The Carlat Psychiatry Report

MEDICATION FACT BOOK

For Psychiatric Practice

2nd Edition

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Second Edition

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Introduction

How to Use This Book

Medication information is presented in two ways in this book.

Medication Fact Sheets: In-depth prescribing information for select medications. There are 78 fact sheets in this book. These don't cover all psychiatric medications, but we have included most of the commonly prescribed and newer medications.

Quick-Scan Medication Tables: These are located at the beginning of each therapeutic category and list the very basics: generic and brand names, strengths available, starting doses, and target doses. These tables contain most of the commonly prescribed psychiatric medications.

Changes and Additions to the 1st Edition

Medication fact sheets have been updated to reflect availability of newer strengths and formulations, as well as generics. New clinical data have been incorporated into the previous fact sheets. Many categories of medications have been expanded to include a larger number of medications: 30 new fact sheets and 6 new quick-scan medication tables have been added to this edition. Two new appendices have also been added to aid the clinician with potential drug interactions with psychiatric medications and the use of these medications in the context of pregnancy and lactation.

More on the Medication Fact Sheets

The medication fact sheets are derived from those that are posted on the website of *The Carlat Psychiatry Report* (www.TheCarlatReport.com). The goal of these fact sheets is to provide need-to-know information while at the same time ensuring that they are easily and quickly absorbed during a busy day of seeing patients. Our main criterion is that all the information should fit on a single page. Please refer to the PDR (*Physicians' Desk Reference)* when you need more in-depth information.

For the most part, each fact sheet contains the following information:

- Both the brand and generic names.
- FDA-approved indications.
- The name of the manufacturer, including information on whether a generic version exists. (The year of original FDA approval can often be found in the tables.)
- Recommended dosing information that is derived from a variety of sources, including package inserts, clinical trials, and common clinical practice. In other words, don't be surprised when our dosing instructions are at odds with what you find in the PDR.
- Cost information. Pricing information for a one-month supply of a common dosing regimen was obtained from leading US pharmacies in late 2013/early 2014; most notably Walmart, unless otherwise noted.
- Side effects information, generally broken down into "common" vs "serious" side effects. As in dosing, the side effect information is not necessarily what is officially reported in the PDR but rather what clinicians have discovered in everyday practice.
- Pharmacokinetics, with a focus on drug metabolism and/or half-life.
- Drug interactions.
- Clinical pearls, which typically comment on advantages or disadvantages of a medication in comparison to others in its therapeutic category, tips for dosing or avoiding side effects, types of patients who seem to benefit the most, and a fun fact or two.
- Lastly, our bottom line summary or assessment for that particular medication.

Financial Disclosures

Dr. Puzantian has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to the information provided in this book. Dr. Balt is Editor-In-Chief of *The Carlat Psychiatry Report* and discloses that his spouse is employed by Otsuka America, Inc. He has no other pertinent relationships or financial interests.

Disclaimer

The medication information in this book was formulated with a reasonable standard of care, and in conformity with professional standards in the field of psychiatry. Medication prescribing decisions are complex, and you should use these fact sheets as only one of many possible sources of medication information. We do not endorse or recommend the use of any particular drug for a particular patient, and this information is not a substitute for informed medical care. This book is intended for use by licensed professionals only.

If you have any comments or corrections, please let us know by writing to us at info@thecarlatreport.com or *The Carlat Psychiatry Report*, P.O. Box 626, Newburyport, MA 01950.

ADHD Medications

Stimulants have long been a mainstay of attention deficit hyperactivity disorder (ADHD) treatment in children, and, in recent years, adults as well. There are two major chemical classes of stimulants: methyphenidate-type medications (dexmethylphenidate, methylphenidate) and amphetamine-type medications (dextroamphetamine, lisdexamfetamine, methamphetamine, mixed amphetamine salts). Patients who don't tolerate or respond to one class may do well with an agent of the other type.

All stimulants have been shown to improve attention span, impulsivity, and hyperactivity. Clinical effects can be clear and dramatic, often within a day or two of reaching therapeutic stimulant doses. Non-stimulant medications have also been found to be effective in ADHD. These include atomoxetine, bupropion, and guanfacine. Therapeutic effects of these agents may, in some cases, be less robust and seen more gradually, but they can serve as an adjunctive medication, or as an alternative in patients not appropriate for stimulant therapy.

Stimulants are generally safe and well-tolerated, although the package labeling for stimulants includes a black box warning regarding their abuse potential and the risk for dependence. Patients should be monitored for misuse, and the possibility of medication diversion should always be a consideration. When used appropriately in children with ADHD, however, stimulants may actually decrease the risk of developing substance use disorders later in life.

There are several class warnings that apply to all stimulants. These include:

- Potential to cause psychosis or aggression: Rare and dose-related effect and may be more likely in patients with a predisposition for psychosis.
- Worsening or new-onset Tourette's or tic disorders: Stimulants may unmask tics. Of stimulants, methylphenidate is favored. The non-stimulant guanfacine is another alternative.
- Seizures: Stimulants may lower seizure threshold, although data are contradictory; monitor patients with seizure disorders closely.
- Growth inhibition or weight loss: With long-term use, some growth inhibition may occur occasionally in children, but this is generally not a major problem. Monitoring growth and considering "drug holidays" may limit growth suppression.
- Cardiovascular safety: The FDA issued a serious class warning in 2006 with regard to cardiovascular safety. However, newer data, both in children and adults, have been reassuring. Cardiac events occurred at virtually the same or lower rates among people who took stimulants compared to those who did not. From a practical perspective, we recommend getting a careful cardiac history and doing a physical exam. If the history or exam suggests a potential cardiac problem, obtain a baseline EKG. Amphetamines should be avoided in patients with known or suspected cardiovascular disease.

TABLE 1: ADHD MEDICATIONS

Brand Name (Generic Name, if different than heading) Year FDA Approved *Generic available unless otherwise noted*	Available Strengths (mg except where noted)	Usual Dosage Range (starting–max) (mg)	Duration of Action (in hours)	Can it be Split?	Ages Approved for ADHD	Delivery System/Notes (IR = immediate, CR = controlled, DR = delayed release)
Methylphenidates						
Short-acting						
Focalin (Dexmethylphenidate) 2001	2.5, 5, 10	2.5–10 BID	3–4	Yes (not scored)	6–17	Tablet; D-enantiomer of Ritalin; 2x more potent than methylphenidate
Methylin 2002 branded generic of Ritalin	5, 10, 20	2.5 BID–20 TID	3–4	Yes	6–17, adults	IR tablet
Methylin CT 2003 generic not available	2.5, 5, 10	2.5 BID–20 TID	3–4	Yes	6–17, adults	Chewable, grape-flavored tablet
Methylin oral solution 2002	5 mg/5ml, 10 mg/5ml	2.5 BID–20 TID	3–4	NA	6–17, adults	Clear, grape-flavored liquid
Ritalin 1955	5, 10, 20	2.5 BID–20 TID	3–4	Yes	6–17, adults	IR tablet
Intermediate-acting						
Metadate ER 1999 branded generic of Ritalin SR	10, 20	10 QAM–30 BID (max 60/day)	6–8	No	6–17, adults	CR tablet (less predictable because of wax matrix)
Methylin ER 2000 branded generic of Ritalin SR	10, 20	20 QAM–60 QAM	4–8	No	6–17, adults	Hydrophilic polymer tablet; possibly more continuous than others in category
Ritalin SR 1982	20	10–60 QAM	4–8	No	6–17, adults	CR tablet (less predictable because of wax matrix)
Long-acting						
Concerta 2000	18, 27, 36, 54	18 QAM–72 QAM (if 12+ yrs)	10–16	No	6–12: up to 54 mg; 12+: up to 72 mg	22% IR & 78% DR; IR, then CR capsule; hard shell may make it more difficult to abuse
Daytrana patch (Methylphenidate transdermal system) 2006 generic not available	10, 15, 20, 30	10–30 QAM Remove after 9 hours	8–12	No	children >6 years, adults	CR patch; duration can be shortened by decreasing wear time
Focalin XR (Dexmethylphenidate XR) 2005 generic not available	5, 10, 15, 20, 25, 30, 35, 40	6–17 yrs: 5 QAM–30 QAM Adults: 10 QAM–40 QAM	8–12	Can be sprinkled; do not crush or chew	6–17, adults	Capsule of 50% IR beads & 50% DR beads; mimics BID dosing; 2x more potent than methylphenidate

