Perioperative medication management

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INTRODUCTION

At least 50 percent of patients undergoing surgery take medications on a regular basis [1]. Clinicians often must decide if chronic medications should be continued in the perioperative period. Unfortunately, there are few outcome data about the majority of medications taken in the perioperative period.

This lack of medical evidence is reflected by the large variation in perioperative management recommendations [2]. The recommendations in this review are to a large degree expert opinion, based on information from other reviews [3,4] and textbooks, along with clinical experience and theoretic considerations.

This topic will focus on medications known to have perioperative effects, those known to interact with anesthetic agents, and those in common use. An overview of preoperative patient assessment and details about perioperative management for specific medications are presented separately. (See "Overview of the principles of medical consultation and perioperative medicine" and "Perioperative management of hypertension" and "Perioperative management of patients receiving anticoagulants" and "The management of the surgical patient taking glucocorticoids".)

PRINCIPLES OF MEDICATION MANAGEMENT

The following principles inform the management of chronic medications in the perioperative period:

- A complete medication history should be obtained, and all clinicians involved in patient management (eg, surgeon, anesthesiologist, medical consultants) should review the medication history. Medication use reported by the patient should be verified (medication reconciliation) to address accuracy of drugs and doses [5]. This should include all over-the-counter and herbal/complementary medications, as well as prescription drugs. In addition, substance use information (including alcohol, nicotine, and illicit drugs) should be elicited.
- Medications associated with known medical morbidity if withdrawn abruptly should be continued in the perioperative period or tapered if feasible. Intravenous, transdermal, or transmucosal medicines should be substituted when absorption will be impaired because of loss of gastrointestinal function or restrictions on oral intake. Medications thought to increase the risk of anesthetic or surgical complications and not essential for the short-term should be held through the perioperative period [3]. Other medications can be discontinued or continued based upon clinician judgment.
- The many medications administered perioperatively during a relatively short period increase the potential for drug-drug interactions.
- The metabolism and elimination of medications and their metabolites may be altered during the perioperative period. In particular, gastrointestinal absorption of oral medications may be impaired due to changes in splanchnic blood flow and edema [6].
- The majority of medications can be resumed once the patient is able to tolerate oral intake. The main exceptions to this are medications that impact the bleeding or thromboembolic risk and are discussed in detail in the relevant medication sections below.

CARDIOVASCULAR MEDICATIONS

For elective surgery, preoperative planning and care should be optimized to reduce risk and minimize the need for acute changes in medication management perioperatively (table 1). For example, we suggest control of clinical signs of heart failure (HF) for one week or longer preoperatively if time permits. (See "Perioperative management of heart failure in patients undergoing noncardiac surgery", section on 'Intraoperative hemodynamic monitoring' and "Perioperative management of heart failure in patients undergoing noncardiac surgery", section on 'Preoperative management'.)

Beta blockers

- **Benefit/risk** – Beta blockers have a number of potential beneficial effects when taken perioperatively. Beta blockers reduce ischemia by decreasing myocardial oxygen demand due to increased catecholamine release. They may also help prevent or control arrhythmias. Patients who take beta blockers chronically for management of angina are at risk of ischemia with withdrawal of beta blockade. Acute withdrawal of a beta blocker pre- or postoperatively can lead to substantial morbidity and even mortality [7-9]. Withdrawal issues are of less concern when beta blockers are used for hypertension or migraine prophylaxis.

Whether to initiate beta blockers as prophylaxis for ischemia in the perioperative period in patients at increased risk for coronary disease is complex and discussed separately [10]. (See "Management of cardiac risk for noncardiac surgery", section on 'Beta blockers'.)

Potential adverse effects of perioperative beta blockade include bradycardia and hypotension. Nonselective beta blockers can interact with epinephrine, used for infiltration anesthesia or management of intraoperative anaphylaxis [11]. (See "Management of cardiac risk for noncardiac surgery" and "Major side effects of beta blockers", section on 'Beta blocker withdrawal'.)

- **Continue/discontinue** – In light of the potential benefits of perioperative beta blockade, minimal adverse effects, and consequences of acute withdrawal, we recommend that beta blockers be continued in the perioperative period and continued throughout the hospital stay. The dose of the beta blocker should be closely regulated throughout the perioperative period to maintain the blood pressure and heart rate (rate-pressure product) below the patient's ischemic threshold.

  Since adequate beta blockade can take weeks to achieve safely in patients with systolic heart failure, we prefer initiation of beta blockade in the preoperative period only if acute decompensated heart failure is not present and surgery can be substantially delayed. If surgery is urgent, we prefer postponing beta blockade until a later date. (See "Perioperative management of heart failure in patients undergoing noncardiac surgery", section on 'Beta blockers'.)

- **Formulations/alternatives** – Intravenous forms of beta blockade, such as metoprolol, propranolol, and labetalol, should be given if the patient cannot take oral medications [12,13]. Esmolol is also available to be used intraoperatively or in an intensive care unit (ICU) but cannot be administered on a regular hospital floor. We have a slight preference for beta 1 cardioselective beta blockers, since they are less likely to cause adverse pulmonary and peripheral vascular effects and may be associated with a lower risk of postoperative stroke. Several studies suggest that the risk of perioperative stroke may vary with the specific beta blocker used, and that metoprolol, compared with atenolol, has been associated with a greater risk of perioperative stroke [14-18].

  However, patients who are taking a nonselective beta blocker (eg, propranolol) chronically do not need to be switched to a beta 1 selective agent perioperatively.

Alpha 2 agonists

- **Benefit/risk** – Although earlier smaller randomized trials suggested that centrally acting sympatholytic drugs such as clonidine may improve perioperative outcomes [19-21], the larger POISE-2 randomized trial in 10,010 patients undergoing noncardiac surgery found that preoperative initiation of low-dose clonidine resulted in increased harm (no change in mortality or myocardial infarction but increase in clinically significant hypotension and nonfatal cardiac arrest) [22]. A substudy of the trial also found no benefit of perioperatively administered clonidine in reducing the risk of acute kidney injury [23].

  For patients already taking clonidine, abrupt withdrawal of clonidine can precipitate rebound hypertension [24-26]. This usually occurs after abrupt cessation of fairly large oral doses (eg, greater than 0.8 mg/day) but has also been noted in patients using transdermal clonidine [27]. Withdrawal symptoms have also been reported with methyldopa and guanfacine but are less likely because of their slower onset of action [27]. (See "Withdrawal syndromes with antihypertensive drug therapy".)

- **Continue/discontinue** – Given the possible negative consequences of withdrawal, we recommend that alpha 2 agonist drugs be continued in the perioperative period, but not initiated.

- **Formulations/alternatives** – Transdermal clonidine is available for patients who likely will not be able to resume oral medications by 12 hours after surgery. The decision to substitute this form of therapy must be made before surgery; an equivalent dose of the transdermal preparation should be started three days prior to surgery while the oral clonidine is tapered. The persistent effect of transdermal clonidine for 24 to 48 hours after patch removal should be considered when transitioning back to the oral form.

  Other centrally acting sympatholytic agents (eg, methyldopa or guanabenz) are rarely used today. Withdrawal from abrupt discontinuation has been reported but is less common because of their slower onset of action [28,29]. For patients unable to take oral medications perioperatively, we recommend withholding methyldopa and guanabenz and using other parenteral hypertensive agents if hypertension becomes a problem [24]. An intravenous form of methyldopa is available in the rare cases in which abrupt stoppage appears to be leading to a withdrawal syndrome.

Calcium channel blockers

- **Benefit/risk** – Data are limited regarding the risks and benefits of calcium channel blockers in the perioperative setting. Small trials have shown a more stable intraoperative hemodynamic profile in patients treated with continuous diltiazem, compared with placebo, during coronary bypass surgery [30], but these studies are not large enough to demonstrate improved outcomes. In an observational study, continued use of calcium channel blockers was associated with reduced mortality for patients undergoing cardiac surgery [31]. A meta-analysis found that use of calcium channel blockers was associated with reduced ischemia and atrial arrhythmia in patients undergoing noncardiac surgery [32].

  There are no serious interactions between calcium channel blockers and anesthetic agents [33]. A withdrawal syndrome is not typical of calcium channel blockers, although abrupt discontinuation of these drugs has been reported to cause severe vasospasm in patients undergoing coronary revascularization [34].

Concerns have been raised about a possible association between calcium channel blockers and an increased risk of bleeding [35]. A randomized trial in valvular surgery patients found that, compared with placebo, patients receiving nimodipine had increased bleeding [36,37]. Reports conflict on whether there is a greater incidence of anemia in patients receiving calcium channel blockers after hip surgery [38,39]. Two large trials in cardiac surgery patients did not find any association between bleeding risk and use of calcium channel blockers [40].

- **Continue/discontinue** – Despite little data regarding calcium channel blockers during the perioperative period, these agents appear safe and have theoretic benefit [41]; data regarding bleeding risk are contradictory. Thus, we recommend that calcium channel blockers be continued in patients who are already taking them preoperatively [41].

- **Formulations/alternatives** – Intravenous diltiazem is available for patients who are unable to tolerate oral agents.

  Most oral calcium channel blockers are formulated as extended release and should not be crushed for administration in enteral tubes. Short-acting calcium channel blockers are available (diltiazem, verapamil) and can be substituted with appropriate dosing interval adjustments. Short-acting nifedipine should be avoided, however, because it can cause rapid decreases in blood pressure. Amlodipine has a long washout period, and short-acting substitutes may not be necessary.

ACE inhibitors and angiotensin II receptor blockers

- **Benefit/risk** – The management of patients taking angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) preoperatively is controversial. ACE inhibitors and ARBs can theoretically blunt the compensatory activation of the renin-angiotensin system during surgery and result in prolonged hypotension. Also, the effect of these drugs may be different in noncardiac and cardiac surgery as well as with general and neuraxial anesthesia.

  Data regarding use of ACE inhibitors and ARBs in the perioperative period are inconsistent, with most studies indicating some increased risk for peri- and postoperative hypotensive episodes but variable adverse effect on cardiovascular outcomes or respiratory outcomes when the medications are continued. Representative studies of outcomes involving noncardiac surgery include the following [42-46]:

  - In a randomized controlled trial of 275 patients on ACE inhibitors undergoing noncardiac (mainly orthopedic and spine) surgery, those who omitted their last preoperative ACE inhibitor dose were compared with those who continued the medication uninterrupted [44]. Intraoperative and postoperative hypotension occurred less frequently in the group who omitted the last dose, but postoperative hypertensive events were more frequent (RR 1.95, 95% CI 1.14 to 3.34).

  - In an observational cohort study of almost 15,000 patients (with 4802 taking either ACE inhibitors or ARBs for unspecified indications), withholding the ACE inhibitor/ARB 24 hours before noncardiac surgery was associated with a reduction in composite 30-day all-cause death, stroke, or myocardial injury (adjusted relative risk [ARR] 0.82, 95% CI 0.70-0.96) and intraoperative hypotension (ARR 0.80, 95% CI 0.72-0.93) [46]. Withholding perioperative ACE inhibitor/ARB was not associated with risk of myocardial infarction or postoperative hypotension.

  - In an observational study of over 12,000 patients on chronic diuretic therapy undergoing noncardiac surgery, ACE inhibitor/ARB treatment was associated with more frequent episodes of hypotension [42]. However, there were no differences in the rates of postoperative myocardial infarction or renal failure between the two groups.

  - In a propensity match study of 18,000 patients undergoing noncardiac surgery, no association was found between continued use of ACE inhibitors and intraoperative or postoperative upper-airway complications [43]. Furthermore, uninterrupted perioperative ACE inhibitor use was not associated with in-hospital complications or increased 30-day mortality.

  - In a meta-analysis including nine studies and over 6000 patients taking ACE inhibitors or ARBs undergoing noncardiac surgery, withholding these medications preoperatively was associated with significantly less intraoperative hypotension (odds ratio [OR] 0.63; 95% CI 0.47-0.85). There was, however, no difference in mortality (OR 0.97; 95% CI 0.62-1.52) or in the occurrence of major cardiovascular events (OR 1.12; 95% CI 0.82-1.52) [45].

