration, the dose increase can be delayed for 4 weeks.	
Tirzepatide	5% weight loss after achieving dose titration to a maintenance dose of 5 mg, 10 mg, or 15 mg once weekly (titration duration ranges 4-16 weeks depending on maintenance dose). Per the prescribing information, if a maintenance dose is not tolerated, a lower maintenance dose should be considered.	

Prescribing Considerations[3-8]

- General considerations for prescribing chronic weight management medications are included in Table 2 below.

Table 2: Comparison of General Prescribing Considerations

Medication for Weight Loss	Formulary Status	REMS	Controlled Substance	Boxed Warning	Administration
Phentermine/topiramate	VANF PA-F (CFU)	Yes [teratogenic risk]	CIV	No	Once daily [initial dose titration] Oral capsule
Orlistat	VANF PA-F (CFU)	No	No	No	Three times daily Oral capsule
Naltrexone/bupropion	Not available in VA	No	No	Yes [suicidal thoughts and behaviors]	Twice daily [initial dose titration] Oral tablet
Liraglutide	Nonformulary (CFU)	No	No	Yes [thyroid C-cell tumors]	Once daily [initial dose titration] Subcutaneous injection
Semaglutide	Nonformulary (CFU)	No	No	Yes [thyroid C-cell tumors]	Once weekly [initial dose titration] Subcutaneous injection
Tirzepatide	Nonformulary (CFU)	No	No	Yes [thyroid C-cell tumors]	Once weekly [initial dose titration] Subcutaneous injection

Comparison of Efficacy and Safety[9-15]

- As there are few comparative trials of weight management medications, the choice of drug can be determined by several factors including efficacy, tolerability, previous response, patient preferences, and comorbidities. Table 3 organizes the five weight management medications for chronic therapy based on their extent of weight loss and odds ratio (OR) of patients able to achieve a 5% or greater weight loss, or discontinuation due to an adverse event in clinical trials compared to lifestyle modification.

Table 3: Chronic WMM Comparison of Weight Loss and Discontinuation Due to Adverse Events

Medication for Weight Loss	% Weight Loss vs Baseline	≥ 5% Weight Loss (OR)	≥ 10% Weight Loss (OR)	Discontinuation Due to Adverse Events (OR)
Orlistat [14]	-3.2%	2.73	2.43	1.72
Naltrexone/bupropion[14]	-4.1%	5.04	5.19	2.69
Liraglutide [14]	-4.7%	4.91	4.80	2.45
Phentermine/topiramate[14]	-8.0%	8.02	9.74	2.40
Semaglutide[14]	-11.4%	9.82	13.32	1.99
Tirzepatide[15]	-15 to -20.9%	10.8 to 19	9.4 to 21.8	2.11

Treatment Considerations and Comorbidities[3-8,10-25]

- Outcome data on long-term morbidity and mortality with pharmacotherapy in the management of patients with overweight and obesity are not currently available. Therefore, treatment selection should be individualized and based on efficacy, potential for adverse effects and patient tolerability, patient preferences, and comorbidities. Treatment considerations depending on comorbidities are noted in Table 4 below.

Table 4. Comorbidities and Chronic Weight Management Medications Treatment Considerations				
Comorbidity	Phentermine/topiramate	Orlistat	Naltrexone/bupropion	Liraglutide, Semaglutide, or Tirzepatide
Hypertension	↓ BP in HTN[16] **Warning/Precaution** Risk of hypotension in patients on antihypertensive medications	↓ BP in HTN[16]	**Contraindication** Uncontrolled HTN **Warning/Precaution** May ↑BP/cause HTN	
Cardiac or Cerebrovascular Disease	**Warning/Precaution** ↑ HR, monitor (especially in cardiac or cerebrovascular disease); ↓ or DC if sustained *Not recommended or studied in recent or unstable disease*		**Warning/Precaution** ↑ HR or BP, monitor *Unknown impact on listed comorbidity as several conditions excluded from clinical trials*	**Warning/Precaution** ↑ HR, monitor per usual practice; DC if sustained *No specific precaution for listed comorbidity* Semaglutide: ↓ risk of death from CV cause, nonfatal MI, or nonfatal stroke in preexisting CV disease without diabetes[21]
Diabetes **Risk of Diabetes**	Improved glycemic parameters in DM[17,19] ↓ risk of DM[18,19]	Improved glycemic parameters in DM[20] ↓ risk of DM[20]	Improved glycemic parameters in DM[17]	Improved glycemic parameters in DM[1124] Liraglutide: ↓ risk of DM[25,26] Semaglutide and Tirzepatide: Improved glycemic parameters in preDM[10,15,27-29]
Depression	Dose related ↑ depression, anxiety adverse events[19] **Warning/Precaution** ↑ risk for recurrent depression, other mood disorders; risk for suicidal behavior or ideation		**Boxed Warning** Suicidal behavior or ideation **Warning/Precaution** Monitor patients treated with bupropion (antidepressant), especially during initial months, dose changes	**Warning/Precaution** Monitor for emergence or ↑ depressive symptoms, suicidal thoughts or behavior; avoid if history of suicide attempts or active suicidal ideation