Metadate CD 2001 generic not available	10, 20, 30, 40, 50, 60	20–60 QAM	8–12	Can be sprinkled; do not crush or chew	6+	Capsule of 30% IR beads & 70% DR beads; mimics BID dosing
Quillivant XR 2012 generic not available	25/5 ml	20–60 QAM	8–12	No	6+	20% IR & 80% ER in oral solution; shake prior to use
Ritalin LA 2002 generic not available	10, 20, 30, 40	20–60 QAM	8–12	Can be sprinkled; do not crush or chew	6+	Capsule of 50% IR beads & 50% DR beads
Amphetamines						
Short-acting						
Desoxyn (Methamphetamine) 1943	5	5 QAM–10 BID	3–5	Yes	6–17	Slow release tablet
Dexedrine (Dextroamphetamine) 1976	5, 10	3–5 yrs: 2.5 QAM–20 BID; 6–16 yrs: 5 QAM–20 BID	3–5	Yes	3–16	Scored tablet
ProCentra (Dextroamphetamine) 2008 generic not available	5 mg/5 ml	5–20 BID	3–5	NA	3–16	Bubblegum-flavored liquid
Zenzedi (Dextroamphetamine) 2013 generic not available	2.5, 5, 7.5, 10	3–5 yrs:2.5–20 BID; 6–16 yrs: 5 QAM–20 BID (Same as Dexedrine dosing)	3–5	Yes	3–16	Unscored tablet
Intermediate-acting						
Adderall (Mixed amphetamine salts) 1960	5, 7.5, 10, 12.5, 15, 20, 30	3–5 yrs: 2.5 QAM–20 BID; 6–17 yrs: 5 QAM–20 BID; Adults: 5 QAM–20 BID	6–8	Can be crushed	3+	Tablet; mixed salt of l- and d-amphetamine
Long-acting						
Adderall XR (Mixed amphetamine salts) 2001	5, 10, 15, 20, 25, 30	6–12 yrs: 5 QAM–30 QAM; 13–17 yrs: 10 QAM–40 QAM; Adult: 20 QAM–60 QAM	8–12	Can be sprinkled; do not crush or chew	6+	Capsule of 50% IR beads & 50% DR beads; mixed salt of l- and d-amphetamine; mimics BID dosing
Dexedrine Spansules (Dextroamphetamine) 1976	5, 10, 15	5 QAM–20 BID	10–14	Can be sprinkled; do not crush or chew	6+	Capsule of 50% IR & 50% sustained release beads

Brand Name (Generic Name, if different than heading) Year FDA Approved *Generic available unless otherwise noted*	Available Strengths (mg except where noted)	Usual Dosage Range (starting–max) (mg)	Duration of Action (in hours)	Can it be Split?	Ages Approved for ADHD	Delivery System/Notes (IR = immediate, CR = controlled, DR = delayed release)
Vyvanse (Lisdexamfetamine) 2007 generic not available	20, 30, 40, 50, 60, 70	30 QAM–70 QAM	8–12	Can be dissolved in water	6–17, adults	Capsule; lisdexamfetamine is prodrug of dextroamphetamine
Non-Stimulants						
Intuniv (Guanfacine ER) 2009 generic not available	1, 2, 3, 4	1–4 QD (do not increase faster than 1 mg/wk)	24	No	6–17	Extended release tablet; do not stop abruptly (orthostatic hypotension); not a 1:1 conversion from IR; do not give with high-fat meals
Kapvay (Clonidine XR) 2009 generic available in immediate release only	0.1, 0.2	0.1 QHS; increase by 0.1 mg/day weekly and give divided BID; max 0.4 QD	12–16	No	6–17	Extended release tablet; titrate gradually (orthostatic hypotension); avoid abrupt discontinuation; somnolence
Provigil (Modafinil) 1998 generic not available	100, 200	100 QAM–400 QAM	18–24	Yes (200 mg tabs are scored)	Not FDA-approved for ADHD	Tablet; studies have shown modafinil to be helpful for ADHD, but low incidence of serious rash; minimal data in children
Strattera (Atomoxetine) 2002 generic not available	10, 18, 25, 40, 60, 80, 100	Dosage varies. See below *	24	No	6–17: max daily dose of 70 mg; 18+: max dose of 100 mg	Capsule; norepinephrine reuptake inhibitor
Tenex (Guanfacine IR) 1986	1, 2	1–4 QD (do not increase faster than 1 mg/wk)	17	Can be crushed	Not FDA-approved for kids or ADHD. Approved only for adults 18+ for hypertension	Tablet
Wellbutrin (Bupropion) 1985	75, 100	1.4–6 mg/kg/day	6–9	Yes	Not FDA-approved for ADHD	Tablet; bupropion SR & XL versions exist

*Strattera dosing: Weight <70kg, start 0.5 mg/kg, target 1.2 mg/kg, max 1.4 mg/kg; weight >70 kg, 40–100 mg

ATOMOXETINE (Strattera) Fact Sheet

FDA Indication:

ADHD (adults and children >6 years).

Dosing:

- Supplied as 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg capsules as **Strattera** (Eli Lilly).
- ADHD (children >6 years and >70 kg, and adults):
  - Start with 40 mg QAM for 3 days, ↑ to 80 mg QAM, may ↑ to 100 mg/day after two to four weeks if needed; maximum dose 100 mg/day; may divide doses >40 mg/day (morning and late afternoon/early evening).
- ADHD (children >6 years and <70 kg):
  - Start 0.5 mg/kg QAM for 3 days, ↑ to 1.2 mg/kg QAM, may ↑ to maximum of 1.4 mg/kg/day or 100 mg/day (whichever is less) after two to four weeks, if needed; may divide doses >0.5 mg/kg/day.
- Cost (for one month supply at 80 mg/day, priced Nov 2013):
  - Strattera: $477.68

Side Effects:

- Most common (most bothersome in bold): in *children* and *adolescents*—**abdominal pain**, decreased appetite, vomiting, somnolence, fatigue, **nausea**, dizziness; in *adults*—**dry mouth**, nausea, insomnia, **decreased appetite**, **constipation**, fatigue, erectile dysfunction, hot flush, urinary hesitation and/or retention, dysmenorrhea.
- Serious but rare: class warning for suicidal ideation in children and teens. Severe hepatic injury manifested by increased hepatic enzymes (up to 40 times normal) and jaundice (bilirubin up to 12 times upper limit of normal). Increased blood pressure (↑ 15–20 mmHg) and heart rate (↑ 20 bpm) reported. Potential for temporary suppression of normal growth patterns in pediatric patients; rebound in height and weight gains reported with continued therapy.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily via CYP2D6 and 2C19; t ½: 5 hours (24 hours in poor metabolizers).
- Avoid use with MAOIs. Caution with 2D6 inhibitors such as fluoxetine, paroxetine, quinidine (increased atomoxetine serum levels); use slower titration and do not exceed 80 mg/day.

Clinical Pearls:

- Selective norepinephrine reuptake inhibitor (NRI) originally studied for treatment of depression but ineffective in clinical trials and not approved for this use.
- Ocular irritant; swallow capsules whole, do not open capsules or sprinkle contents on food.
- QAM dosing is as effective as BID, but BID dosing has better GI tolerability.
- Appears to be more effective in improving attention than in controlling hyperactivity.
- Atomoxetine did not show improvement in ADHD symptoms in children <6 years old.

Fun Fact:

Atomoxetine was originally known as “tomoxetine”; however, the FDA requested the name be changed because the similarity to “tamoxifen” could lead to dispensing errors.

Bottom Line:

No abuse potential, good for comorbid tic disorder and less insomnia compared to stimulants, but delayed onset of therapeutic effect (2–4 weeks), lower efficacy rates compared to stimulants and potential for severe hepatic side effects worth considering before prescribing.

DEXMETHYLPHENIDATE (Focalin, Focalin XR) Fact Sheet

FDA Indications:

ADHD in children >6 years (IR and XR); ADHD in adults (XR only).

Dosing:

- Supplied as:
  - 2.5 mg, 5 mg, 10 mg unscored tablets as **Focalin** (Novartis) and generic.
  - 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg extended release capsules as **Focalin XR** (Novartis).
  - C-II controlled substance.
- IR (adults and children):
  - Start at 2.5 mg BID, ↑ by 5 mg–10 mg/day every 7 days. Maximum daily dose is 20 mg/day; divide IR doses by at least 4 hours.
- XR (adults):
  - Start 10 mg QAM, ↑ by 10 mg/day every 7 days. Maximum daily dose of XR in adults is 40 mg/day.
- XR (children):
  - Start 5 mg QAM, ↑ by 5 mg/day every 7 days. Maximum daily dose of XR in children is 30 mg/day.
- Cost (for one month supply at target dose, priced Nov 2013):
  - Generic: $21.78, 10 mg, CVS Pharmacy
  - Brand: $45.30, 10 mg, Kroger Pharmacy

Side Effects:

- Most common (most bothersome in bold): **decreased appetite**, **insomnia**, anxiety, GI distress, irritability, tics, headache, tachycardia, hypertension, **dry mouth (XR).**

Pharmacokinetics and Drug Interactions:

- Metabolized primarily via de-esterification, not CYP450; t ½: 2–4.5 hours (2–3 hours in children); XR delivers 50% of dose immediately and 50% about 5 hours later.
- Avoid use with MAOIs. Caution with pressors (additive effects).