  Additional studies have evaluated the effect of ACE inhibitor therapy in patients undergoing coronary artery bypass graft (CABG) surgery:

  - A trial randomly assigned 40 patients with good left ventricular function who were undergoing CABG surgery to continue or omit ACE inhibitors before surgery [47]. Patients who omitted their ACE inhibitors required less vasopressors during surgery but required more vasodilators to control hypertension in the early postoperative period.

  - A randomized trial of 47 patients on ramipril undergoing CABG on cardiopulmonary bypass (CPB) found that ACE inhibitor therapy predisposed to hypotension upon induction and in the post-CPB period, but prophylactic low-dose vasopressin infusion prevented post-CPB hypotension [48].

  - Nonrandomized studies suggest a possible myocardial protective effect of ACE inhibitors in patients undergoing CABG surgery [49,50].

  - Reports conflict on the effect of ACE inhibitors on the risk of acute kidney injury (AKI) [51-55].

- **Continue/discontinue** – We individualize the decision to continue or discontinue ACE inhibitors based on the indications for the drug, the patient's blood pressure, and the type of surgery and anesthesia planned. For most patients, we usually withhold them on the morning of surgery. However, when the indication is for heart failure or poorly controlled hypertension, we continue them to avoid further exacerbation of these conditions. Many

anesthesiologists may prefer to withhold these medications on the morning of surgery based on concerns about possible hypotension, and in such cases when we favor continuation, we inform the anesthesiologist of our justification.

We recommend resuming these agents as soon as possible postoperatively, as failure to restart ARBs within 48 hours after surgery has been associated with increased 30-day mortality (see "Anesthesia for noncardiac surgery in patients with heart failure", section on 'Medications'). A number of organizations have issued guidelines regarding the perioperative use of ACE inhibitors and ARBs [56-60].

As above, most findings suggest that continuing ACE inhibitors up to the time of surgery increases perioperative hypotension but possibly reduces the incidence of postoperative hypertension.

- **Formulations/alternatives** – Enalapril is available for short-term intermittent intravenous administration, although it is used infrequently.

Diuretics

- **Benefit/risk** – The two major physiologic effects of concern of loop and thiazide-type diuretics are hypokalemia and hypovolemia.

  Hypokalemia can theoretically increase the risk of perioperative arrhythmia, although observational studies of patients with structural heart disease have failed to find such a relationship [61,62]. Additionally, hypokalemia might potentiate the effects of muscle relaxants used during anesthesia, as well as provoke paralytic ileus.

  Systemic vasodilatation induced by anesthetic agents may cause hypotension in patients who are intravascularly depleted from diuretics. However, in a study of elective, noncardiac surgeries in patients chronically treated with furosemide, the administration of furosemide on the day of surgery did not significantly increase the risk for intraoperative hypotension [63].

- **Continue/discontinue** – There is no consensus on whether diuretics should be discontinued prior to elective surgery [2]. Our approach depends upon the reason for diuretic use and on an individual patient's history.

  - We advise patients who are taking diuretics for hypertension to hold the medication on the morning of surgery. Diuretics may theoretically increase the risk of intraoperative hypotension, and although unlikely to occur in patients on chronic therapy, it is reasonable to hold the medication for this reason.

  - For patients receiving diuretic therapy to treat heart failure, diuretic continuation is based upon assessment of volume status, which should be evaluated and optimized preoperatively whenever possible. For patients with well-controlled heart failure and stable volume status, we generally recommend holding the morning dose of diuretic on the day of surgery. For patients with heart failure in whom fluid balance has historically been more difficult to control, we recommend continuing the diuretic without interruption.

    If diuretics are held the morning of surgery and volume overload develops, a quick diuresis can be initiated by intravenous administration perioperatively. (See "Perioperative management of heart failure in patients undergoing noncardiac surgery", section on 'Diuretics' and "Perioperative management of heart failure in patients undergoing noncardiac surgery", section on 'Fluid management'.)

    For patients who require perioperative diuretics, clinicians should pay close attention to potassium replacement.

- **Formulations/alternatives** – Intravenous preparations of loop diuretics are available.

Non-statin hypolipidemic agents

- **Benefit/risk** – Niacin and fibric acid derivatives (gemfibrozil, fenofibrate) cause myopathy and rhabdomyolysis. The risk is higher when these agents are used in combination with statins, and surgery may also increase the risk of myopathy [64-68]. (See "Statin muscle-related adverse events".)

  Lipid-lowering agents that are bile sequestrants (cholestyramine and colestipol) interfere with bowel absorption of multiple medications that may be required perioperatively.

  The benefits or risks of ezetimibe in the perioperative period are unknown.

- **Continue/discontinue** – We recommend temporary discontinuation of niacin, fibric acid derivatives, bile sequestrants, and ezetimibe perioperatively. Discontinuation is likely to be safe since these agents are given for the goal of long-term reduction in vascular morbidity [65].

  The optimal interval to discontinue these agents before surgery is unknown; we recommend they be stopped the day before surgery to allow for drug elimination.

Digoxin

- **Benefit/risk** – Studies on digoxin in the perioperative period are limited. The two indications for digoxin are to prevent hospitalization and readmission in patients with reduced left ventricular function and to control ventricular response in atrial fibrillation. One study found perioperative use of digoxin to be a predictor of postoperative ischemia, but this was probably because it was a marker of underlying cardiac disease [69]. A subgroup analysis of patients undergoing intrathoracic surgery found that digoxin decreased the incidence of postoperative supraventricular arrhythmias [70].

- **Continue/discontinue** – We recommend continuing digoxin perioperatively. Obtaining a drug level preoperatively is not usually required.

- **Formulations/alternatives** – Intravenous digoxin is available if needed.

Statins — Evidence has become convincing that HMG CoA reductase inhibitors (statins) may prevent vascular events in the perioperative period. This is discussed in detail separately. (See "Management of cardiac risk for noncardiac surgery", section on 'Statins'.)

GASTROINTESTINAL AGENTS

Recommendations for perioperative management of these agents are summarized in the table (table 2).

H2 blockers and proton pump inhibitors

- **Benefit/risk** – There are several potential advantages of continuing H2 blockers or proton pump inhibitors perioperatively. The stress of surgery and other conditions (eg, intensive care unit [ICU] stay and mechanical ventilation) can increase the risk of stress-related mucosal damage, which may be minimized by administration of these drugs. (See "Stress ulcers in the intensive care unit: Diagnosis, management, and prevention".)

  In addition, gastric aspiration during anesthesia, though rare, can lead to severe pulmonary injury. Both H2 blockers and proton pump inhibitors decrease gastric volume and raise gastric fluid pH, thereby reducing the risk of chemical pneumonitis from aspiration [71,72]. (See "Aspiration pneumonia in adults", section on 'Chemical pneumonitis'.)

  Although H2 blocker therapy is generally safe, rare central nervous system (CNS) reactions including confusion and delirium are associated with the use of intravenous H2 blockers in critically ill postoperative patients [73]. Patient risk factors for CNS reactions include advanced age, organ dysfunction, and preexisting cognitive impairment. It is uncertain whether any H2 blocker is less likely to cause CNS effects than others. (See "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Adverse effects'.)

  An increased risk of *Clostridioides difficile* infection has been associated with proton pump inhibitor use. (See "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology" and "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Gastric acid suppression'.)

  Neither H2 blockers nor proton pump inhibitors have been shown to interact with common anesthetic agents, although cimetidine can alter the metabolism of several drugs.

- **Continue/discontinue** – Based upon the potential benefits and lack of contraindications, we recommend that patients who are taking either H2 blockers or proton pump inhibitors remain on these medications in the perioperative period.

- **Formulations/alternatives** – Patients who are unable to take oral medications for a prolonged period should be switched to an intravenous form of H2 blocker or proton pump inhibitor (table 2). Intravenous H2 blockers are less costly.

PULMONARY AGENTS

Recommendations for perioperative management of these agents are summarized in the table (table 2).

Inhaled beta agonists and anticholinergics

- **Benefit/risk** – Inhaled medications used to control obstructive pulmonary disease, such as beta agonists (albuterol, salmeterol, formoterol) and anticholinergics (ipratropium, tiotropium), have been found to reduce the incidence of postoperative pulmonary complications in patients with asthma and chronic obstructive pulmonary disease and should be continued perioperatively. (See "Strategies to reduce postoperative pulmonary complications in adults".)

- **Continue/discontinue** – We recommend continuing beta agonists in the perioperative period, including the day of surgery.

- **Formulations/alternatives** – Inhaled beta agonists and anticholinergics are normally administered on the morning of surgery. The drugs can be administered through a nebulizer or in the circuit of the ventilator when use of metered-dose inhalers is not possible.

Theophylline

- **Benefit/risk** – There are no data indicating whether continuation of theophylline in the perioperative period decreases pulmonary complications. Theophylline has the potential to cause serious arrhythmias and neurotoxicity at a level just beyond the therapeutic range, and theophylline metabolism is affected by many common perioperative medications.

- **Continue/discontinue** – We recommend theophylline medications be discontinued the evening before surgery.

- **Formulations/alternatives** – Other medications for treatment of obstructive lung disease can be initiated or adjusted, including inhaled beta agonists, glucocorticoids, and anticholinergic medications. (See "Strategies to reduce postoperative pulmonary complications in adults".)

Glucocorticoids

- **Benefit/risk** – Patients with pulmonary disease who are maintained on glucocorticoids (corticosteroids) are at risk of adrenal insufficiency if steroids are abruptly withdrawn, particularly in the face of increased stress related to surgery. Additionally, glucocorticoids in such patients may be necessary to maintain optimal lung functions. The risk of possible perioperative complications related to glucocorticoids, including wound infections, is low [74].

- **Continue/discontinue** – Both inhaled and systemic glucocorticoids should be continued during the perioperative period. Issues related to preoperative stress dosing are discussed below. (See 'Glucocorticoids' below.)

Leukotriene inhibitors

- **Benefit/risk** – The leukotriene inhibitors zafirlukast and montelukast help maintain asthma control but are not used for acute therapy. (See "Antileukotriene agents in the management of asthma".)

  The elimination half-life of these agents is relatively short, but their effect on asthma symptoms and pulmonary function continues for up to three weeks after cessation of treatment [75].

  There is no evidence of a withdrawal syndrome with abrupt stoppage of these agents. We are aware of no evidence of harmful interactions of these drugs with anesthetics.

- **Continue/discontinue** – We recommend that leukotriene inhibitors be given on the morning of surgery and resumed when the patient is tolerating oral medications.

- **Formulations/alternatives** – No parenteral substitution is available or necessary given the long duration of action for leukotriene inhibitors.

ENDOCRINE AGENTS

(table 3)

Glucocorticoids — The management of patients taking glucocorticoids preoperatively is discussed in detail separately. (See "The management of the surgical patient taking glucocorticoids" and "Preoperative evaluation and perioperative management of patients with rheumatic diseases", section on 'Medication management'.)

Diabetic medications — The management of diabetes mellitus, including management of oral agents and insulin in the perioperative period, is discussed in detail separately. (See "Perioperative management of blood glucose in adults with diabetes mellitus".)

Oral contraceptives

- **Benefit/risk** – Oral contraceptives (OCs) are statistically the most frequent cause of thrombosis in young women due to their widespread use. The risk of thrombosis increases within four months of initiation and decreases to previous levels within three months of stopping treatment. Surgery itself is a risk factor for thrombosis and compounds the risk associated with oral contraceptive use.

  OCs with higher estrogen content (≥35 mcg) have a greater risk of thromboembolism compared with those with lower estrogen content (≤30 mcg). Nevertheless, even the lower estrogen content pills are associated with an increased risk of thrombosis [76,77]. Estrogen/progestin patches also increase thrombosis risk. Risk also varies with type of progestin. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects'.)

- **Continue/discontinue** – In general, we typically recommend continuation of OCs and provision of appropriate perioperative thromboprophylaxis (table 3). In patients at higher risk for VTE who are undergoing high-risk surgery (table 4), discontinuation of OCs may be reasonable to mitigate the additional VTE risk; if the decision is made to discontinue, OCs should be stopped four weeks prior to surgery. Women who discontinue OCs that are used for contraceptive purposes should use an alternative method of birth control, which should be continued for the first week after resuming OCs postoperatively; if they cannot or prefer not to use an alternative method, continuing the OC is appropriate (with appropriate perioperative thromboprophylaxis). Prevention of thromboembolic disease in the surgical patient is discussed elsewhere. (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

  We recommend a serum pregnancy test prior to surgery in all women of childbearing age.