Seizure disorder	**Warning/Precaution** Abrupt DC may cause seizures (regardless if history of seizure disorder); taper if DC		**Contraindication** **Warning/Precaution** ↑ risk for seizures	
Nephrolithiasis	**Warning/Precaution** Risk may be ↑ with ketogenic diet or concomitant carbonic anhydrase inhibitors; may ↓ risk with ↑ fluid intake	**Warning/Precaution** May ↑ urinary oxalate; caution if history hyperoxaluria or calcium oxalate stones		
Glaucoma	**Contraindication** **Warning/Precaution** Acute myopia with secondary angle closure glaucoma may occur; DC if acute onset ↓ visual acuity or ocular pain		**Warning/Precaution** Pupillary dilation may lead to attack in those at risk for narrow angle glaucoma	

Additional Safety Considerations [3-7] In addition to treatment comparisons based on comorbidities as per Table 4, additional contraindications and warnings and precautions are included in Table 5 below.

Table 5: Contraindications and Warnings for the Weight Management Medications for Chronic Use

Medication for Weight Loss	Contraindications	Warnings and Precautions
Phentermine/ topiramate	• Pregnancy • Glaucoma • Hyperthyroidism • MAOI use during or within 14 days	• Fetal toxicity [Risk Evaluation and Mitigation Strategies (REMS)] • Increased heart rate • Suicidal behavior and ideation • Acute myopia and secondary angle closure glaucoma; visual field defects • Mood and sleep disorders • Cognitive impairment • Metabolic acidosis • Hypokalemia • Elevated creatinine; adjust dose per CrCl, avoid in ESRD • Nephrolithiasis • Adjust dose in moderate hepatic impairment • Hypoglycemia with use of antidiabetic medications • Hypotension with use of antihypertensive medications • Oligohidrosis and hyperthermia • Serious skin reactions • Avoid abrupt withdrawal due to potential for seizures • Contains phentermine, which is related to amphetamines that have potential for abuse
Orlistat	• Pregnancy • Chronic malabsorption syndrome • Cholestasis	• Interference with absorption of fat-soluble vitamins, cyclosporine, warfarin, amiodarone, thyroid hormone, antiepileptic drugs, and antiretroviral drugs • Hepatotoxicity • Cholelithiasis • Oxalate nephrolithiasis and oxalate nephropathy with renal failure • Gastrointestinal events if taken with a diet high in fat

Naltrexone/ Bupropion*	• Uncontrolled hypertension • Seizure disorder • Bulimia or anorexia nervosa • Chronic opioid use or acute opioid withdrawal • Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs • MAOI use during or within 14 days	• Suicidal behavior and ideation [Boxed Warning] • Neuropsychiatric adverse events and suicide risk (in smoking cessation) • Seizures; increased risk with factors that decrease seizure threshold • Vulnerability to opioid overdose; precipitated opioid withdrawal • Increased blood pressure and heart rate • Hepatotoxicity; adjust dose in hepatic impairment, not recommended in severe hepatic impairment • Activation of mania • Angle-closure glaucoma • Hypoglycemia with use of antidiabetic medications • Adjust dose in moderate to severe renal impairment, avoid in ESRD
Liraglutide, Semaglutide, or Tirzepatide	• Pregnancy* (liraglutide only) • Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2)	• Thyroid C-cell tumors [Boxed Warning] • Acute pancreatitis • Acute cholelithiasis or cholecystitis • Hypoglycemia; may need to adjust concomitant DM agents • Increased heart rate • Renal impairment, use with caution in existing CKD (liraglutide); acute kidney injury (semaglutide and tirzepatide) • Suicidal behavior and ideation • Diabetic retinopathy complications in patients with type 2 diabetes (semaglutide and tirzepatide)