Clinical Pearls:

- Methylphenidate (Concerta, Metadate, Methylin, Ritalin) is a mixture of d- (dex-)methylphenidate and l-methylphenidate; d-methylphenidate is the more active form.
- Methylphenidate → dexmethylphenidate: dexmethylphenidate is 2x more potent than methylphenidate, so use half of daily dose.
- Dexmethylphenidate IR → XR: dexmethylphenidate IR is equipotent to dexmethylphenidate XR, so use same total daily dose.
- Focalin XR capsules use a bimodal release: half of dose is provided in IR beads and half of dose is in DR beads. A single, once-daily dose of XR capsule provides the same amount of dexmethylphenidate as two IR tablets given 4 hours apart.
- Do not cut, crush, or chew XR formulation. XR capsules may be carefully opened and the beads sprinkled over a spoonful of food and consumed immediately in its entirety.
- Give with food if GI side effects occur.

Fun Fact:

With two stereoactive centers, methylphenidate has four possible stereoisomers. Of the four, dexmethylphenidate is the most active biologically.

Bottom Line:

Focalin is just Ritalin but more potent. It's available as a generic and may mean fewer tablets for patients. Focalin XR is hard to justify due to its high cost.

DEXTROAMPHETAMINE (Dexedrine Spansules, ProCentra, Zenzedi) Fact Sheet

FDA Indications:

ADHD (adults and children >3 years); narcolepsy (adults and children >6 years).

Dosing:

- Supplied as:
  - 5 mg, 10 mg, 15 mg ER capsules as **Dexedrine Spansules** (Amedra) and generic.
  - 5 mg, 10 mg scored tablets (generic only; formerly available as Dexedrine, Dextrostat) and 2.5 mg, 5 mg, 7.5 mg, 10 mg tablets as **Zenzedi** (Arbor).
  - 5 mg/5 ml bubblegum flavored oral solution as **ProCentra** (Tiber Labs).
  - C-II controlled substance.
- ADHD (children >6 years to adults):
  - Start 5 mg QAM, ↑ by 5 mg/day at weekly intervals to maximum of 40 mg/day; use lowest effective dose. Divide IR dose QD–TID.
- ADHD (children 3–5 years old):
  - Start 2.5 mg QAM, ↑ by 2.5 mg/day weekly to maximum of 40 mg/day; divide IR dose QD–TID.
- Narcolepsy (adults):
  - Start 10 mg QAM, ↑ by 10 mg/day weekly to maximum of 60 mg/day.
- Cost (for one month supply at 40 mg/day, priced Jan 2014):
  - Dextroamphetamine (generic): $286.97; $413 (ER)
  - Zenzedi (5 mg tablets): $456.05

Side Effects:

- Most common (most bothersome in bold): abdominal pain, **anorexia**, nausea, **twitching (motor or vocal tics)**, **insomnia**, tachycardia, and headache.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP450 2D6 (minor) and glucuronidation; t ½: 10–13 hours.
- Avoid use with MAOIs, antacids. Caution with pressors (additive effects).

Clinical Pearls:

- Dextroamphetamine is the more potent d-isomer of the amphetamine molecule; potentially less peripheral (motor) effects than racemic mix (eg, mixed amphetamine salts, methamphetamine).
- Administer initial dose upon awakening; do not administer doses late in the evening due to potential for insomnia.
- IR tablets and oral solution: One or two additional daily doses may be given at intervals of 4–6 hours.
- ER capsules: Do not cut, crush, or chew.
- Dextroamphetamine and mixed amphetamine salts are the only stimulants, other than Adderall IR, approved for children <6 years (approved for children >3 years).
- New Zenzedi branded product offers more dosing flexibility options, but splitting generic likely much more cost effective.

Fun Fact:

Dexy's Midnight Runners, the British band famous for its song "Come On Eileen" (1982) derived their name from "Dexys" or Dexedrine, while "midnight runners" referred to the energy it provides.

Bottom Line:

Good drug, with very long history of experience, available in short- and long-acting formulations as generics.

GUANFACINE (Intuniv, Tenex) Fact Sheet

FDA Indication:

ADHD (children >6 years), as monotherapy or adjunctive therapy to stimulants (not approved for ADHD in adults).

Dosing:

- Supplied as:
  - 1 mg, 2 mg tablets as **Tenex** (AH Robins) and generic.
  - 1 mg, 2 mg, 3 mg, 4 mg ER tablets as **Intuniv** (Shire).
- ADHD (children >6 years):
  - 27 kg–40.5 kg (59.5 to 90 lbs): start with 0.5 mg QHS, ↑ by 0.5 mg/day at weekly intervals up to 1.5 mg/day, may ↑ to 2 mg/day after 2 weeks; maximum of 2 mg/day in two to four divided doses.
  - 40.5 kg–45 kg (90 to 99 lbs): start with 0.5 mg QHS, ↑ by 0.5 mg/day at weekly intervals; maximum 1 mg per dose, 3 mg/day.
  - >45 kg (99 lbs): start 1 mg QHS, ↑ by 1 mg/day at weekly intervals up to 3 mg/day, may ↑ to 4 mg/day after 2 weeks; maximum 1 mg per dose, 4 mg/day.
  - ER: start 1 mg QHS, ↑ by 1 mg/day at weekly intervals; maximum 4 mg/day. Alternative: 0.05 mg/kg–0.12 mg/kg QD or QHS; maximum 4 mg/day.
- Guanfacine IR and ER are not interchangeable on a mg:mg basis. When switching from one formulation to the other, taper and retitrate.
- If patient misses 2 or more consecutive doses, consider repeating titration.
- Cost (for one month supply at 4 mg/day, priced Nov 2013):
  - Guanfacine (generic): $17.62
  - Intuniv: $240.70, Kroger Pharmacy

Side Effects:

- Most common (most bothersome in bold): **dry mouth**, **somnolence**, **dizziness**, constipation, fatigue, headache.
- Serious but rare: hypotension, syncope, orthostasis.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 13–14 hours in children (16–18 in adults).
- Avoid use with MAOIs. Caution with 3A4 inhibitors (eg, clarithromycin, fluvoxamine) and inducers (eg, St. John's wort, carbamazepine).

Clinical Pearls:

- Centrally acting, selective α2-adrenergic agonist; not a controlled substance.
- Do not administer ER tablets with a high-fat meal due to increased medication exposure.
- Minimize side effects, especially somnolence, by administering at bedtime.
- Monitor BP, especially during initial dosing titration.
- Risk of nervousness, anxiety, and possibly rebound hypertension 2–4 days after abrupt discontinuation. Taper dose in 1 mg/day decrements, every 3–7 days.

Fun Fact:

Some prescribers have taken advantage of guanfacine's sympatholytic properties for the treatment of nightmares and dissociative symptoms in PTSD.

Bottom Line:

Benefits in children with comorbid tic disorders, lack of abuse potential, and less insomnia make this an attractive alternative to stimulants. However, delayed onset of effect (2–4 weeks) and lower efficacy rates lead us to choose stimulants as the drugs of choice in ADHD. Consider when stimulants aren't an option, but go with the cheaper generic IR first.

LISDEXAMFETAMINE (Vyvanse) Fact Sheet

FDA Indication:

ADHD (adults and children >6 years).

Dosing:

- Supplied as:
  - 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg IR oral capsules as **Vyvanse** (Shire).
  - C-II controlled substance.
- ADHD (adults and children >6 years):
  - Start at 30 mg QAM, ↑ by 10 mg–20 mg/day at weekly intervals, to maximum of 70 mg/day. Use lowest effective dose.
- Cost (for one month supply at 70 mg/day, priced Nov 2013):
  - Vyvanse: $197.85

Side Effects:

- Most common (most bothersome in bold): headache, **insomnia, anorexia**, abdominal pain, irritability, agitation, tics.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through non-CYP-mediated hepatic and/or intestinal metabolism; t ½: lisdexamfetamine <1 hour (dextroamphetamine 10–13 hours).
- Avoid use with MAOIs and antacids. Caution with pressors (additive effects), antihypertensives (decreased efficacy of antihypertensive).