  Manufacturer product package inserts state that estrogen-containing OCs should be stopped four weeks prior to elective major operations and surgery to the legs, and they can be restarted at the first menses occurring at least two weeks after surgery or after full mobilization. However, evidence to support these recommendations is insufficient and these recommendations are inconsistent with typical clinical practice.

Postmenopausal hormone therapy

- **Benefit/risk** – The estrogen content of preparations used for postmenopausal hormone therapy (HT) is much lower than in oral contraceptive pills. However, use of HT, with either estrogen alone or estrogen plus a progestin, still appears to increase the risk of venous thromboembolism (VTE) [78,79]. Although a case-control study did not find an increased risk of thromboembolism in women undergoing arthroplasty who received HT (odds ratio [OR] 0.66, 95% CI 0.35-1.18), the results may have been confounded by women at lower risk for thromboembolism being more likely to be prescribed HT [80].

  The risks associated with temporary discontinuation of hormone therapy are mainly discomfort from hot flashes and other menopausal symptoms.

- **Continue/discontinue** – We usually individualize the decision to continue HT perioperatively based on the VTE risk of the procedure and the woman's preference, but overall we feel the risk of continuing HT is relatively low (table 3). Ideally, women undergoing procedures associated with

moderate to high risk for VTE should stop hormone therapy at least two weeks prior to elective surgery and resume treatment postoperatively once the period of elevated risk for VTE has resolved. HT can be continued uninterrupted for surgical procedures associated with a low risk of VTE . Definitions of low-, moderate-, and high-risk procedures, and appropriate VTE prophylaxis, are discussed elsewhere (table 4). (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

Manufacturers recommend that estrogens should be discontinued at least four to six weeks prior to a surgical procedure with increased risk of VTE or during periods of prolonged immobilization, but evidence to support this recommendation is insufficient, particularly for HT, as above.

Selective estrogen receptor modulators

- **Benefit/risk** – The indications for use of selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene include breast cancer treatment, breast cancer chemoprevention, and, at least for raloxifene, the prevention and treatment of osteoporosis (see "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention" and "Selective estrogen receptor modulators for prevention and treatment of osteoporosis"). Both tamoxifen and raloxifene increase the risk of VTE [81,82].

  Brief discontinuation of SERMs used for the prevention/treatment of osteoporosis or the prevention of breast cancer is unlikely to result in harm. For patients with breast cancer who are being treated with SERMs, the risk of disease progression with preoperative cessation of treatment is a consideration.

- **Continue/discontinue** – SERMs can be continued without interruption for low- and moderate-risk surgeries while providing appropriate VTE prophylaxis (table 3). Definitions of low-, moderate-, and high-risk procedures, and appropriate VTE prophylaxis, are discussed elsewhere (table 4). (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

  For surgeries with a high-risk of VTE, our approach depends upon the specific SERM and the indication for its use:

  - For patients taking raloxifene for osteoporosis treatment/prevention or breast cancer prevention, we suggest discontinuing the medication three days prior to a surgical procedure associated with a high risk of VTE. The raloxifene can be resumed as soon as the period of elevated VTE risk is resolved. However, if the patient has taken the medication within three days of the procedure, we do **not** recommend postponing the surgery for this reason; the procedure can be done as planned and appropriate VTE prophylaxis provided. (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

  - For patients taking tamoxifen for breast cancer prevention (ie, in women without a history of breast cancer), we suggest discontinuing the medication two weeks prior to a surgical procedure associated with a high risk of VTE. The tamoxifen can be resumed as soon as the period of elevated VTE risk has resolved. However, if the patient has taken the medication within two weeks of the procedure, we do **not** recommend postponing the surgery for this reason; the procedure can be done as planned and appropriate VTE prophylaxis provided. (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

  - For patients taking a SERM (eg, tamoxifen) for breast cancer treatment, the decision to discontinue is more difficult, and consultation with an oncologist is recommended. We typically recommend continuing SERMs in this setting while providing appropriate VTE prophylaxis. (See "Prevention of venous thromboembolic disease in adult nonorthopedic surgical patients".)

  The package insert for tamoxifen states that in the case of surgery and immobility, the medication should only be stopped if the risk of tamoxifen-induced thrombosis clearly outweighs the risks associated with interrupting treatment. If continued, all patients should receive appropriate thrombosis prophylactic measures. The manufacturers of raloxifene, however, recommend stopping it at least three days before surgery.

Drugs used for thyroid disease — The management of medications to control hypothyroid and hyperthyroid states is discussed in detail separately. (See "Nonthyroid surgery in the patient with thyroid disease".)

- **Continue/discontinue** – We recommend perioperative continuation of therapy for both hyperthyroidism and hypothyroidism.

  In the case that a patient cannot take oral medications for several days, the approach depends upon the thyroid medication:

  - Thyroxine (T4) has a long half-life, and patients on chronic T4 therapy who are unable to take oral medication for several days do not need parenteral T4. If oral T4 cannot be resumed within five to seven days, it should then be administered parenterally (intravenously or intramuscularly).

  - The antithyroid thionamide medications (methimazole and propylthiouracil) have a very short half-life. The decision on how long to hold antithyroid medications for a patient who is unable to take oral medications must be individualized based upon several factors, including the patient's history of thyroid disease and length of previous treatment with antithyroid medications. (See "Nonthyroid surgery in the patient with thyroid disease", section on 'Preexisting hyperthyroidism'.)

- **Formulations/alternatives** – T4 can be given intravenously or intramuscularly. When administered parenterally, the dose of T4 should be reduced to approximately 80 percent of the patient's usual oral dose to reflect the fraction of oral T4 that is absorbed.

  There are rectal (suppository and retention enema) options for administration of either of the antithyroid medications (table 5).

Drugs used for osteoporosis/osteopenia

- **Benefit/risk** – Bisphosphonate use, especially in malignancy, has been associated with osteonecrosis of the jaw in patients undergoing dental surgery. The absolute risk is very low, but osteonecrosis is difficult to manage. The duration of effect of bisphosphonates on bone remodeling is long, and the discontinuation of these agents for weeks or even months before surgery has not been shown to decrease the risk of osteonecrosis. Likewise, there is no evidence that short-term discontinuation of these agents results in reduction in treatment efficacy for prevention of osteoporotic bone fractures.

- **Continue/discontinue** – We recommend withholding bisphosphonates only on the morning of surgery, as they are typically taken with at least 8 ounces of water and the patient is supposed to remain upright for at least 30 minutes and until after eating a meal.

  For patients undergoing dental surgery, we advise that bisphosphonates not be held in advance of the procedure nor dental surgery delayed since the absolute risk of jaw osteonecrosis is low and the benefit of holding the medication in advance is not clear. For patients believed to be at very high risk due to need for extensive bony surgery, concomitant glucocorticoid or chemotherapy, or long-term bisphosphonate use, a delay of surgery for two months is reasonable but these cases are uncommon. (See "Risks of bisphosphonate therapy in patients with osteoporosis", section on 'Osteonecrosis of the jaw'.)

  Guidelines from the American Association of Oral and Maxillofacial Surgeons recommend proceeding as usual with dental surgery in patients who have been treated with oral bisphosphonates for less than four years and have no clinical risk factors [83]. They suggest discontinuing bisphosphonates for two months prior to performing the dental surgery if a patient has been treated for more than four years or has taken concomitant glucocorticoids. Bisphosphonates are restarted when the bone has healed.

MEDICATIONS AFFECTING HEMOSTASIS

Many patients undergoing surgery are taking medications that are intended to impair normal hemostasis or appropriate thrombosis (eg, warfarin, aspirin, or other antiplatelet agents), or take medications for another indication that have an unintended effect on hemostasis, such as nonsteroidal antiinflammatory drugs (NSAIDs) (table 6).

Aspirin

- **Benefit/risk** – Aspirin irreversibly inhibits platelet cyclooxygenase, which may increase intraoperative blood loss and hemorrhagic complications [84-89]. However, the same effect can help to prevent perioperative vascular complications, in particular cardiac and thromboembolic complications. The perioperative benefits and risks of aspirin depend on the patient's indication for aspirin and the planned surgery.

  For example, observational studies suggest that withdrawal of aspirin preoperatively is associated with increased in-hospital mortality in patients undergoing coronary artery bypass graft surgery (CABG) [90,91]. However, in patients undergoing noncardiac surgery, the large randomized POISE-2 trial found that perioperative aspirin increases bleeding risk but does not improve cardiovascular or mortality outcomes [92]. A substudy of the trial also found no benefit for perioperative aspirin administration at reducing the risk of acute kidney injury [23] and no benefit for prevention of venous thromboembolism (VTE), although two-thirds of the patients also received anticoagulants and there were few VTE events overall [93]. (See "Medical therapy to prevent complications after coronary artery bypass graft surgery", section on 'Aspirin' and "Management of cardiac risk for noncardiac surgery", section on 'Antiplatelet therapy'.)

- **Continue/discontinue** – Recommendations to continue or discontinue aspirin vary depending on what surgery is planned and the patient's indication for aspirin. As examples:

  - Patients undergoing CABG (see "Medical therapy to prevent complications after coronary artery bypass graft surgery", section on 'Aspirin')
  - Patients undergoing vascular surgery (see "Carotid endarterectomy", section on 'Antiplatelet therapy' and "Surgical and endovascular repair of popliteal artery aneurysm", section on 'Antiplatelet therapy')
  - Patients who have undergone percutaneous coronary interventions and are on aspirin as part of dual antiplatelet therapy (see "Noncardiac surgery after percutaneous coronary intervention", section on 'Our approach')
  - Patients who have recently had an acute coronary syndrome (see "Management of cardiac risk for noncardiac surgery", section on 'Patients with a recent acute coronary syndrome')
  - Patients with cardiac risk who are undergoing non-cardiovascular surgery (not including cataract surgery) (see "Management of cardiac risk for noncardiac surgery", section on 'Antiplatelet therapy')
  - Patients undergoing cataract surgery (see "Cataract in adults", section on 'Aspirin and other antiplatelet agents')

  Aspirin can be safely continued in most patients undergoing minor dental surgery or dermatologic procedures. For other patients taking aspirin for secondary prevention, the risks and benefits of perioperative aspirin should be discussed with the patient, surgeon, cardiologist, or neurologist.

  Guidelines from the American Society of Regional Anesthesia (ASRA) indicate that NSAIDs, including aspirin, do not create a level of risk that will interfere with the performance of neuraxial blocks, and should not impact catheter techniques, timing of neuraxial catheter removal, or postoperative monitoring [94].

- **Formulations/alternatives** – Aspirin is not available in parenteral forms but is available as a rectal suppository for patients who are felt to need ongoing therapy but cannot take oral medication.

Other antiplatelet agents

- **Benefit/risk** – The platelet $P2Y_{12}$ receptor blockers clopidogrel, prasugrel, ticagrelor, and ticlopidine are used in patients who have had previous cerebrovascular events, recent acute coronary syndromes, or recent percutaneous coronary or vascular interventions with stenting. Issues related to continuation or discontinuation, as well as postoperative reinstitution of clopidogrel and other $P2Y_{12}$ receptor blockers, are discussed separately. (See "Noncardiac surgery after percutaneous coronary intervention", section on 'Our approach'.)

  Dipyridamole has both vasodilator and antiplatelet activity. With the publication of the ESPS-2 trial [95], its use has become more common in patients with past stroke or transient ischemic attack (TIA). The half-life of the modified-release preparation is approximately 10 hours. (See "Antiplatelet therapy for secondary prevention of stroke" and "Secondary prevention for specific causes of ischemic stroke and transient ischemic attack".)

  Cilostazol is a selective phosphodiesterase-3 enzyme inhibitor with weaker reversible antiplatelet activity than the $P2Y_{12}$ receptor blockers and is used primarily for treatment of claudication symptoms. Its half-life is approximately 21 hours. (See "Management of claudication due to peripheral artery disease".)