Refer to the respective prescribing information for comprehensive list and accompanying information. Naltrexone/bupropion not available in VA. *Note: use of weight loss medications are not recommended during pregnancy[2,30]

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Note: VA Academic Detailing Service Weight Management Documents and Resources are available at: https://vaww.portal2.va.gov/sites/ad/SitePages/WeightManagement.aspx

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5/2017; revised 6/2020, 9/2021, 3/2023, 6/2023 (breastfeeding added as exclusion), 8/2023, 10/2023, 1/2024
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Appendix A. Participation in a Comprehensive Lifestyle Intervention

Chronic Weight Management Medication Inclusion Criterion: Issues for Consideration

All *Inclusion Criteria* for use of the chronic weight management medications includes the following:

- Verifiable participation in a comprehensive lifestyle intervention that targets all three aspects of weight management (diet, physical activity, behavioral changes)

Comprehensive Lifestyle Intervention

Participation in a comprehensive lifestyle intervention is an essential component to overall weight management. Use of weight management medications should be prescribed in conjunction with comprehensive lifestyle intervention.

- Clinically supported (i.e., includes repeated group or individual contact with a coach or clinical staff) comprehensive lifestyle intervention that targets all three aspects of weight management including behavioral, dietary, and physical activity*: e.g., VA MOVE! Weight Management Program, Weight Watchers, TOPS club, HMR Program, Optifast, Curves Complete, etc.
  - *Note that a comprehensive lifestyle intervention should be able to adapt the physical activity component to address any limitations due to a chronic condition or disability.[31]
- Clinically supported web-based or mobile application weight loss programs are acceptable. There must be some form of clinical contact, for example face-to-face or telephone encounters, secure messaging with a clinician or clinically supervised coach, or home telehealth interaction with a clinician.
- Weight management treatment programs that target only one or two aspects of weight management (e.g., Nutrisystem, Curves Fitness, etc.) do not fulfill the requirements for the weight management medication criteria for use for an initial prescription.

Participation in a VA or non-VA Comprehensive Lifestyle Intervention

- As per the VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity, although there is insufficient evidence to recommend a specific number of sessions of comprehensive lifestyle intervention, most offer at least 12 intervention sessions in the first 12 months of intervention.
- Veterans who have documentation of comprehensive lifestyle intervention participation within the past year on at least one occasion (as part of a course of intervention) are eligible for consideration of a weight management medication according to the criteria for use. The intent is to allow for use in patients who may be at the initial period of their weight management program, as well as those who have completed a weight management program within the past year.
- Acceptable **documentation** could include:
    - Clinic notes specifying the provision of weight management counseling or treatment in group or individual formats. Methods of delivery could include face-to-face visits, phone calls, home telehealth, or clinical video telehealth encounters.
    - Evidence that the patient is participating in MOVE! Telephone Lifestyle Coaching (MOVE! TLC) or the VHA Telephone Lifestyle Coaching program with a chosen focus on weight management.
    - Evidence that the patient is participating in a home telehealth version of MOVE! (sometimes called TeleMOVE! and may be delivered through an in-home messaging device or interactive voice response).
    - Evidence that the patient is using the MOVE! Coach mobile application in conjunction with clinical support provided in-person, by phone, or via secure messaging (MOVE! Coach with Care).
    - Notation from the clinician that the patient is participating in a non-VA, clinically-supported (i.e., includes group or individual contact with a coach or clinical staff) weight management program that targets all three aspects of weight management (e.g., Weight Watchers, TOPS Club, HMR Program, Optifast, Curves Complete, etc.).
        - Clinically supported web-based or mobile application weight loss programs are acceptable.
        - Weight management treatment programs that target only one or two aspects of weight management (e.g., Nutrisystem, Curves Fitness, etc.) do not fulfill the requirement for an initial prescription according to the criteria for use.
- Ideally, patients should continue to actively participate in an ongoing comprehensive lifestyle intervention; however, it is understood that ongoing comprehensive lifestyle intervention may need to be tailored to the individual patient.