Clinical Pearls:

- Lisdexamfetamine is a prodrug of dextroamphetamine bound to lysine; it remains inactive until GI enzymes cleave off lysine and convert it to active dextroamphetamine.
- Manufacturer claims lower potential for abuse because active ingredient (d-amphetamine) is only released when swallowed (thus, not likely to be snorted or injected).
- Administer in the morning without regard to meals; swallow capsule whole, do not chew; capsule may be opened and the entire contents dissolved in glass of water prior to administration. Use immediately.
- Some prescribers claim they see a response in as little as one to two hours, and that it can last up to 13–14 hours. Two to four hours and 12 hours, respectively, are more conservative estimates.
- Lisdexamfetamine 70 mg is equivalent to 30 mg of mixed amphetamine salts.

Fun Fact:

The manufacturer of Vyvanse is in mid-stage clinical trials investigating its use in treating adults with binge eating disorder, but has given up on seeking an indication as an add-on medication for depression after announcing disappointing results in clinical trials in early 2014.

Bottom Line:

No evidence that lisdexamfetamine offers any therapeutic advantage over other amphetamines, other than perhaps a lower risk of diversion or abuse. High cost may be a prohibitive factor in its use.

METHAMPHETAMINE (Desoxyn) Fact Sheet

FDA Indications:

ADHD (children >6 years); obesity (adults and adolescents >12 years).

Dosing:

- Supplied as 5 mg tablets as **Desoxyn** (Lundbeck) and generic.
- C-II controlled substance.
- ADHD (adults and children >6 years):
  - Start with 5 mg QAM–BID, ↑ by 5 mg/day at weekly intervals to maximum of 20 mg/day, divided BID.
- Cost (for one month supply at 20 mg/day, priced Nov 2013):
  - Methamphetamine (generic): $216.96
  - Desoxyn: $604.08

Side Effects:

- Most common (most bothersome in bold): anorexia, **tachycardia,** dizziness, **insomnia,** tremor, tics, restlessness, headache, constipation (decreased GI motility), dental complications, such as poor dental hygiene, diffuse cavities, bruxism and tooth wear, may develop with abuse.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2D6 to active metabolite (amphetamine); t ½: 4–5 hours.
- Avoid use with MAOIs and antacids. Caution with pressors (additive effects).

Clinical Pearls:

- High risk of abuse.
- Not widely used (DEA reports that there were only 15,000 prescriptions written for this in 2011). When prescribed for obesity, the recommendation is for short-term (ie, a few weeks) use only and as an adjunct to caloric restriction due to its high addiction potential.
- CNS stimulating effect is approximately equal to or greater than that of amphetamine but less than that of dextroamphetamine; pressor effect is less than that of amphetamine.

Fun Facts:

Desoxyn is the same as the abused street drug methamphetamine, just pharmaceutical grade. Although methamphetamine and amphetamine were long thought to be synthesized only by humans, methamphetamine has been reported to occur naturally in certain acacia trees that grow in West Texas.

Bottom Line:

Highly addictive substance; its use is generally not recommended.

METHYLPHENIDATE IR (Methylin, Methylin CT, Ritalin) Fact Sheet

FDA Indications:

ADHD (adults and children >6 years); narcolepsy.

Dosing:

- Supplied as:
  - 5 mg, 10 mg, 20 mg IR tablets as **Ritalin** (Novartis), and generic.
  - 2.5 mg, 5 mg, 10 mg chewable tablets as **Methylin CT** (Shionogi).
  - 5 mg/5 mL, 10 mg/5 mL oral solution as **Methylin** (Shionogi) and generic.
  - C-II controlled substance.
- Short-acting (IR tablets, oral solution, chewable tablets):
  - Start at 5 mg–10 mg BID, ↑ by 10 mg/day at weekly intervals to maximum of 60 mg/day.
  - Children >6 years: start at 0.3mg/kg BID or 2.5 mg–5 mg BID before breakfast and lunch, increase by 0.1mg/kg/dose or 5 mg–10 mg/day at weekly intervals to a maximum of 2 mg/kg/day or 60 mg/day.
- Cost (for one month supply at 60 mg/day, priced Nov 2013):
  - Methylphenidate IR (generic): $105.38
  - Ritalin: $136.28
  - Methylin chewable tablets: $603.78

Side Effects:

- Most common (most bothersome in bold): **insomnia,** headache, nervousness, abdominal pain, nausea, vomiting, **anorexia,** weight loss, affect lability, tics.

Pharmacokinetics and Drug Interactions:

- Hepatic metabolism via carboxylesterase CES1A1, not CYP450 isoenzymes; t ½: 2–4 hours.
- Avoid use with MAOIs, antacids. Caution with pressors (additive effects).

Clinical Pearls:

- Some patients may require 3 doses/day (eg, additional dose at 4 pm).
- While all stimulants may cause tics, a Cochrane review of 8 randomized trials showed that methylphenidate did not worsen tics in children with ADHD and a tic disorder; in some cases it even improved tics.
- Methylin chewable tablet: Administer with at least 8 ounces of water or other fluid.
- Less peripheral (motor) effects than with amphetamine class of stimulants.

Fun Fact:

Methylphenidate was synthesized by Ciba (now Novartis) chemist Leandro Panizzon. His wife, Marguerite, had low blood pressure and would take the stimulant before playing tennis. He named the substance Ritaline, after his wife's nickname, Rita.

Bottom Line:

It's important to be familiar with a couple of the methylphenidate products, ideally a short-acting one, and a long-acting one for patients who don't do well on amphetamine-type stimulants.

METHYLPHENIDATE ER (Concerta, Metadate ER and CD, Methylin ER, Ritalin-SR and LA, Quillivant XR) Fact Sheet

FDA Indications:

ADHD (adults and children >6 years); narcolepsy.

Dosing:

- Supplied as:
  - 10 mg, 20 mg ER tablets as **Metadate ER** (UCB) and **Methylin ER** (Mallinckrodt).
  - 20 mg SR tablet as **Ritalin-SR** (Novartis) and generic.
  - 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg ER capsules as **Metadate CD** (UCB).
  - 10 mg, 20 mg, 30 mg, 40 mg ER capsules as **Ritalin LA** (Novartis).
  - 18 mg, 27 mg, 36 mg, 54 mg ER tablets as **Concerta** (Janssen) and generic.
  - 25mg/5ml extended release oral suspension as **Quillivant XR** (Pfizer).
  - C-II controlled substance.
- Intermediate-acting (Ritalin SR, Metadate ER, Methylin ER) (not recommended for initial treatment):
  - Titrate to effective daily dose with IR; then switch to equivalent 8 hour SR or ER dose QAM–BID (eg, 20 mg ER QAM or BID); maximum: 60 mg/day.
- Long-acting (Metadate CD, Ritalin LA, Quillivant XR):
  - Start 20 mg QAM; ↑ by 10–20 mg/day at weekly intervals; maximum 60 mg/day.
- Long-acting (Concerta):
  - Start 18 mg–36 mg QAM, ↑ by 18 mg/day at weekly intervals; maximum 72 mg/day.
  - Children >6 years: start with 18 mg QAM, ↑ by 18 mg/day in weekly intervals to maximum of 54 mg/day (ages 6–12) or 72 mg/day (age 13+).
  - If switching from different form of methylphenidate:
  - 10 mg–15 mg/day: use 18 mg QAM
  - 20 mg–30 mg/day: use 36 mg QAM
  - 30 mg–45 mg/day: use 54 mg QAM
  - 40 mg–60 mg/day: use 72 mg QAM
  - 27 mg dose is available for situations in which dose between 18 mg–36 mg is desired.
- Cost (for one month supply at 60–72 mg/day, priced Jan 2014):
  - Methylphenidate (generic): $162.05 (CR 60 mg/day); $284.30 (ER 72 mg/day)
  - Ritalin SR: $216.23
  - Ritalin LA: $504.42
  - Concerta: $514.46

Side Effects and Pharmacokinetics and Drug Interactions:

See Methylphenidate IR fact sheet.

Clinical Pearls:

- See Methylphenidate IR fact sheet.
- **Metadate CD** contains mixture of 30% IR and 70% ER beads; mimics BID dosing of IR.
- **Ritalin LA** is combination of 50% IR and 50% DR beads; mimics BID dosing of IR.
- **Concerta** is based on the OROS osmotic delivery system (also used for Invega). 22% of dose is immediate (in one to two hours) and 78% is delayed.
- Do not crush or allow patient to chew SR or ER dosage forms. To avoid insomnia, dosing of these formulations should be completed by noon.
- **Concerta:** May be taken with or without food, but must be taken with water, milk, or juice.
- **Metadate CD**, **Ritalin LA:** Capsules may be opened and contents sprinkled onto small amount (1 tablespoon) of cold applesauce (swallow without chewing).