- **Continue/discontinue** – Many patients take both aspirin and platelet $P2Y_{12}$ receptor blocker therapy to prevent coronary stent thrombosis. Premature cessation of dual antiplatelet therapy is associated with an increased risk for stent thrombosis. Management of such patients is discussed elsewhere. (See "Noncardiac surgery after percutaneous coronary intervention".)

  There are no data on the safety of dipyridamole if continued in the perioperative period. Like aspirin, factors to consider in deciding whether to continue or hold dipyridamole reflect a balance between the risk of bleeding and risk of ischemic events. If discontinued, the drug should be stopped at least two days before surgery. Aggrenox (combination aspirin and dipyridamole) should be discontinued 7 to 10 days before surgery.

  Cilostazol should be discontinued for at least two to three days prior to elective surgery, but the manufacturer recommends stopping it at least five days before. Claudication symptoms may recur when the medication is stopped, but should respond once cilostazol is reinitiated postoperatively.

Nonsteroidal antiinflammatory drugs

- **Benefit/risk** – The antiplatelet effects of NSAIDs are due to reversible inhibition of cyclooxygenase (COX)-1, an isoform of cyclooxygenase, leading to decreased production of thromboxane A2 (TxA2). TxA2 is released by platelets in response to a number of agonists, leading to platelet aggregation (see "Nonselective NSAIDs: Overview of adverse effects", section on 'Antiplatelet effects'). These antiplatelet effects increase the bleeding risk perioperatively but, like aspirin, may reduce the risk of perioperative vascular events [96].

  The selective COX-2 inhibitors, such as celecoxib, have minimal effects on platelet function [97], although the potential for renal toxicity remains [98]. Most selective COX-2 inhibitors and nonselective NSAIDs appear to have deleterious cardiovascular effects. (See "Overview of COX-2 selective NSAIDs" and "NSAIDs: Adverse cardiovascular effects".)

  Non-acetylated nonsteroidals, such as salsalate, do not have an antiplatelet effect.

- **Continue/discontinue** – On balance, we recommend discontinuing NSAIDs, including selective COX-2 inhibitors, prior to surgery. For certain patients, however, pain control may not permit extensive periods of time without these medications, and consultation with the surgeon regarding risk of procedural bleeding should be weighed against pain control. For patients whose pain is dramatically responsive to COX-2 inhibitors, consideration may be given to continuing these agents since they have minimal effects on platelet function.

  Although some experts recommend discontinuing NSAIDs based upon drug-specific elimination half-lives [99], the elimination half-life correlates poorly with cyclooxygenase inhibition and effects on platelet aggregation [100,101]. In healthy individuals receiving ibuprofen for one week, platelet function appears to return to normal within 24 hours after the last dose [102]. However, the relationship between time of discontinuation of NSAIDs with intra- and postoperative clinical bleeding is not well-defined. For most NSAIDs, platelet function normalizes within three days of discontinuation [103], suggesting that NSAIDs should generally be discontinued at least three days before surgery; ibuprofen can be stopped 24 hours prior to surgery.

  Nonacetylated NSAIDs (eg, diflunisal, choline magnesium trisalicylate, salsalate) can be continued in the perioperative period and may be considered as alternatives to other NSAIDs for pain control. The nonacetylated NSAIDs have a slow onset of effect which may limit their usefulness in the perioperative period.

- **Formulations/alternatives** – Intravenous preparations of ketorolac and ibuprofen are available for short-term treatment of moderate acute pain and febrile conditions when oral administration is not available and as an adjunct to other analgesics for the treatment of moderate to severe postoperative pain. Patients should be well-hydrated and without significant renal impairment.

  Intravenous acetaminophen (paracetamol) is also available and is a useful alternative for patients at risk for NSAID-associated gastropathy or renal impairment. Selection and use of the non-opiate analgesics is discussed separately. (See "Sedative-analgesic medications in critically ill adults: Selection, initiation, maintenance, and withdrawal".)

Anticoagulants — The perioperative management of patients taking warfarin and other oral anticoagulants is discussed separately. (See "Perioperative management of patients receiving anticoagulants".)

MEDICATIONS AFFECTING RENAL FUNCTION

Several medications and agents used during the perioperative period may lead to acute kidney injury, including nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, antibiotics (eg, aminoglycosides, vancomycin), and intravenous contrast agents [104]. The benefits and risks vary based on each drug. (See "Major side effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers", section on 'Reduction in GFR' and "Epidemiology and pathogenesis of analgesic-related chronic kidney disease", section on 'Nonsteroidal antiinflammatory drugs' and "Aminoglycosides", section on 'Nephrotoxicity' and "Beta-lactam antibiotics: Mechanisms of action and resistance and adverse effects", section on 'Renal reactions' and "Prevention of contrast nephropathy associated with angiography" and "Loop diuretics: Dosing and major side effects", section on 'Diuresis related'.)

Optimizing volume status and medications to prevent acute tubular necrosis are discussed elsewhere. (See "Possible prevention and therapy of ischemic acute tubular necrosis", section on 'Prevention'.)

PSYCHOTROPIC AGENTS

The perioperative management of patients taking psychotropic agents varies with the class of drugs used (table 7) and severity of mental illness. Evidence-based guidelines for these drugs are lacking; data are primarily derived from case reports and open trials [105]. Perioperative decisions about use of these drugs must balance their potential for side effects and interaction with anesthetic agents with psychiatric and physiologic consequences of withdrawal of these agents. In general, psychotropic medications for treatment of patients with serious or unstable mental illness should be continued throughout the perioperative period to avoid psychiatric decompensation. However, the optimal choice of anesthesia and analgesia in combination with many psychotropic agents is unknown. Other than antipsychotics, many psychotropic agents do not have a parenteral delivery mode. Appropriate pharmacologic management includes consideration of parenteral alternatives of the same or different class to maintain mood and behavior stability.

Tricyclic and tetracyclic antidepressants

- **Benefit/risk** – Cyclic antidepressants inhibit the uptake of norepinephrine and serotonin at the synaptic cleft. Unlike most newer antidepressants, cyclic antidepressants lower the seizure threshold and possess significant anticholinergic, antihistaminic, and alpha-1 blocking properties. These agents delay gastric emptying, prolong the QTc interval, and may increase the risk for arrhythmias in combination with some volatile anesthetics or sympathomimetic agents, although literature to support this concern is scant. Abrupt withdrawal of tricyclic antidepressants can lead to insomnia, nausea, headache, increased salivation, and sweating and should be avoided if feasible [106]. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

  Cyclic antidepressants can amplify the systemic pressor effects of norepinephrine and epinephrine; however, use with epinephrine-containing local anesthesia is generally safe. Use with atropine or scopolamine may increase postoperative confusion. Due to additive serotoninergic effects, use with tramadol and meperidine is not recommended. (See "Serotonin syndrome (serotonin toxicity)".)

- **Continue/discontinue** – Most textbooks and journals recommend continuing these agents in the perioperative period [2]. However, the US Food and Drug Administration (FDA) and some experts advise that tricyclic antidepressants (imipramine, amitriptyline, nortriptyline, desipramine, and clomipramine) be discontinued prior to elective surgery, when possible, and this information is provided in package labelling for these medications [105]. The stability of the patient's depression should be considered prior to tapering or discontinuing the medication to avoid worsening of depression. If depression is moderate or severe, best practice would be to continue the antidepressant and notify the anesthesia team to monitor for cardiac arrhythmias in the perioperative period. If depression is mild, the antidepressant is not felt to be essential for short-term quality of life, and if arrhythmias are of concern, the agent should be tapered to minimize the chance of withdrawal.

  We generally recommend continuation of cyclic agents throughout the perioperative period, in particular for patients on high doses without cardiac disease. For patients on low doses or in whom the risk of perioperative arrhythmia is increased, the agents should be tapered off over a period of 7 to 14 days before surgery. The elimination half-life of various cyclic antidepressants ranges from one to three days or more. For detail, refer to the Lexicomp drug monographs included with UpToDate.

- **Formulations/alternatives** – Parenteral amitriptyline and clomipramine preparations are available in many countries, but not in the United States. In consultation with the patient's psychiatrist, consider substitution of another class of agent, such as a selective serotonin reuptake inhibitor, if it is felt that the tricyclic antidepressant is truly contraindicated.

Selective serotonin reuptake inhibitors

- **Benefit/risk** – Selective serotonin reuptake inhibitors (SSRIs) may increase bleeding risk and the consequent need for transfusion with surgery, perhaps because of their effects on platelet aggregation. Bleeding risk with SSRIs has been documented primarily in association with antiplatelet or nonsteroidal antiinflammatory drug (NSAID) use [107-109]. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Bleeding'.)

Results from several studies differ regarding risk and type of surgery. In the largest multicenter study (375 hospitals, more than 530,000 patients), after adjusting for multiple morbidities, patients who received SSRIs had a small increase in risk of perioperative bleeding (odds ratio [OR] 1.09, 95% CI 1.04-1.15) [110]. A prospective cohort study involving 767 patients undergoing cardiac, vascular, spinal, and intracranial surgery at two academic medical centers found that preoperative use of SSRIs was associated with a twofold increase (OR = 2.2; 95% CI 1.2-3.98) in exposure to allogeneic hemostatic blood products in surgical patients at high risk for perioperative bleeding [111].

Smaller studies suggest that the risk in orthopedic surgery is likely to be clinically insignificant, if present. One retrospective study in total hip arthroplasty patients noted a statistically significant 95 mL higher mean blood loss in patients on SSRIs compared with non-serotonergic antidepressants and controls; however, the authors felt this was of limited clinical significance [112]. An association between bleeding risk and SSRI continuation in patients undergoing orthopedic surgeries was not found in other studies that controlled for confounding variables (eg, use of NSAIDs) [113].

Several studies noted no increased risk of bleeding with coronary artery bypass procedures and with plastic surgery [114-117]. A large metaanalysis found SSRIs to be associated with an increased risk of transfusion but not an increase in mortality [118].

Stopping SSRIs could lead to exacerbation of mood and other disorders. The washout period for SSRIs may be as long as three weeks, and reinitiation may not lead to clinical benefit for several weeks. Half-life varies widely from 15 hours (ie, paroxetine, fluvoxamine, sertraline) up to seven days (fluoxetine). Abrupt withdrawal of short-acting SSRIs should be avoided, as it can cause a discontinuation syndrome including dizziness, chills, muscle aches, and anxiety (see "Discontinuing antidepressant medications in adults"). Determining whether perioperative continuation or withdrawal of SSRIs produces a net clinical benefit requires randomized controlled trials.

- **Continue/discontinue** – For most patients, we recommend continuing SSRI therapy through the perioperative period. The decision to withhold SSRIs perioperatively should balance the consequences of bleeding with the severity of the underlying psychiatric disorder.

  For patients undergoing surgical procedures with substantial risks of postoperative bleeding that could lead to significant morbidity (such as central nervous system procedures), or in patients requiring ongoing antiplatelet therapy for secondary prevention (eg, aspirin and thienopyridine for a drug-eluting cardiac stent), consider discontinuing SSRIs by tapering several weeks prior to surgery and starting an alternative antidepressant regimen, in consultation with a psychiatrist if possible. Patients with severe mood disorders and those undergoing surgery with low to moderate risks of abnormal bleeding should generally be maintained on SSRIs through surgery.

  Antiplatelet agents should be discontinued preoperatively if at all possible in patients taking SSRIs. If aspirin or thienopyridine therapy is required for secondary prevention through surgery (eg, presence of a drug-eluting cardiac stent), then the SSRI should be discontinued in advance of surgery and an alternative antidepressant regimen considered, in consultation with a psychiatrist if possible.

Selective norepinephrine reuptake inhibitors and bupropion

- **Benefit/risk** – There are limited data regarding selective norepinephrine reuptake inhibitor (SNRI) agents in the perioperative period. A retrospective study of 4136 patients undergoing coronary artery bypass graft (CABG) surgery showed that SNRI use was associated with an increased risk of renal dysfunction and prolonged ventilation but not bleeding events or long-term mortality [115]. This has not been replicated in other studies.

  No literature exists regarding perioperative considerations with bupropion.