Appendix B. Medications and Potential for Weight Gain

Considerations of Medications and Effect on Weight[1]

In the overall management of patients with obesity or overweight, it is critical to consider the impact of prescribed medications on the potential for weight gain and whether alternate medications may be a more appropriate option for patients who are overweight, obese, or at risk. Providers should review the patient's current medications for any that may be contributing to increased weight. The side effects of weight gain should be considered when prescribing a medication for a patient where weight gain may be of concern. If an alternate medication is not an option, participation in a weight management program may benefit the patient whose only option is a medication associated with weight gain. The information in the table below is provided as only one aspect of medication selection for a patient with overweight or obesity (or at risk for transition to overweight or obesity). Optimal medication management should consider the potential effect on weight, as well as other patient factors, efficacy, safety, and available long-term outcome data.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BPH = benign prostatic hyperplasia; DMARD = disease-modifying antirheumatic drugs; DPP-4 = Dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1 receptor; HTN = hypertension; IUD = intrauterine device; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; SGLT2 = sodium-glucose transport protein 2; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic anti-depressant; TZD = thiazolidinediones
Note: the information provided in the table is not to be considered all-inclusive and is a compilation of information from the medical literature (systematic reviews, meta-analyses, subgroup analysis of clinical trials, cohort studies, reviews), some of which may have included differing comparators with variable results based on length of follow-up, baseline weight, patient comorbidities, etc.; medical and pharmacy resources; and select product information (adverse events, post-marketing and case reports)
* Weight gain and weight loss have been reported

Appendix Table 1 Selected Medications and Potential Effect on Weight

Medication Classes	Medications with Potential for Weight Gain	Medications that may be Weight Neutral or have Potential for Weight Loss
Antipsychotics	• Clozapine • Olanzapine • Quetiapine • Risperidone • Thioridazine	• Aripiprazole • Haloperidol • Ziprasidone
Antidepressants	• Mirtazapine • MAOIs (e.g., phenelzine) • SSRIs (e.g., paroxetine, sertraline, citalopram*, escitalopram*, fluoxetine*) • TCAs (e.g., amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, protriptyline*)	• Bupropion • Desvenlafaxine • Venlafaxine
Antiepileptic drugs or mood stabilizing agents	• Gabapentin • Pregabalin • Carbamazepine • Divalproex • Valproic acid • Vigabatrin • Lithium	• Lamotrigine • Topiramate • Zonisamide

Antihyperglycemic agents	• Insulin • Meglitinides (e.g., nateglinide, repaglinide) • Sulfonylureas (e.g., chlorpropamide, glimepiride, glipizide, glyburide) • TZDs (e.g., pioglitazone, rosiglitazone)	• Metformin • GLP-1 agonists (e.g., semaglutide, liraglutide, exenatide, dulaglutide, lixisenatide) • SGLT2 inhibitors (e.g., empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) • Alpha-glucosidase inhibitors (e.g., acarbose, miglitol) DPP-4 inhibitors (e.g., alogliptin, linagliptin, saxagliptin, sitagliptin) • Pramlintide
Beta-blockers	• Metoprolol • Atenolol • Propranolol	• Carvedilol • Nebivolol Note: other alternative classes of antihypertensive medications may be an option depending on the indication (e.g., angina, heart failure, HTN, migraine) consider calcium channel blockers, ACEIs, ARBs, and thiazide or loop diuretics, as indicated
Alpha-blockers	• Terazosin	• For BPH (e.g., doxazosin; alfuzosin, tamsulosin)
Glucocorticoids	• Hydrocortisone • Methylprednisolone • Prednisone	Alternatives for rheumatologic disorders: • NSAIDs • Biologics/DMARDs • Nontraditional therapies
Hormonal agents	• Progestins (e.g., medroxyprogesterone or megestrol acetate)	For contraception, consider alternative methods (e.g., copper IUD)
Antihistamines	• Cetirizine • Cyproheptadine	Depending on symptoms, consider ipratropium nasal spray, decongestants, inhalers, nonpharmacologic measures (e.g., nasal irrigation)