Bottom Line:

It is important to be familiar with a couple of the methylphenidate products, ideally a short-acting one and a long-acting one for patients who don't do well on amphetamine-type stimulants.

METHYLPHENIDATE TRANSDERMAL (Daytrana) Fact Sheet

FDA Indication:

ADHD (adults and children >6 years).

Dosing:

- Supplied as:
  - 10 mg, 15 mg, 20 mg, 30 mg/9 hour patch as **Daytrana** (Shire).
  - C-II controlled substance.
- ADHD (children >6 years to adults):
  - Start at 10 mg/9 hour patch QAM (for initial therapy or for patients switching from other methylphenidate preparations, regardless of dose). Apply to hip 2 hours before an effect is needed and remove 9 hours after application (drug effects may persist for 5 hours after removal). Increase dose at weekly intervals by using next larger dose system. May be removed in <9 hours if shorter duration is desired or if late day side effects occur. Rotate application sites. Maximum 30 mg QD.
- Cost (for one month supply at 30 mg/day, priced Nov 2013):
  - Daytrana: $224.47

Side Effects:

- Most common (most bothersome in bold): headache, **insomnia**, irritability, decreased appetite, **anorexia**, nausea, tic, **application site reaction** (10%–40% incidence in children).
- Serious but rare: allergic contact dermatitis/sensitization, characterized by intense local reactions (eg, edema, papules) that may spread beyond patch site; sensitization may subsequently manifest systemically with other routes of methylphenidate administration.

Pharmacokinetics and Drug Interactions:

- Hepatic metabolism via carboxylesterase CES1A1, not CYP450 isoenzymes; t ½: 3–4 hours.
- Avoid use with MAOIs, antacids. Caution with pressors (additive effects).

Clinical Pearls:

- Apply patch to clean, dry area of the hip; don't apply to waistline or to areas under tight clothing, as it may rub off. Press patch firmly in place for 30 seconds, ensuring good contact with skin, and wash hands afterward. Alternate sites daily (opposite hip). Absorption not affected by perspiration. Remove after 9 hours. If dislodged, replace with a new patch but remove within the 9 hour total wear time.
- Clinical effect observed in 2 hours; total duration of action approximately 12 hours.
- Exposure of application site to a heat source (eg, hair dryer, heating pad, electric blanket) may increase the amount of drug absorbed.

Fun Fact:

Since 2006, Shire Pharmaceuticals has issued at least 10 recalls of Daytrana patches because users have had difficulty removing the protective cover from the patch. Recall costs have reached into the millions.

Bottom Line:

Use not recommended due to high cost, lag time for onset of effect, and more side effects than Concerta. For patients who don't want to swallow pills, there are other alternatives (chewable tablets, oral solutions, and extended release products that can be sprinkled on food), although the transdermal option may be ideal for young children who refuse any type of oral administration.

MIXED AMPHETAMINE AND DEXTROAMPHETAMINE SALTS (Adderall, Adderall XR) Fact Sheet

FDA Indication:

ADHD (adults and children >3 years for IR, >6 years for XR); narcolepsy (adults and children >6 years).

Dosing:

- Supplied as:
  - 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg tablets as **Adderall** (Teva) and generic.
  - 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg ER capsules as **Adderall XR** (Shire) and generic.
  - C-II controlled substance.
- Each dose contains a mixture of salts (25% each): dextroamphetamine sulfate; dextroamphetamine saccharate; d-, l-amphetamine aspartate monohydrate; and d-, l-amphetamine sulfate (resulting in a 75:25 ratio of dextro and levo isomers of amphetamine).
- Rule of thumb for both preparations: initial dose should be 0.5 mg/kg but shoot for a target dose of 1.0 mg/kg–1.2 mg/kg.
- ADHD (children >3 years):
  - IR: start at 2.5–5 mg BID, max of 40 mg/day divided BID.
  - XR: start 5 mg–10 mg QAM, increase gradually to max of 30 mg/day, or 40 mg/day QAM in adolescents.
- ADHD (adults):
  - IR: start at 5 QAM–BID, max of 40 mg/day divided BID.
  - XR: start 20 mg QAM, increase to max of 60 mg/day QAM.
- May convert from IR to XR at same total daily dose, given QAM.
- Cost (for one month supply at 40 mg/day, priced Jan 2014):
  - Mixed amphetamine and dextroamphetamine salts (generic): $55.58; $238.90 (XR)
  - Adderall: $296.94 ; $459.39 (XR)

Side Effects:

- Most common (most bothersome in bold): **insomnia, headache, decreased appetite**, abdominal pain, weight loss, agitation.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2D6; t ½: 9–14 hours. Duration of action: 6–8 hours (IR). 8–10 hours (XR).
- Avoid use with MAOIs, antacids. Caution with pressors (additive effects).

Clinical Pearls:

- Adderall may provide more of a "kick" and therefore feel more immediately effective than methylphenidate preparations. Roughly twice as potent (per mg) as methylphenidate.
- XR may be swallowed whole or opened and sprinkled on applesauce. Use immediately; do not divide contents.
- Dextroamphetamine and mixed amphetamine salts are the only stimulants approved for children <6 years (approved for children >3 years).

Fun Fact:

Was briefly pulled from the market in Canada in 2005 because of cardiac concerns…then authorities changed their minds.

Bottom Line:

It is important to be familiar with a couple of the amphetamine products, ideally a short-acting one and a long-acting one for patients who don't do well on methylphenidate-type stimulants.

Antidepressants

Antidepressants are often classified by medication class—selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), serotonin norepinephrine reuptake inhibitor (SNRI), monoamine oxidase inhibitor (MAOI), dopamine norepinephrine reuptake inhibitor, noradrenergic and specific serotonergic antidepressant (NaSSA)—although, clinically, no one class or agent is more effective in treating depression than another. There is great interindividual variability from one class of medication to another, as well as among medications within the same class.

Intuitively, this implies that patients who don't respond or tolerate one agent from a particular class may do well on another agent in the same class, although this is by no means guaranteed. Similarly, switching to a medication from a different class might work better, although results from large naturalistic studies like STAR*D don't always support this either. Finally, combining medications from two classes—while theoretically appealing—often does not result in an additive benefit.

Antidepressants can be effective not only for treating depressive disorders, but also for anxiety disorders (TCAs, SSRIs), bulimia (fluoxetine), smoking cessation (bupropion), ADHD (bupropion), fibromyalgia (duloxetine), diabetic neuropathic pain (duloxetine), and premenstrual dysphoric disorder (SSRIs). Their ease of use and wide range of approved indications make them some of the most prescribed medications in the world.

Side effects of antidepressant medications vary. TCAs can be sedating, and cause weight gain and anticholinergic side effects (dry mouth, constipation). MAOIs can cause weight gain, sexual side effects, and edema. SSRIs may cause headache, nausea, and diarrhea, particularly early in therapy (first 1 to 2 weeks); patients generally become tolerant of these effects. More long-term side effects of SSRIs include sexual side effects and apathy. SNRIs are similar to SSRIs in their side effect profiles. See fact sheets for further details on individual agents.

There are some side effects or warnings which apply to **all** antidepressants. They are listed here in order to minimize repetition in the fact sheets that follow.

Suicide Risk:

A black box warning regarding an increased risk of suicidal ideation in children and adolescents was added to the labeling for all antidepressants by the FDA in 2004. The warning was based on retrospective reports that showed a very slight increase in suicidal ideation in patients on nine different antidepressants. The warning was revised in 2007 to apply also to adolescents and young adults, up to age 24. Since then, more prospective data have emerged that do not support an association, and this warning has been called further into question. In fact, the data suggest that severity of depression itself is associated with increased risk of suicide. For now, however, the warning remains, and is applied to the labeling of all medications approved for the treatment of depression. Thus, you should monitor all patients closely—especially early in therapy or after medication discontinuation—for clinical worsening, changes in behavior, or suicidality.

Mania Switch:

Activation of mania or hypomania may occur with the use of any antidepressant in individuals who are at risk. Antidepressants should be used with caution in patients with a history of mania or hypomania, or in those with a family history of bipolar disorder.

Serotonin Syndrome:

A rare but potentially life-threatening serotonin syndrome (agitation, hallucinations, other mental status changes, hyperthermia, tachycardia, labile BP, myoclonus, hyperreflexia, incoordination, nausea, vomiting, diarrhea) has been reported when serotonergic antidepressants have been used with other serotonergic agents (including SSRIs, SNRIs, buspirone, lithium, MAOIs).