- **Continue/discontinue** – Considerations regarding cessation versus continuation in the perioperative period should be similar as with SSRIs. (See 'Selective serotonin reuptake inhibitors' above.)

Monoamine oxidase inhibitors

- **Benefit/risk** – Nonselective irreversible monoamine oxidase (MAO) inhibitors for use as antidepressants (isocarboxazid, pargyline, phenelzine, and tranylcypromine) are prescribed far less commonly than other antidepressants but are used in patients with refractory mood disorders in whom withdrawal and recurrent depression may be problematic. MAO inhibitors are also used for treatment of conditions other than depression (table 8).

  Use of nonselective MAO inhibitors results in the accumulation of biogenic amines in central and autonomic system neurons. Concomitant administration of sympathomimetic agents, like ephedrine during anesthesia, can result in massive release of stored norepinephrine and severe hypertensive crisis. In addition, two types of central nervous system (CNS) reactions may occur relevant to surgery and anesthesia. The "Type I" reaction occurs with the administration of anticholinergics (such as dextromethorphan) and meperidine with MAO inhibitors, leading to a serotonin syndrome (agitation, headache, fever, and seizures, with possibility of coma and death) [105] (see "Serotonin syndrome (serotonin toxicity)"). The "Type II" reaction occurs when the MAO inhibitor inhibits hepatic microsomal enzymes involved in opiate metabolism, subsequently leading to accumulation of free narcotic, sedation, respiratory depression, and cardiovascular collapse [119]. As the use of morphine and fentanyl are recommended to avoid a Type I reaction, patients continuing MAO inhibitors requiring these opiates should be monitored closely for CNS depressive effects. Phenelzine may prolong the effect of succinylcholine. Use with epinephrine-containing local anesthetics is generally safe.

  A designated MAO-safe anesthetic technique has been reported for use in patients unable to discontinue the MAO inhibitor, such as in emergency procedures [120]. This involves avoidance of meperidine and dextromethorphan and cautious use of only direct acting intravenous sympathomimetic agents such as norepinephrine, epinephrine, phenylephrine, and isoproterenol.

- **Continue/discontinue** – The decision to continue or withhold nonselective MAO inhibitors before surgery requires close collaboration with the anesthesiologist and psychiatrist.

  MAO inhibitors generally should be continued when two criteria are met: (1) the anesthesiologist is comfortable with use of MAO-safe procedures; and (2) the psychiatrist believes temporary withdrawal of the agent will exacerbate or precipitate a depressive syndrome.

  In the absence of either criteria, we recommend discontinuing MAO inhibitors before surgery. Many MAO inhibitors are irreversible antagonists, and recovery of MAO function requires two weeks after discontinuation of the drug. Thus, patients should taper and discontinue MAO inhibitors two weeks before elective surgery. An alternative drug regimen for depression, such as tricyclic antidepressant or SSRI therapy, may be used for the perioperative period.

  If MAO inhibitors are continued perioperatively, the patient must be prescribed a diet that excludes foods containing high amounts of tyramine while an inpatient to avoid precipitating a hypertensive crisis (table 9). Intraoperative and perioperative drug interactions must be closely monitored. Specific interactions of MAO inhibitors with other medications may be determined using the Lexicomp drug interactions tool included in UpToDate.

Mood stabilizing agents (lithium and valproate)

- **Benefit/risk** – Lithium has a number of physiologic effects that may be important perioperatively. Lithium decreases release of neurotransmitters and may prolong the effect of neuromuscular blockers. Lithium has a narrow therapeutic index, is highly dependent upon maintained renal function for clearance, and is subject to drug interactions with diuretics, NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, and serotoninergic drugs (eg, meperidine, methylene blue, tramadol). Chronic lithium use has a multitude of effects on the thyroid. (See "Lithium and the thyroid" and "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of side effects", section on 'Managing lithium side effects'.)

  In addition, nephrogenic diabetes insipidus has been described in up to 20 percent of patients taking lithium. Patients who have impaired renal concentrating ability maintain euvolemia and a normal serum sodium through polydipsia. Access to free water may be impaired during the perioperative period and lead to volume depletion and hypernatremia. (See "Renal toxicity of lithium".)

  Valproate (valproic acid) is another mood stabilizer used in patients with bipolar disorder. Valproate drug interactions include NSAIDs and some antibiotics. There are no reports demonstrating problems in patients continuing valproic acid perioperatively.

- **Continue/discontinue** – Lithium and valproate are used for treatment of serious mental illness. We therefore recommend continuation of lithium perioperatively with increased attention to fluid and electrolyte monitoring and a low threshold to check thyroid function tests before surgery.

  We recommend that valproic acid be continued.

  Serum levels of lithium and valproate should be monitored regularly. Serum lithium levels are affected by medications that affect sodium and fluid balance. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of side effects", section on 'Laboratory tests and monitoring' and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Valproate or divalproex'.)

- **Formulations/alternatives** – Lithium must be temporarily discontinued in patients who cannot take oral medications since no parenteral substitution is available. Restarting enteral lithium (with close monitoring of electrolytes) within 24 hours postoperatively should avoid the need for alternative pharmacologic coverage.

  Valproate sodium is available as a parenteral form. Valproate or second-generation antipsychotics (eg, risperidone, aripiprazole, olanzapine, or ziprasidone) may be used in lieu of lithium for patients who cannot take oral medications. (See "Bipolar disorder in adults: Choosing maintenance treatment".)

Antipsychotics

- **Benefit/risk** – Antipsychotics are effective in controlling psychoses that may become problematic in the perioperative period in patients with underlying psychiatric illness. However, findings from a large observational study indicate that use of antipsychotics, both typical and atypical, is associated with an increased risk for sudden death [121]. Both typical and atypical antipsychotics may prolong the QT interval and cause arrhythmia, particularly when coadministered with volatile anesthetic agents or drugs such as erythromycin, quinolones, amiodarone, and sotalol. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Acquired long QT syndrome: Definitions, causes, and pathophysiology".)

  In a randomized trial of 495 patients at risk for delirium undergoing joint replacement surgery, olanzapine versus placebo was administered to prevent delirium [122]. The incidence of delirium decreased from 40 to 1 percent, although those who experienced delirium in the olanzapine group had more severe and longer-lasting delirium. Resource use during hospitalization (sitters, consultations) did not decrease. More patients in the olanzapine arm were discharged to home versus rehabilitation facilities. A randomized controlled trial in intensive care unit (ICU) patients in China showed that the administration of prophylactic haloperidol for seven days after noncardiac surgery significantly decreased the incidence of postoperative delirium, while the mean time to onset of delirium and the mean number of delirium-free days was significantly longer [123]. ICU stay was significantly shorter. No difference in mortality or drug-related side effects was noted. Further studies are needed prior to widespread use of perioperative antipsychotics for delirium prevention.

- **Continue/discontinue** – Antipsychotics should be used cautiously in patients at risk for exacerbation of psychoses. These agents should be withheld in patients whose baseline or follow-up electrocardiogram (ECG) demonstrates prolongation of the QT interval. Shorter-acting and low-dose

antipsychotics should be considered, and complete discontinuation may be preferable after consultation with a psychiatrist. The half-life of antipsychotics varies widely. Rarely, withdrawal symptoms (eg, nausea, vomiting, insomnia) or rebound psychoses can occur following abrupt discontinuation.

Antipsychotics may potentiate sedative and hypotensive effects of anesthetics and opiate analgesics. They variably cause extrapyramidal side effects and, rarely, neuroleptic malignant syndrome (see "Neuroleptic malignant syndrome") Several antipsychotics undergo or inhibit CYP2D6 and/or CYP3A4 drug metabolism and thereby can interact with other drugs used perioperatively (eg, antibiotics, midazolam, ketamine). Parenteral administration of antipsychotics seems to increase the perioperative risk of additive sedation, hypotension, or QTc prolongation with other drugs.

- **Formulations/alternatives** – Many typical antipsychotics are available in short-acting intramuscular form, with the high-potency agents more likely to cause extrapyramidal effects and low-potency agents more likely to cause hypotension and sedation. Both haloperidol decanoate and fluphenazine decanoate are long-acting depot preparations that are given monthly and every two weeks, respectively. Haloperidol, although not approved by the US Food and Drug Administration (FDA) for intravenous use, is the most common intravenous antipsychotic used in the hospital setting. It has minimal hemodynamic or extrapyramidal side effects [124] and progressive dosing guidelines have been published for the agitated patient [125,126].

  Several parenteral formulations of atypical antipsychotics are available, including short-acting forms of intramuscular olanzapine and ziprasidone, and a long-acting risperidone preparation used as a maintenance treatment. Olanzapine and risperidone have an oral dissolvable tablet formulation that can be used for the patient in need of an antipsychotic who cannot take oral medication (table 10) [127].

Antianxiety agents

- **Benefit/risk** – Abrupt withdrawal of chronic benzodiazepines can lead to an excitatory state with hypertension, agitation, delirium, and seizures. Many of these agents have active metabolites, and withdrawal can occur several days to weeks after discontinuation. Withdrawal symptoms can occur in less than 24 hours following abrupt discontinuation of chronic alprazolam use. Conversion to an extended release preparation of alprazolam prior to surgery may be useful for delaying the need for postoperative re-dosing.

  In one center, anxiolytic medication use on admission (present in 16 percent of 1846 patients) was associated with a greater risk of postoperative complications after noncardiac surgery (OR = 1.72, 95% CI: 1.08-2.73) [128]. However, it is uncertain as to whether the risk was attributable to medication or to the presence of anxiety.

  Benzodiazepines are commonly used short-term to relieve preoperative anxiety and are generally safe, with proper monitoring, in the perioperative period. Additive sedation or increased tolerance to perioperative anesthetic and sedative agents may be observed.

  Buspirone is felt to be safe in the perioperative period; it has been reported to reduce the shivering threshold intraoperatively in conjunction with dexmedetomidine with minimal sedation and no respiratory depression [129]. It has a slow onset of effect (ie, weeks) and does not prevent withdrawal reactions due to discontinuation of benzodiazepines. Due to its serotoninergic effect, its use with meperidine and tramadol is not recommended.

  Continue/discontinue – We recommend that benzodiazepines or buspirone used chronically for antianxiety or sedative effects be continued perioperatively.

- **Formulations/alternatives** – Parenteral forms of benzodiazepines are available, including diazepam and lorazepam. Buspirone is only available in oral formulation; parenteral benzodiazepines can be substituted if the patient cannot take oral medications and anxiety is a significant problem. Intravenous administration can cause blood pressure lability.

Psychostimulants — Psychostimulant medications, used in the treatment of attention deficit hyperactivity disorder, may increase risk for hypertension and arrhythmias, lower the seizure threshold, and interact with medications that could be needed in the perioperative period (eg, vasopressors). There is a risk of sudden blood pressure increase when halogenated anesthetics are used in conjunction with methylphenidate, and, per drug labeling, the stimulant should be withheld on the day of surgery.

A case series report of eight patients found no adverse effects when amphetamines were continued on the day of surgery [130]. However, none of the patients required vasopressor support.

- **Benefit/risk** – Psychostimulants are not associated with adverse effects when discontinued in the non-abusing patient. Patients generally do not need to be concerned about alertness on the day of surgery.

- **Continue/discontinue** – Data are limited but risks are low of temporarily discontinuing psychostimulant medications. We recommend they be withheld on the day of surgery and resumed when the patient is stable.

CHRONIC OPIOID THERAPY

Peri- and postoperative pain management in opioid dependent patients (including those taking buprenorphine and methadone) are discussed elsewhere. (See "Management of acute perioperative pain", section on 'Opioid-dependent patients'.)

NALTREXONE

- **Benefit/risk** – Naltrexone is a derivative of oxymorphone that acts as a competitive antagonist at opioid receptor sites, showing the highest affinity for mu receptors. It decreases cravings and helps maintain abstinence in opioid addicted patients and is also used for the treatment of alcoholism [131]. (See "Pharmacotherapy for opioid use disorder", section on 'Naltrexone'.)

  As with buprenorphine, chronic naltrexone use may increase central nervous system (CNS) opioid receptor concentration, potentially resulting in a transient exaggerated response to agonists in an acute pain situation.

- **Continue/discontinue** – Naltrexone should be discontinued (or the intramuscular dose held) in anticipation of surgery, and a multimodal approach to pain management should be implemented, including the use of local anesthetics with or without sedation, nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, corticosteroids, tricyclic antidepressants, or nerve stabilizers such as gabapentin. Opioids should be used for acute pain, and agents with a higher affinity for the mu receptor (such as morphine, fentanyl, or hydromorphone) are recommended. In addition, a "reverse ladder" approach has been suggested to de-escalate opioid agonist therapy in the postoperative period, utilizing nonopioid alternatives for pain control in conjunction with resumption of the antagonist agent [132].

- **Formulations/alternatives** – Naltrexone is available in both intramuscular and oral form.

NEUROLOGIC AGENTS

The drugs taken by patients with neurologic disease around the time of surgery are discussed in detail separately (See "Perioperative care of the surgical patient with neurologic disease".).

RHEUMATOLOGIC AGENTS

Perioperative medication management of patients with rheumatic diseases is discussed in detail separately. (See "Preoperative evaluation and perioperative management of patients with rheumatic diseases".)

GOUT THERAPY

- **Benefit/risk** – Surgery is known to precipitate acute gouty arthropathy [133]. The optimal management strategy for patients who are maintained on chronic hypouricemic therapy or colchicine in the perioperative period is unknown. Colchicine has a narrow therapeutic index and can cause muscle weakness and polyneuropathy in the setting of renal impairment or drug interactions [134].

- **Continue/discontinue** – We recommend that colchicine be held on the morning of surgery and resumed when the patient is able to tolerate oral medications. Allopurinol can be continued.

- **Formulations/alternatives** – There are no parenteral substitutions for allopurinol or probenecid. Parenteral colchicine is no longer available in the United States; it can cause myelotoxicity, as well as significant skin necrosis if infiltration occurs [135].

  Should an acute gouty flare occur in a postoperative patient unable to tolerate oral medications, intraarticular steroids or systemic steroids can be used. (See "Treatment of gout flares".)

MEDICATIONS FOR BENIGN PROSTATIC HYPERTROPHY

- **Benefit/risk** – Some patients treated with alpha-1-antagonists (eg, terazosin, doxazosin, tamsulosin, alfuzosin) have developed intraoperative floppy iris syndrome (IFIS), a condition involving intractable intraoperative iris prolapse with cataract surgery [136-138].

- **Continue/discontinue** – Patients should be asked about use of alpha-1-antagonists during the preoperative evaluation. It is not known if discontinuing alpha-1-antagonists reduces the risk of IFIS; clinical impression is that the drug effect is long-lasting (weeks, months, or years), and most eye surgeons do not insist that these agents be discontinued. Various operative regimens can reduce the occurrence of IFIS. It is important to make sure the surgeon is aware if the patient was receiving such a medication. Otherwise, these drugs should be continued as they may be beneficial in preventing postoperative urinary retention. (See "Cataract in adults".)

HERBAL MEDICATIONS

Herbal medications, used frequently, may have effects that could be deleterious in the perioperative period, including clotting abnormalities and interactions with anesthetics [139]. Clinicians should specifically inquire about herbal medication use in presurgical patients, as patients often do not readily disclose use.

There is no evidence that herbal medications improve surgical outcomes, and there are theoretic reasons that these agents may increase perioperative morbidity. For simplicity and because the purity and nature of some herbal medications is unclear, we recommend stopping herbal agents at least one week before surgery. (See "Overview of herbal medicine and dietary supplements".)

A review that examined eight commonly used herbal remedies found the following [140]:

- Ephedra (ma huang) may increase the risk of heart attack and stroke and should be discontinued at least 24 hours prior to surgery.
- Garlic may increase bleeding risk and should be discontinued at least seven days prior to surgery.
- Ginkgo may increase bleeding risk and should be discontinued at least 36 hours prior to surgery.
- Ginseng lowers blood sugar and may increase bleeding risk and should be discontinued at least seven days prior to surgery.
- Kava may increase the sedative effect of anesthetics and should be discontinued at least 24 hours prior to surgery. An association between kava use and fatal hepatotoxicity has been reported. (See "Hepatotoxicity due to herbal medications and dietary supplements".)
- St. John's wort may diminish the effects of several drugs by induction of cytochrome P450 enzymes and should be discontinued at least five days prior to surgery.
- Valerian may increase the sedative effect of anesthetics and is associated with benzodiazepine-like withdrawal. There are no data on preoperative discontinuation. Ideally it is tapered weeks before surgery; if not, withdrawal is treated with benzodiazepines.
- Echinacea is associated with allergic reactions and immune stimulation. There are no data on preoperative discontinuation.

ANTIRETROVIRAL AGENTS

The perioperative management of patients taking antiretroviral agents is discussed separately. (See "Surgical issues in HIV infection".)

RECOMMENDATIONS

General recommendations for the management of several medications are summarized as follows:

- Cardiovascular agents (table 1)
- Gastrointestinal and pulmonary agents (table 2)
- Estrogen and related hormonal agents (table 3)
- Agents affecting hemostasis (table 6)
- Psychotropic agents (table 7)
- Opioids (see "Management of acute perioperative pain", section on 'Opioid-dependent patients')
- Neurologic agents (see "Perioperative care of the surgical patient with neurologic disease")
- Rheumatologic agents (see "Preoperative evaluation and perioperative management of patients with rheumatic diseases")

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GRAPHICS

Perioperative management of cardiovascular agents

Name or class of drug	Clinical considerations	Recommended strategy for surgery with brief NPO state	Recommended strategy for surgery with prolonged NPO state
Beta blockers	Abrupt withdrawal can result in hypertension, tachycardia, and myocardial ischemia. Perioperative initiation can prevent postoperative myocardial ischemic events in patients with significantly-increased cardiac risk but may increase risk for stroke. Perioperative initiation of beta blockers is recommended in patients with CAD or ischemia on stress testing who are undergoing vascular surgery; and reasonable in patients with at least one cardiac risk factor who are undergoing vascular surgery, or with CAD or >1 cardiac risk factor undergoing intermediate risk surgery. Perioperative initiation of beta blockers is not recommended in patients with baseline heart rate <60 beats per minute, systolic blood pressure <90 mmHg, or when time is not sufficient for titration.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. Substitute IV propranolol, metoprolol, or labetalol during NPO state.
Alpha 2 agonists	Withdrawal can cause extreme hypertension and myocardial ischemia.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. Substitute transdermal clonidine.
Calcium channel blockers	Conflicting evidence on whether there is an increased risk of bleeding.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. No IV substitution necessary unless poor hemodynamics (hypertension or arrhythmia).
ACE inhibitors and angiotensin receptor blockers	Continuation can result in hypotension.	Continue therapy up to day of surgery and hold morning dose unless indication is heart failure or poorly controlled hypertension.	Continue therapy up to day of surgery and hold morning dose unless indication is heart failure or poorly controlled hypertension. Use parenteral enalapril as needed in postoperative period.
Diuretics	Continuation can result in hypovolemia and hypotension.	For the majority of patients we continue therapy up to day of surgery but hold the morning dose. For patients with heart failure whose fluid balance is difficult to manage, we often continue the diuretic without interruption.	Continue therapy up to day of surgery but discontinue morning dose. However, for patients with heart failure whose fluid balance is difficult to manage, we often continue the diuretic without interruption. Use parenteral forms as needed in postoperative period.
Statins	Continuation may elevate risk of myopathy, but provides cardiovascular protection.	Continue statins.	Continue statins up to and including day of surgery.
Non-statin lipid-lowering agents	Niacin and fibric acid derivatives may cause rhabdomyolysis. Bile acid sequestrants interfere with absorption of other medications.	Discontinue day before surgery.	Discontinue day before surgery. Resume with oral intake.

NPO: nil per os (nothing by mouth); CAD: coronary artery disease; IV: intravenous; ACE: angiotensin-converting enzyme; HF: heart failure.

Graphic 62659 Version 6.0

Perioperative management of gastrointestinal and pulmonary agents

Name or class of drug	Clinical considerations	Recommended strategy for surgery with brief NPO state	Recommended strategy for surgery with prolonged NPO state
H2 blockers	No known adverse effects.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. Substitute IV forms available for prolonged postoperative NPO state.
Proton pump inhibitors (PPIs)	May increase risk for *Clostridioides* (formerly *Clostridium*) *difficile*.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. Substitute IV H2 blockers or IV PPIs for prolonged postoperative NPO state.
Inhaled bronchodilators (beta agonists and anticholinergics)	No known adverse effects.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. Use nebulized forms if patient unable to comply with inhalation maneuver.
Theophylline	No known adverse effects but very narrow range between therapeutic and toxic level.	Discontinue the evening before surgery.	Discontinue the evening before surgery. Resume with PO intake. Use nebulized or inhaled beta agonist or anticholinergics.
Leukotriene inhibitors	No known adverse effects.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery and resume when patient able to take oral medications.

NPO: nil per os (nothing by mouth); IV: intravenous; PO: per os (by mouth).

Graphic 56778 Version 6.0

Perioperative management of estrogen and related hormones

Name or class of drug	Clinical considerations	Recommended strategy for surgery with brief NPO state	Recommended strategy for surgery with prolonged NPO state
Oral contraceptives	Continuation may increase risk of VTE. Discontinuation can result in unwanted pregnancies.	▪ For patients undergoing surgery with a low to moderate risk of VTE, continue without interruption (with appropriate perioperative VTE prophylaxis). ▪ For patients undergoing surgery with a high risk of VTE, stop 4 weeks before surgery. For women using them for contraceptive purposes, instruct on alternate forms of contraception and obtain serum pregnancy test immediately before surgery.	▪ See recommendations for surgery with brief NPO state. ▪ Resume when tolerating oral medications.
Postmenopausal hormone therapy	Continuation may increase risk of VTE.	▪ For patients undergoing surgery with a low to moderate risk of VTE, continue without interruption (with appropriate perioperative VTE prophylaxis). ▪ For patients undergoing surgery with a high risk of VTE, stop at least 2 weeks prior to surgery and resume once elevated risk of VTE has resolved.	▪ See recommendations for surgery with brief NPO state. ▪ Resume when tolerating oral medications.
Selective estrogen receptor modulators (SERMs)	Continuation may increase risk of VTE.	▪ For patients undergoing surgery with a low to moderate risk of VTE, continue without interruption (with appropriate perioperative VTE prophylaxis). ▪ For patients undergoing surgery with a high risk of VTE, our recommendations for timing of discontinuation depend upon the specific SERM and the indication for its use: ▪ For raloxifene (taken for breast cancer prevention or osteoporosis treatment/prevention), discontinue 3 days prior to surgery and resume once elevated risk of VTE has resolved. ▪ For tamoxifen (taken for breast cancer prevention), discontinue 2 weeks prior to surgery and resume once elevated risk of VTE has resolved. ▪ For tamoxifen (taken for breast cancer treatment), we typically recommend continuing while providing appropriate VTE prophylaxis. However, consultation with oncology is advised.	▪ See recommendations for brief NPO state. ▪ Resume when tolerating oral medications.

NPO: nil per os (nothing by mouth); VTE: venous thromboembolism.

Refer to other UpToDate content for details on VTE risk assessment in surgical patients.

Graphic 77781 Version 8.0

Modified Caprini risk assessment model for VTE in general surgical patients

Risk score			
1 point	**2 points**	**3 points**	**5 points**
Age 41 to 60 years	Age 61 to 74 years	Age ≥75 years	Stroke (<1 month)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI >25 kg/m^2	Major open surgery (>45 minutes)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (>45 minutes)	Factor V Leiden	Acute spinal cord injury (<1 month)
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (>72 hours)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (<1 month)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (<1 month)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure (<1 month)			
History of inflammatory bowel disease			
Medical patient at bed rest			

Interpretation		
Surgical risk category*	**Score**	**Estimated VTE risk in the absence of pharmacologic or mechanical prophylaxis (percent)**
Very low (see text for definition)	0	<0.5
Low	1 to 2	1.5
Moderate	3 to 4	3.0
High	≥5	6.0

VTE: venous thromboembolism; BMI: body mass index.
* This table is applicable only to general, abdominal-pelvic, bariatric, vascular, and plastic and reconstructive surgery. See text for other types of surgery (eg, cancer surgery).