Discontinuation Syndrome:

Abrupt discontinuation of antidepressants, particularly SSRIs and SNRIs, may result in a discontinuation syndrome. While not medically dangerous and generally self limiting, the discontinuation syndrome may be uncomfortable for patients. Symptoms include dizziness, nausea, headache, irritability, insomnia, diarrhea, agitation, sensory disturbances (eg, electric shock sensations), lethargy and abnormal dreams. In general,

symptoms are more severe with higher dose antidepressant use and longer term antidepressant use. Agents that are particularly short-acting may have a higher likelihood of causing a discontinuation syndrome (eg, paroxetine, venlafaxine IR) compared to longer-acting agents (eg, fluoxetine). In cases of planned discontinuation, antidepressant dose should be gradually reduced.

Bleeding Risk:

Increased bleeding episodes (eg, GI bleed, bruising, nosebleed) have been reported with serotonergic antidepressants, particularly when they are used concomitantly with aspirin, NSAIDs, anticoagulants, or antiplatelet agents.

TABLE 2: ANTIDEPRESSANTS

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg)	Usual Adult Dosage Range (starting–max) (mg)
Selective Serotonin Reuptake Inhibitor (SSRI)			
Citalopram (Celexa) 1998	MDD	10, 20, 40; 10/5mL	20–40
Escitalopram (Lexapro) 2002	MDD, GAD	5, 10, 20, 5/5mL	10–20
Fluoxetine (Prozac) 1987	MDD, OCD, panic disorder, bulimia, PMDD	10, 20, 40, 60, 20/5mL	20–80
Fluoxetine DR (Prozac Weekly) 2001	MDD, OCD, panic disorder, bulimia	90 DR	90 Qweek
Fluvoxamine (Luvox) 1994	OCD	25, 50, 100	50–300
Fluvoxamine ER (Luvox CR) 2008 generic not available	OCD	100, 150 ER	100–300
Paroxetine (Paxil) 1992 (Pexeva) 2003 (Brisdelle) 2013	MDD, OCD, panic disorder, social anxiety, GAD, PTSD, PMDD, menopausal hot flashes	7.5 (Brisdelle), 10, 20, 30, 40, 10/5mL	20–50
Paroxetine CR (Paxil CR) 1999	MDD, panic disorder, PTSD, PMDD	12.5, 25, 37.5	25–62.5
Sertraline (Zoloft) 1991	MDD, OCD, panic disorder, PTSD, PMDD, social anxiety	25, 50, 100, 20/mL	50–200
Serotonin Norepinephrine Reuptake Inhibitor (SNRI)			
Desvenlafaxine (Khedezla, Pristiq) 2008	MDD	50, 100 ER	50–100
Duloxetine (Cymbalta) 2004 generic approved Dec 2013	MDD, GAD	20, 30, 60 DR	30–120
Levomilnacipran (Fetzima) 2013 generic not available	MDD	20, 40, 80, 120 ER	20–120
Venlafaxine 1993 Effexor discontinued in early 2014	MDD	25, 37.5, 50, 75, 100	75–375
Venlafaxine ER (Effexor XR) 1997	MDD, GAD, social anxiety disorder, panic disorder	37.5, 75, 150, 225 ER	75–225

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg)	Usual Adult Dosage Range (starting–max) (mg)
Tricyclic Antidepressant (TCA)			
Amitriptyline (Elavil) 1961	MDD	10, 25, 50, 75, 100, 125, 150	50–300
Clomipramine (Anafranil) 1989	OCD	25, 50, 75	25–250
Desipramine (Norpramin) 1964	MDD	10, 25, 50, 75, 100, 150	50–300
Nortriptyline (Pamelor) 1977	Depression	10, 25, 50, 75, 10/5mL	25–150
Monoamine Oxidase Inhibitor (MAOI)			
Isocarboxazid (Marplan) 1959 generic not available	MDD	10	20–60
Phenelzine (Nardil) 1961	MDD	15	45–90
Selegiline transdermal (EMSAM) 2006 generic not available	MDD	6, 9, 12/24 h patch	6/24h–12/24h
Tranylcypromine (Parnate) 1961	MDD	10	30–60
Dopamine Norepinephrine Reuptake Inhibitor			
Bupropion (Wellbutrin) 1985	MDD, seasonal affective disorder, smoking cessation	75, 100	200–450
Bupropion SR (Wellbutrin SR, Budeprion SR) 1996	MDD	100, 150, 200	150–400
Bupropion XL (Wellbutrin XL, Forfivo XL) 2003	MDD, seasonal affective disorder	150, 300 (Wellbutrin XL), 450 (Forfivo XL)	150–450
Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)			
Mirtazapine (Remeron) 1996	MDD	7.5, 15, 30, 45	15–45
Mirtazapine ODT (Remeron SolTab) 2001	MDD	15, 30, 45	15–45
Serotonin Reuptake inhibitor and 5-HT2A and 5-HT2C Antagonist			
Trazodone (No brand on market) 1981	MDD	50, 100, 150, 300	50–600
Trazodone ER (Oleptro) 2010 generic not available	MDD	150, 300	150–375

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg)	Usual Adult Dosage Range (starting–max) (mg)
Serotonin Reuptake Inhibitor and 5-HT1A Agonist			
Vilazodone (Viibryd) 2011 generic not available	MDD	10, 20, 40	10–40
Serotonin Reuptake Inhibitor and 5-HT1A Agonist, 5-HT1B Partial Agonist, and 5-HT3 & 5-HT7 Antagonist			
Vortioxetine (Brintellix) 2013 generic not available	MDD	5, 10, 15, 20	10–20

BUPROPION (Aplenzin, Budeprion SR and XL, Buproban, Forfivo XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban) Fact Sheet

FDA Indications:

major depression; seasonal affective disorder; smoking cessation.

Dosing:

- Supplied as:
  - 75 mg, 100 mg unscored IR tablets as **Wellbutrin** (GSK) and generic.
  - 100 mg, 150 mg, 200 mg SR unscored tablets (HCl salt) as **Wellbutrin SR** (GSK) and generic.
  - 100 mg, 150 mg SR tablets as **Budeprion SR** (Teva) branded generic.
  - 150 mg, 300 mg XR tablets as **Wellbutrin XL** (GSK), **Budeprion XL** (150 mg only) and generic.
  - 450 mg XR tablets as **Forfivo XL** (Edgemont).
  - 150 mg SR tablets as **Zyban** (GSK) and **Buproban** (Teva) branded generic.
- Hydrobromide salt formulation:
  - 174 mg, 348 mg, 533 mg XR tablets as **Aplenzin** (Sanofi-Aventis) (equivalent to 150, 300, 450 mg of HCl salt, respectively).
- Depression (target dose 300 mg/day):
  - IR: start 100 mg BID, ↑ to 100 mg TID after >3 days; max dose 450 mg/day, 150 mg/dose, separate doses by at least 6 hours.
  - SR: start 150 mg QAM, ↑ to 150 mg BID as early as fourth day; max dose 400 mg/day, 200 mg/dose, separate doses by at least 8 hours.
  - XL: start 150 mg QAM, ↑ to 300 mg QAM as early as fourth day; max dose 450 mg QAM. Give dose as early in the morning as possible to minimize insomnia.
- Cost (for one month supply at 400–450 mg/day, priced Jan 2014):
  - Bupropion (generic): $46.01
  - Wellbutrin: $385.79
  - Bupropion SR (generic): $31.70
  - Wellbutrin SR: $393.06
  - Bupropion XL (generic): $31.70
  - Wellbutrin XL: $1,048.84
  - Forfivo XL: $176.10

Side Effects:

- Most common (most bothersome in bold): agitation, **insomnia, headache,** nausea, vomiting, tremor, tachycardia, dry mouth, weight loss.
- Serious but rare: seizures; risk higher with rapid and large dose increases and in patients at risk for seizures.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2B6; also inhibits CYP2D6; t ½: 21 hours.
- Avoid use with MAOIs. Levels of drugs metabolized by CYP2D6 (eg, paroxetine, fluoxetine, aripiprazole, iloperidone, atomoxetine, beta blockers) may be increased.

Clinical Pearls:

- Used off-label for ADHD (children >6 years and adults) and bipolar depression.
- Risk of seizure depends on dose and formulation: IR: 300 mg/day–450 mg/day (0.4%) vs 450 mg/day–600 mg/day (4%). SR/ XL: 100 mg/day–300 mg/day (0.1%) vs 400 mg/day (0.4%). Do not chew, divide, or crush SR or XL tablets as risk of seizures may be increased.

Not-So-Fun Fact:

There have been case reports of teenagers and prisoners snorting crushed tablets (believing it to be a stimulant), with subsequent seizures.

Bottom Line:

May be particularly useful for individuals whose depression is associated with fatigue and poor concentration. Absence of sexual side effects and weight gain make this an appealing option for many depressed patients; seizure risk is not a concern for most patients when dosed appropriately.