From: Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practical guidelines. Chest 2012; 141:e227S. Copyright © 2012. Reproduced with permission from the American College of Chest Physicians.

Graphic 83739 Version 14.0

Preparation of rectal formulations of thionamides

Methimazole	
Suppository	Dissolve 1200 mg methimazole in 12 mL of water and add to 52 mL cocoa butter containing two drops of polysorbate (Span) 80. Stir mixture to form an emulsion and pour into 2.6 mL suppository molds to cool.[1]
Propylthiouracil	
Suppository	Dissolve 200 mg of propylthiouracil in a polyethylene glycol base and put into suppository tablets
Retention enema	Dissolve eight to twelve 50 mg tablets of propylthiouracil in 90 mL of sterile water **OR** Dissolve eight 50 mg tablets of propylthiouracil in 60 mL of mineral oil enema (eg, Fleet mineral oil) or in 60 mL of sodium phosphates enema solution* (eg, Fleet enema phospho soda)[2] For either enema preparation: Administer by Foley catheter inserted into the rectum, with balloon inflated to prevent leakage for two hour retention

Additional information on preparation described in:

- Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am 2006; 35:663.
- Yeung SC, Go R, Balasubramanyam A. Rectal administration of iodide and propylthiouracil in the treatment of thyroid storm. Thyroid 1995; 5:403.
- Jongjaroenprasert W, Akarawut W, Chantasart D, et al. Rectal administration of propylthiouracil in hyperthyroid patients: comparison of suspension enema and suppository form. Thyroid 2002; 12:627.

* Avoid phosphate containing rectal preparations in patients with renal insufficiency or heart failure.

References:

1. *Nabil N, Miner DJ, Amatruda JM. Methimazole: an alternative route of administration. J Clin Endocrinol Metab 1982; 54:180.*
2. *Walter RM Jr, Bartle WR. Rectal administration of propylthiouracil in the treatment of Graves' disease. Am J Med 1990; 88:69.*

Graphic 79245 Version 6.0

Perioperative management of agents affecting hemostasis

Name or class of drug	Clinical considerations	Recommended strategy for surgery with brief NPO state	Recommended strategy for surgery with prolonged NPO state
Aspirin	Continuation may cause perioperative hemorrhage. Discontinuation may increase the risk of vascular complications. **Discussion with cardiologist appropriate for patients with cardiovascular indications.**	Discontinue aspirin approximately seven days prior to noncardiovascular surgery.	Resume with oral intake.
P2Y12 receptor blockers (clopidogrel, prasugrel, ticlopidine, ticagrelor)	When used after cardiac stenting procedure, if discontinued can cause cardiac ischemia perioperatively. If continued can result in bleeding complications. Should discuss management with cardiologist.	Ideally, elective procedures should be delayed until the mandatory period of platelet inhibition with these agents is completed. When used for long-term stroke prophylaxis, should be discontinued 7 to 10 days. If discontinuing, stop clopidogrel and ticagrelor at least five days, prasugrel seven days, and ticlopidine 10 days before surgery. When restarting clopidogrel, consider using a loading dose.	Resume with oral intake.
Warfarin	Refer to UpToDate topic on perioperative management of patients receiving anticoagulants.		
Dabigatran, rivaroxaban, apixaban, edoxaban	Refer to UpToDate topic on perioperative management of patients receiving anticoagulants.		

NPO: nil per os (nothing by mouth).

Graphic 68515 Version 13.0

Perioperative management of psychotropic agents

Name or class of drug	Clinical considerations	Recommended strategy for surgery with brief NPO state	Recommended strategy for surgery with prolonged NPO state
Antipsychotics	Some agents are associated with QT prolongation and occasionally cause hypotension or arrythmias.	Continue therapy up to and including day of surgery in patients with high risk of developing psychoses.	Continue therapy up to and including day of surgery. Parenteral formulations are available for haloperidol, chlorpromazine, aripriprazole, olanzapine, and ziprasidone. If prolonged NPO state is anticipated, depot formulations (eg, haloperidol decanoate) could be considered, to begin well before surgery in consultation with psychopharmacologist.
Benzodiazepines	Abrupt withdrawal can result in agitation, hypertension, delirium, and seizures.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. Parenteral diazepam, lorazepam, and chlordiazepoxide are available for prolonged NPO state.
Buspirone	No known adverse effects.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. No parenteral substitution available but parenteral diazepam, lorazepam, or chlordiazepoxide can be used for prolonged NPO state.
Lithium	Continuation may prolong the effect of muscle relaxants and, due to impaired renal concentrating ability, can cause hypovolemia and hypernatremia.	Continue therapy up to and including day of surgery with close monitoring of electrolytes and volume status.	Resume with oral intake. No parenteral substitution available. When needed, may use parenteral valproate or a second-generation antipsychotic.
Monoamine oxidase (MAO) inhibitors	If continued and direct acting sympathomimetic agents like ephedrine are used during anesthesia, can result in severe hypertension. If agents like meperidine or dextromethorphan are used, can result in "serotonin syndrome."	For emergency procedures, a MAO-safe anesthetic technique should be used. For other surgeries, anesthesiologist and psychiatrist should collaborate and decide either to use MAO-safe anesthetic technique or discontinue the medication. If discontinued should be stopped for two weeks prior to surgery.	Resume with oral intake. No parenteral substitution available.
Serotonin reuptake inhibitors	Increased risk of bleeding.	Discontinue therapy three weeks prior to surgery in patients undergoing high-risk procedures (such as certain CNS procedures).	Resume with oral intake. No parenteral substitution available.
Tricyclic antidepressants	Continuation may increase the potential for arrythmias. Abrupt withdrawal can lead to insomnia, nausea, headache, increased salivation, and increased sweating.	Continue therapy up to and including day of surgery for patients on high doses. Patients on low doses and in whom perioperative arrhythmia is a concern should discontinue for seven days prior to surgery.	Resume with oral intake. No parenteral substitution available.
Valproic acid	No known adverse effects.	Continue therapy up to and including day of surgery.	Continue therapy up to and including day of surgery. Resume with oral intake. A parenteral formulation (valproate sodium) is available.

NPO: nil per os (nothing by mouth); CNS: central nervous system.

Graphic 66948 Version 6.0

Monoamine oxidase inhibitors

Drug	Trade name*	Class
Furazolidone	Furoxone¶	Antimicrobial
Isocarboxazid[Δ]	Marplan	Antidepressant
Linezolid	Zyvox	Antimicrobial
Moclobemide	Manerix¶	Antidepressant
Pargyline[Δ]	Eutonyl¶	Antidepressant
Phenelzine[Δ]	Nardil	Antidepressant
Procarbazine	Matulane	Antineoplastic
Rasagiline	Azilect	Parkinson disease
Safinamide	Xadago	Parkinson disease
Selegiline	Eldepryl	Parkinson disease
Selegiline transdermal patch	Emsam	Parkinson disease
Tranylcypromine[Δ]	Parnate	Antidepressant

* Trade name in the United States and some other countries.
¶ Not available in the United States.
Δ Potent non-selective monoamine oxidase inhibitor requiring vigilant food and drug interaction monitoring or preferably discontinuation two to three weeks preoperatively.

Graphic 78294 Version 7.0

Diet during therapeutic use of monoamine oxidase inhibitors (MAOIs)

Food	Allowed (not allowed if spoiled or improperly stored)*	Minimize intake¶	Not allowed
Beverages	Decaffeinated beverages (eg, coffee, tea, soda); milk	Caffeine-containing drinks Clear alcoholic spirits (eg, gin, vodka, rum) Red or white wine (no more than two 4-ounce servings per day) Bottled/canned beer, including nonalcoholic (no more than two 12-ounce servings per day) Soy milk	Tap (draft) beer, Korean beer, vermouth
Breads, cereals, crackers	Commercial yeast breads, hot and cold cereals, most crackers (ie, containing no aged cheese)	None	Sourdough bread; crackers and breads that contain aged cheese
Dairy, eggs, cheeses	Butter, cottage cheese, eggs, farmers or pot cheese, cream cheese, ricotta cheese, pasteurized milk, pasteurized cream, ice cream, pudding, yogurt	American processed cheese, mozzarella, parmesan, Romano, sour cream (limit these to one serving of ½ cup)	**All aged cheeses are absolutely not allowed**Δ, including: Blue/bleu, camembert, cheddar, gorgonzola, gouda, gruyere, provolone, Roquefort, Stilton, Swiss
Meat, fish, and poultry	All fresh packaged, fresh frozen, or fresh processed (not aged or smoked) meats, fish, and poultry; fresh breakfast sausage	Pepperoni, hot dogs, bologna	**All aged, smoked, pickled, or cured meats/fish/poultry are absolutely not allowed**, including: Aged, smoked, pickled or dried meats (eg, bacon, aged or dried sausage, all types of salami, Genoa, mortadella, corned beef, pastrami); aged chicken and beef liver; dried, pickled or smoked fish (eg, pickled herring, lox, smoked salmon, smoked trout, shrimp paste); liverwurst; meat extracts; meat alternatives that contain soy product (eg, meatless hot dogs made from tofu)
Starches — potatoes/rice	Potatoes, rice, noodles, pasta, and most stuffings	None	Soy products (eg, tofu, tempeh)
Vegetables and beans	Most fresh, frozen, canned, or dried vegetables, leafy salad greens, lentils, and beans (except fava and soy beans); most veggie burgers (ie, containing no soy product)	Chili peppers	Fava or broad beans (Italian green beans) and their pods, Kim chee (Kimchi), sauerkraut, snow peas, soy beans, bean pastes, edamame beans
Fruit and fruit juices	Most fresh, frozen, or canned fruits and fruit juices	Avocado (not over-ripened), canned figs, raspberries	Avocado (over-ripened), banana (over-ripened), banana peel, dried fruit, any kind of fruit that is over-ripened
Soups, gravies, casseroles, pizza	Home prepared (not prepackaged) soups, gravies, casseroles that contain **no** aged cheese, bouillons, flavoring cubes, or meat extracts	Occasional consumption of one to two slices of pizza from large chain commercial outlets appears safe (ie, generally made with low tyramine cheese); avoid: larger quantities, extra cheese, or pizzas containing aged cheese	Soups, gravies, casseroles, pizzas that contain aged cheese; soups or casseroles with flavoring meat extracts (eg, flavor cubes, bouillon), miso, broad or fava beans and their pods, tofu, tempeh, soy products (eg, soy sauce, teriyaki sauce) or yeast extracts
Fats and oils	Butter, cream cheese, margarine, mayonnaise, olive oil, vegetable oils	Moderate amount (eg, 2 to 4 ounces) of peanut butter is considered safe	Fats and oils included in fermented, aged, cured, smoked, pickled, or other foods that are not allowed
Snacks	Potato chips, popcorn, most nuts, most crackers (ie, containing no aged cheese)	Moderate consumption of peanuts is considered safe	Snack foods containing aged cheeses
Sweets	Sugar, hard candy, honey, molasses, syrups	One serving of chocolate (eg, 2 ounces) is considered safe	None
Desserts	Cakes, cookies, gelatin, pastries, pies, sherbets, sorbets	One serving of chocolate-containing dessert (eg 4 ounces) is considered safe	None
Condiments and miscellaneous	Ketchup, mustard, mayonnaise, non-cheese salad dressings, salt, spices, herbs, Worcestershire sauce	None	All aged or fermented soy and yeast products (eg, soy sauce, teriyaki sauce, soy paste, Thai or Vietnamese fish sauce, marmite/vegemite and other concentrated yeast extracts), sauerkraut

- Foods and beverages listed as "not allowed" often contain significant amounts of tyramine that can interact with nonselective monoamine oxidase inhibitors (MAOIs), or potentially with selective MAOI-b inhibitors at high doses, and may result in elevated blood pressure or hypertensive crisis.
- The ingredients of all foods and beverages (including those listed in this table as "allowed") should be reviewed prior to consumption to confirm they do not also include ingredients that are not allowed.
- Tyramine avoidance should be continued for two weeks following discontinuation of a MAOI.

* **No leftover, improperly stored, handled, or spoiled foods of any type should be consumed.** It is important to purchase and consume only fresh meats, poultry, and fish that are properly wrapped and stored under refrigeration and eaten the same day or frozen right away. Fresh produce should be consumed within 48 hours of purchase and not eaten if overripe. Use canned or frozen foods immediately upon opening or thawing.

¶ Eat these foods occasionally; no more than one serving (eg, ½ cup) of one to three of these foods or beverages each day.

Δ The majority of cases of food-related hypertensive crisis during treatment with MAOIs are associated with consumption of aged cheeses.

Data from:

1. *Hirsch M, Birnbaum RJ. An Approach to psychopharmacological treatment. In: The Ten-Minute guide to psychiatric diagnosis and treatment, Stern TA (Ed). New York: Professional Publishing Group, Ltd, 2005. p.355. Copyright © 2005 Castle Connolly Graduate Medical Publishing, Ltd.*
2. *McCabe-Sellers BJ, Staggs CG, and Bogle ML. Tyramine in foods and monoamine oxidase inhibitor drugs: A crossroad where medicine, nutrition, pharmacy and food industry converge; J Food Comp Anal. 2006; 19:S58.*
3. *Lexicomp Online. Copyright © 1978-2019 Lexicomp, Inc. All Rights Reserved.*

Graphic 80345 Version 9.0

Pharmacology of antipsychotics: Dosing (adult), formulations, kinetics and potential for drug interactions

Agent	Usual oral dose range (mg/day)	Initial oral dose (mg/day)	Adjustment of oral dose in older* or medically compromised patients¶	Usual maximum oral dose (mg/day)Δ	Formulations	Half-life after oral administration (hours)	Primary metabolism◇	Enzyme(s) inhibited (see note)§	Note
First-generation antipsychotics (FGAs)									
Chlorpromazine	400 to 600	25 to 200	Use low initial dose and increase more gradually	800	Tab, IM	30	CYP2D6, other CYPs and UGT-glucuronidation to active and inactive metabolites	CYP2D6	Oral absor is variable may requi dose adjustmen based on patient response. Older adul and medic patients ar unlikely to tolerate cardiovasc sedating, a anticholine side effect
Fluphenazine	2 to 15	2 to 10	1 to 2.5 mg daily initially, adjust dose gradually based on response	12	Tab, IM, LAI, oral solution	33	CYP2D6	CYP2D6	Oral absor is highly variable ar dose must individuali based on patient response.
Haloperidol	2 to 20	2 to 10	1 to 5 mg daily; adjust dose gradually based on response	30	Tab, IM, LAI, oral solution	20	CYPs 2D6, 3A4 and UGT-glucuronidation; some metabolites potentially active or toxic	CYPs 2D6, 3A4 (moderate)	The US lab maximum recommen dose of 10 mg/day (o considerab higher tha more rece practice supports. Bioavailab with oral d is about 60 dose adjustmen between o and parent administra should be accordingl Intravenou has not be approved b the US Foo and Drug Administra and is associated increased of QT prolongatio refer to accompan text.
Loxapine	20 to 80	20	Generally follows standard adult dosing, although a dose reduction may be indicated in some cases	100	Capsule; oral inhalation for use in healthcare settings as alternative to IM injection. Oral solution and IM injection available in countries other than United States.	6 to 8 (parent drug) 12 (active metabolites)	CYPs 1A2, 2D6, 3A4 and UGT-glucuronidation to active and inactive metabolites	None	Onset of o (swallowed capsule) a within 30 minutes.
Perphenazine	12 to 24	8 to 16	Initiate dose at 8 mg/day and titrate more gradually to the usual adult range	24 (a higher daily dose may be acceptable, refer to notes)	Tab	9 to 12 (parent drug) 10 to 19 (active metabolite)	CYPs 2D6, 3A4 and other CYPs to active and inactive metabolites	CYP2D6	Bioavailab variable (6 80%). Higher dail doses, eg, 32 mg per were show be similar tolerability efficacy to some SGA

									and in pra up to 64 m day total n be accepta some circumstar
Pimozide[¥]	8 to 10	1 to 2	1 mg/day initially and titrate more gradually to the usual adult range	10 4 (CYP2D6 poor metabolizer)	Tab	55 150 (CYP2D6 poor metabolizers)	CYPs 1A2, 2D6, 3A4 and others	CYP2D6	Bioavailab variable du extensive hepatic firs pass metabolisr
Thiothixene[¥] (tiotixene)	10 to 20	5 to 10	Use low initial dose and titrate more gradually to the usual adult dose range	30	Capsule	34	CYP1A2 and other CYPs	None	Oral absor is variable dose must individualiz based on patient response.
Thioridazine	200 to 600	150	Use low initial dose and titrate more gradually to the usual adult dose range	600	Tab	4 to 10 (parent drug) 21 to 25 (active metabolites)	CYP2D6 and other CYPs to active (mesoridazine) and inactive metabolites	CYP2D6	
Trifluoperazine[¥]	15 to 20	4 to 10	Initiate dose at 4 mg/day and titrate more gradually to the usual adult range	40	Tab	3 to 12 (parent drug) 22 (active metabolites)	CYP1A2 and other CYPs to active and inactive metabolites	None	Bioavailab variable.
Second-generation antipsychotics (SGAs)									
Aripiprazole	10 to 15	10 to 15	None	30	Tab, ODT, LAI, oral solution Aripiprazole lauroxil LAI	75 to 94	CYPs 2D6 and 3A4 to active and inactive metabolites	None	For augmentat antidepres a lower da dose of 2 t mg is usef
Asenapine[¥]	10 to 20	10	None. Exception: Use contraindicated in severe hepatic impairment.	20	Sublingual tab	24	CYP1A2 and UGT-glucuronidation	None	Patient sho not eat or within 10 minutes of sublingual administra SL prepara should not swallowed to poor gastrointes absorption
Brexpiprazole	2 to 4	0.5 to 1	Dose adjustments are needed in renal or hepatic impairment[‡]	4	Tab	91	CYP2D6 and 3A4	None	
Cariprazine	1.5 to 6	1.5	Not recommended in severe renal or hepatic impairment	6	Capsule	48 to 96 (parent drug) 7 to 21 **days** (active metabolites)[†]	CYP3A4 to active[†] and inactive metabolites	None	
Clozapine[¥]	150 to 600	25 to 50	Titrate gradually to reduced maintenance range of 100 to 150 mg/day; maximum 300 mg/day. Lower doses advised in renal or hepatic impairment; specific dose adjustment recommendations are not available.	900	Tab, ODT, oral suspension	12	CYP1A2, other CYPs, and UGT-glucuronidation	CYP2D6 (moderate)	Hypotensic the most frequent d limiting fac during titra Other side effects req monitoring include agranulocy sedation, a sialorrhea. Once titrat 300 to 450 daily, rate titration m increased 100 mg on twice week
Iloperidone	12 to 24	2	Not recommended in severe hepatic impairment	24 12 (CYP2D6 poor metabolizer or receiving 2D6 inhibitor cotreatment)	Tab	18 to 26	CYP2D6 and other CYPs to active and inactive metabolites	CYP3A4 (moderate)	Orthostatic hypotensic usually the limiting fac titration.
Lurasidone	40 to 80	40 20 (renal or hepatic insufficiency)	Dose adjustments are needed in renal and hepatic impairment[‡]	160 80 (moderate or severe renal impairment,	Tab	29 to 37 (at steady state)	CYP3A4 to active and inactive metabolites	None	Needs to b taken with meal to be adequately absorbed.

				moderate hepatic impairment) 40 (severe hepatic insufficiency)					
Olanzapine[¥]	10 to 20	5 to 10	Initially 1.25 to 2.5 mg/day; typical maintenance 5 mg/day; maximum 10 mg/day	30	Tab, ODT, IM, LAI	30 to 38	CYP1A2 and UGT-glucuronidation	None	
Paliperidone	6 to 12	6	Older adults or renal impairment: 3 mg/day[‡]	12	ER tab, LAI	23	Paliperidone is excreted mainly unchanged in urine necessitating dose reduction in renal insufficiency[‡]	None	Tablets ne be swallow whole.
Pimavanserin	34	34	Not recommended in hepatic impairment or severe renal impairment (not studied)	34	Tab	57 parent drug (200 for active metabolite)	CYP3A4 and 3A5 to active metabolite	None	Approved reducing Parkinson disease re psychosis. Dose adjustmen needed if u with strong inhibitors c CYP3A. Eff may be re if used with strong indu of CYP3A. to separat table of CY inhibitors a inducers available i UpToDate.
Quetiapine	400 to 800 (According to the label, the usual range for acute therapy using immediate release tab is 150 to 750 mg/day)	50 (immediate release) 300 (extended release)	Initially 25 to 50 mg/day; use substantially lower maintenance dose. Dose adjustment needed in hepatic impairment[‡].	800	Tab, ER tab	6 to 12	CYP3A4	None	Titration m often limite excessive sedation o orthostatic hypotensio which shou monitored
Risperidone	2 to 6	1 to 2	Initially 0.25 to 0.5 mg/day; typical maintenance 1 mg/day; maximum 2 mg/day. Dose adjustments are needed in renal and hepatic impairment[‡].	8	Tab, ODT, LAI, oral solution	20	CYP2D6 to active (paliperidone) and inactive metabolites; P-gp substrate	CYP2D6 (moderate)	
Ziprasidone	40 to 160	40 to 80	Lower doses advised in hepatic impairment; specific adjustment recommendations are not available	200	Capsule, IM	7 oral 2 to 5 IM	CYP3A4	None	Oral preparatio not depend on renal function fo clearance componen the IM inje is cleared the kidney

Important note: Doses shown are total daily dose, oral administration, for maintenance treatment of schizophrenia in otherwise healthy adults. The dosing and other information provided in this table differs from dosing used in management of behavioral symptoms of dementia in older adults; in general these medications are not recommended for that use. For additional information, refer to the relevant UpToDate clinical topics and the Lexicomp drug monographs included within UpToDate.

ODT: orally dissolving tablet; Tab: tablet; ER tab: extended-release tablet; IM: short-acting intramuscular injection; LAI: long-acting injectable (eg, depot); CYP: cytochrome P-450; P-gp: membrane P-glycoprotein transporters; UGT-glucuronidation: uridine 5'diphosphate-glucuronyltransferases.

* First- and second-generation antipsychotics are included on the Beers list of medications to be used with caution in older adults and should in general be avoided except for schizophrenia and bipolar disorder.[2]

¶ First-generation antipsychotics (FGAs) undergo extensive hepatic metabolism; levels may be elevated in hepatic impairment necessitating dose reduction and more gradual dose titration to avoid toxicity. FGAs should be used with caution at significantly reduced doses or avoided in severe hepatic impairment.

Δ Usual maximum total oral daily dose for maintenance treatment of schizophrenia in adult patients without significant comorbidity. Doses shown may not be the maximum dose used in some clinical trials or in exceptional patients.

◇ Dose adjustments of several antipsychotic medications listed in this table are recommended in presence of strong or moderate inhibitors or inducers of CYP drug metabolism; for specific recommendations refer to the individual Lexicomp drug monographs.

§ Only potent to moderate inhibitor effects are listed in this table. For additional information including moderate to weak inhibitor or inducer effects, and to determine specific drug

interactions, refer to individual drug monographs section on drug interactions and the Lexi-Interact program included with UpToDate.
¥ Smoking may decrease blood concentrations of antipsychotics primarily metabolized by CYP1A2.
‡ For specific dose adjustments in setting of renal or hepatic impairment, refer to Lexicomp drug monograph.
† Active metabolites of cariprazine are equipotent to cariprazine. Due to the long half-life of cariprazine and active metabolites, changes in dose will not reach plasma steady-state for several weeks or months.

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1. *Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209.*
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Prepared with data from:

1. *US product information (available online at http://dailymed.nlm.nih.gov/dailymed/about.cfm) and Health Canada product monograph.*
2. *Lexicomp Online. Copyright © 1978-2019 Lexicomp, Inc. All Rights Reserved.*
3. *Wynn GH, et al (eds) Clinical Manual of Drug Interaction Principles for Medical Practice APA publishing, Washington DC. Copyright © 2009.*

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