DESVENLAFAXINE (Khedezla, Pristiq) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Supplied as 50 mg, 100 mg XR tablets as **Khedezla** (Par), **Pristiq** (Pfizer), and as generic.
- Depression: Start at 50 mg QD. Doses up to 400 mg/day have been studied; flat dose response curve for efficacy (no added benefit to doses >50 mg/day but increase in side effects).
- Cost (for one month supply at 50 mg/day, priced Feb 2014):
  - Desvenlafaxine (generic): $126.90
  - Pristiq: $191.59

Side Effects:

- Most common (most bothersome in bold): **nausea, dizziness, insomnia**, excessive sweating, constipation, dry mouth, somnolence, decreased appetite, anxiety, and sexual side effects.
- Serious but rare: dose-related increases in systolic and diastolic blood pressure. Monitor BP regularly, and if increases are sustained, consider reducing dose or discontinuing.

Pharmacokinetics and Drug Interactions:

- Active metabolite of venlafaxine, metabolized primarily through conjugation and oxidation via CYP3A4 (minor). Minimally inhibits CYP2D6; t ½: 11 hours.
- Avoid use with MAOIs, other serotonergic medications. Not likely to cause other clinically significant interactions.

Clinical Pearls:

- Desvenlafaxine is the principal active metabolite of venlafaxine. In clinical trials, desvenlafaxine has not been shown to be any more effective than venlafaxine. Unlike venlafaxine, increasing the dose of desvenlafaxine beyond the recommended 50 mg/day may not improve response, as no clear dose-response relationship has been shown. However, increasing desvenlafaxine dose clearly leads to greater side effects.
- Do not cut, crush, chew, or dissolve; swallow extended-release tablets whole with fluid.
- Claims of fewer drug interactions with desvenlafaxine are likely unimportant for the majority of patients as the risk of clinically significant interactions with venlafaxine is already relatively low.
- Currently, desvenlafaxine is available as the succinate salt (Pristiq), desvenlafaxine base (both generic and Khedezla), and desvenlafaxine fumarate extended-release tablets. What is the difference among these products? Other than solubility and clinically insignificant differences in half-life, nothing. Clinical data in the package inserts for the newer products are all based on the original desvenlafaxine succinate studies so no new clinical data were made available for approval.

Fun Fact:

Desvenlafaxine has not been approved for any indication in the European Union whose FDA-equivalent expressed concern that desvenlafaxine seemed to be less effective than venlafaxine with no advantages in terms of safety and tolerability.

Bottom Line:

For the majority of patients, no real advantage to using desvenlafaxine over other agents, particularly venlafaxine XR.

DULOXETINE (Cymbalta) Fact Sheet

FDA Indications:

major depression; generalized anxiety disorder; diabetic peripheral neuropathic pain; fibromyalgia; chronic musculoskeletal pain (including osteoarthritis and chronic low back pain).

Dosing:

- Supplied as 20 mg, 30 mg, 60 mg DR capsules as **Cymbalta** (Eli Lilly) and as generic.
- All Indications: Start at 40 mg–60 mg/day; dose may be divided (20 or 30 mg BID) or given as a single daily dose; target dose 60 mg QD; for doses >60 mg/day, titrate in increments of 30 mg/day over 1 week to a maximum of 120 mg/day, although doses >60 mg/day not shown to be more effective.
- Cost (for one month supply at 60 mg/day, priced Mar 2014):
  - Duloxetine (generic): $131
  - Cymbalta: $235.36

Side Effects:

- Most common (most bothersome in bold): **nausea**, **dry mouth**, **constipation, diarrhea**, **decreased appetite,** vomiting, **fatigue, somnolence**, insomnia, dizziness, asthenia, agitation, sweating, headache, and sexual side effects.
- Serious but rare: rare cases of hepatic failure (including fatalities) have been reported. Hepatitis with abdominal pain, hepatomegaly, elevated transaminases >20 times normal, with and without jaundice observed. May cause orthostatic hypotension or syncope, especially in first week of therapy and after dose increases. Urinary retention reported; hospitalization and/or catheterization were necessary in some cases.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP1A2 and 2D6. Inhibitor of CYP2D6; t ½: 12 hours.
- Avoid use with MAOIs, other serotonergic medications. Caution with drugs metabolized by CYP2D6 (eg, paroxetine, fluoxetine, aripiprazole, iloperidone, atomoxetine, beta blockers) as their levels may be increased. Potent inhibitors of CYP2D6 (eg, paroxetine, fluoxetine, quinidine) and CYP1A2 (eg, fluvoxamine, ciprofloxacin) may increase duloxetine levels.

Clinical Pearls:

- Swallow delayed-release capsules whole; do not chew or crush. Although the manufacturer does not recommend opening capsule, contents may be sprinkled on applesauce or in apple juice and swallowed immediately.
- Avoid in patients with a history of heavy alcohol use or chronic hepatic disease because of the possibility that duloxetine and alcohol may interact to cause hepatic injury or that duloxetine may aggravate preexisting hepatic disease.

Fun Fact:

Duloxetine is approved in Europe for stress urinary incontinence, but the FDA refused this indication in the US because of concerns regarding liver toxicity and potential suicidal ideation.

Bottom Line:

Although compared to SSRIs or venlafaxine, duloxetine may be as effective for response and remission, it can cause more side effects, is potentially hepatotoxic, and has a higher risk for significant drug interactions; not for first line use.

LEVOMILNACIPRAN (Fetzima) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Supplied as 20 mg, 40 mg, 80 mg, 120 mg ER capsules as **Fetzima** (Forest).
- Start at 20 mg QD. Increase to 40 mg QD after 2 days, then by increments of 40 mg/d every 2 or more days to a maximum dose of 120 mg QD.
- Cost (for one month supply at 120 mg/day, priced Feb 2014):
  - Fetzima: $218.88

Side Effects:

- Most common (most bothersome in bold): **nausea,** vomiting, **constipation, sweating,** increased heart rate (7–9 beats/minute), erectile dysfunction, and urinary hesitation.
- Serious but rare: urinary retention, increased blood pressure and tachycardia possible.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 12 hours.
- Avoid use with MAOIs, other serotonergic medications. Use lower doses (no more than 80 mg/d) in presence of potent 3A4 inhibitors.

Clinical Pearls:

- This is the most recently approved antidepressant with three 8-week studies showing efficacy compared to placebo at doses of 40, 80 and 120 mg/day. No studies comparing to other antidepressants are available to date.
- According to the manufacturer, levomilnacipran has greater potency for norepinephrine reuptake inhibition than for serotonin reuptake inhibition.
- Noradrenergic effects may contribute to urinary hesitation or retention in about 4–6% of patients and is dose-related.
- Do not cut, crush, chew, or dissolve; swallow extended-release tablets whole with fluid.

Fun Fact:

Levomilnacipran is an enantiomer of milnacipran (Savella, also a Forest drug), an SNRI approved for use in the US in patients with fibromyalgia. Milnacipran has not shown robust antidepressant efficacy and does not have that indication in the US though it is used for depression in other countries.

Bottom Line:

More experience will give us a better understanding of the ideal dose and this drug's place in therapy. Until then, consider as second line SNRI.

MIRTAZAPINE (Remeron, Remeron SolTab) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Supplied as:
  - 15 mg (scored), 30 mg (scored), 45 mg tablets as **Remeron** (Merck) and generic.
  - 15 mg, 30 mg, 45 mg orange-flavored orally disintegrating tablets as **Remeron SolTab** (Merck) and generic.
  - 7.5 mg tablets as generic.
- Start 15 mg QHS, ↑ to 15–45 mg/day, ↑ dose every 1–2 weeks. Maximum 45 mg/day.
- Cost (for one month supply at 30 mg/day, priced Jan 2014):
  - Mirtazapine (generic): $13.60
  - Remeron: $161.62
  - Remeron SolTab: $127.45

Side Effects:

- Most common (most bothersome in bold): **somnolence, increased appetite, weight gain.**
- Serious but rare: agranulocytosis or severe neutropenia (with or without infection) reported very rarely.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP1A2, 2D6, and 3A4; t ½: 20–40 hours.
- Avoid use with MAOIs, other serotonergic agents. Caution with inducers of 1A2 or 3A4 (eg, carbamazepine), which could reduce efficacy of mirtazapine.
- May reduce antihypertensive effect of α2-agonists (eg, clonidine); avoid concurrent use. If combination cannot be avoided, monitor blood pressure.

Clinical Pearls:

- Used off-label for anxiety disorders, insomnia, nausea, and as appetite stimulant.
- Classified as a noradrenergic and specific serotonergic antidepressant (NaSSA) because it functions as central presynaptic α2-adrenergic antagonist, which increases noradrenergic and serotonergic activity, but also has specific and potent 5-HT2 and 5-HT3 antagonism.
- If patients experience too much sedation at initial lower dose, increase dose; mirtazapine has increased noradrenergic effect relative to antihistaminergic effect at higher doses.
- Do not split or break orally disintegrating tablets; place on tongue to dissolve and swallow with saliva; drinking liquid not necessary.

Fun Fact:

Esmirtazapine, the (S)-enantiomer, was under development for the treatment of insomnia and hot flashes associated with menopause but the company pulled the plug in 2010.

Bottom Line:

This is one of the most underutilized antidepressants, likely due to concerns over weight gain (which is only a bit more than most SSRIs). It is particularly useful in depressed patients with anxiety, insomnia, those who have had sexual side effects with other antidepressants and those who may benefit from appetite stimulation (eg, elderly, cancer patients).

MONOAMINE OXIDASE INHIBITORS (MAOIs) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Isocarboxazid (Marplan):
  - Supplied as 10 mg scored tablets as **Marplan** (Validus Pharmaceuticals).
  - Start 10 mg BID, ↑ by 10 mg/day every 2–4 days, to 40 mg/day by end of the first week (divided BID–QID). After first week, may ↑ by up to 20 mg to maximum of 60 mg/day. Use caution in patients on >40 mg/day.
- Phenelzine (Nardil):
  - Supplied as 15 mg unscored tablets as **Nardil** (Pfizer).
  - Start 15 mg TID, ↑ by 15 mg/day every 2–4 days, up to 60 mg–90 mg/day divided TID.
- Tranylcypromine (Parnate):
  - Supplied as 10 mg unscored tablets as **Parnate** (Covis Pharmaceuticals) and generic.
  - Start 10 mg TID, ↑ by 10 mg/day every 2–3 weeks to maximum of 60 mg/day.
- Cost (for one month supply at 30 mg/day (isocarboxazid); 60 mg/day (phenelzine); 60 mg/day (tranylcypromine), priced Jan 2014):
  - Marplan: $200.15
  - Phenelzine (generic): $78.46
  - Nardil: $164.36
  - Tranylcypromine (generic): $363.34
  - Parnate: $1,077.55

Side Effects:

- Most common (most bothersome in bold): **dizziness, headache, orthostatic hypotension,** dry mouth, constipation, drowsiness, tremor, sweating, peripheral edema, sexual side effects.
- Serious but rare: hypertensive crisis may occur (see drug interactions).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through liver, limited data though likely through oxidative CYP450; t ½ irrelevant as it is an irreversible inhibitor; effects continue for 2 weeks after discontinued.
- Avoid with other antidepressants, serotonergic agents, stimulants, sympathomimetics, dextromethorphan, disulfiram, meperidine. Do not use within 5 weeks of fluoxetine discontinuation or 2 weeks of other antidepressant discontinuation. Discontinue at least 10 days prior to elective surgery. Antihypertensives may exaggerate hypotensive effects.
- Avoid use with foods or supplements high in tyramine, tryptophan, phenylalanine, or tyrosine. Examples include aged cheese, air-dried or cured meats (eg, salami), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce, or spoiled foods.

Clinical Pearls:

- Historically, MAOIs have shown benefit for atypical depression, characterized by overeating, oversleeping, rejection sensitivity, and mood reactivity. Used off-label for anxiety, panic disorder, social anxiety disorder.
- Phenelzine and isocarboxazid are hydrazine MAOIs; tranylcypromine is a nonhydrazine. Roughly, 20 mg of tranylcypromine = 40 mg of isocarboxazid = 45 mg phenelzine.
- Monoamine enzymes are irreversibly inhibited by these MAOIs; regeneration of enzymes takes two to three weeks after discontinuation; thus, 2 week period required when switching from MAOI to another antidepressant.

Fun Fact:

Hydrazine MAOIs were the first antidepressants developed, after patients given iproniazid (a drug for tuberculosis) were found to have an elevated mood.

Bottom Line:

Not commonly used due to side effects, dietary restrictions and drug interactions; however, MAOIs should be considered for appropriate patients who do not tolerate or respond to other antidepressants.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) Fact Sheet

See SSRI tables on following page for **medication names, FDA indication(s), off-label use, supplied as, costs, dosing information, pharmacokinetics, and drug interactions.** (Year of FDA approval can be found in the antidepressant table on page 23.)

Side Effects:

- Most common (most bothersome in bold; SSRI with highest incidence in parentheses): nausea, **insomnia** (fluoxetine), sedation (paroxetine), anxiety (fluoxetine), constipation (paroxetine), headache, **sexual side effects**, **weight gain** (paroxetine), apathy.
- Serious but rare: SSRIs have been associated with the development of SIADH: hyponatremia has been reported (including severe cases with serum sodium <110 mmol/L); predominately in the elderly; volume depletion and/or concurrent use of diuretics likely increases risk.
- Avoid use with MAOIs (5-week washout period with fluoxetine, 2-week washout period with all others); avoid other serotonergic agents (serotonin syndrome). Caution with anticoagulants, antiplatelet agents and non-steroidal anti-inflammatory drugs which may increase risk for bleeding episodes. Fluoxetine, fluvoxamine, and paroxetine most likely to cause clinically significant P450 interaction.

Clinical Pearls:

- All SSRIs are generally equivalent in terms of efficacy, and medication selection is usually made on the basis of side effect profile, potential for drug-drug interactions, insurance coverage, patient preference.
- Citalopram maximum daily dose reduced by FDA in August 2011 due to data suggesting increased QTc interval prolongation at doses >40 mg/day. Mean QTc interval prolongation at 60 mg/d was 18.5 msec (vs ziprasidone which has been shown to increase this interval by 20.6 msec). As of this writing, no comparable warning issued for escitalopram.
- Escitalopram (and its racemic mixture, citalopram) is considered the "purest" SSRI and has few, if any, drug-drug interactions.
- Fluoxetine favored in patients who could use some activation; most likely to cause insomnia, anxiety, decreased appetite.
- Fluvoxamine used less often due to twice daily dosing, risk for drug interactions, and fewer data for uses other than OCD even though likely just as effective.
- Paroxetine least favored due to side effect profile (greatest sexual side effects, anticholinergic effects including constipation) and drug interaction profile although it is most sedating.
- Generally, higher doses of SSRI required for treating OCD.
- Use lower initial dose for patients with anxiety disorders, particularly panic disorder.
- SSRIs sometimes prescribed off-label for menopausal symptoms (hot flashes), somatoform disorders, pain syndromes, migraines, and premature ejaculation.

Fun Fact:

SSRIs were the first class of psychotropic drugs discovered using the process called rational drug design, a process that starts with a specific biological target and then creates a molecule designed to affect it.

Bottom Line:

SSRIs have become a mainstay for the treatment of patients with depression and anxiety disorders. Consider as first line treatment for many patients and be familiar with at least a couple of agents within the class.

TABLE 3: Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic Name (Brand Name) *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg unless where noted)	Usual Dosage Range (starting–max) (mg)	Off-label use	Price for one month supply at max target dose (priced Feb 2014)
Citalopram (Celexa)	MDD	10, 20, 40 tabs, 10/5mL	20 QD–40 QD Increase by 20 mg/d in 7d	OCD, PTSD, social anxiety, GAD, panic disorder	Citalopram: $4 Celexa: $171.41
Escitalopram (Lexapro)	MDD (12+ yrs), GAD	5, 10, 20 tabs, 5/5mL	10 QD–20 QD Increase by 10 mg/d in 7d	OCD, PTSD, social anxiety, panic disorder	Escitalopram: $10.60 Lexapro: $191.97
Fluoxetine (Prozac, Prozac Weekly, Sarafem)	MDD (8+ yrs), OCD (7+ yrs), panic disorder, bulimia, PMDD	10, 20, 40, 60 caps/tabs; 90 mg DR; 20/5mL	20 QAM–80 QAM (Starting dose DR: 90 Qweek) Increase 10 mg/d after several weeks	PTSD, social anxiety	Fluoxetine: $8; $108.57 (DR) Prozac: $961.11 Prozac Weekly: $158.36 Sarafem: $1,181.38
Fluvoxamine (Luvox, Luvox CR) generic not available for CR	OCD (8+ yrs), social anxiety (CR)	25, 50, 100 tabs; 100, 150 mg XR	50 QHS–300 QHS (Starting dose CR: 100 QHS) Increase by 50 mg/d Qweek	MDD	Fluvoxamine: $31; $464.02 (ER) Luvox CR: $856.15
Paroxetine (Brisdelle, Paxil, Paxil CR, Pexeva)	MDD, OCD, panic disorder, social anxiety, GAD, PTSD, PMDD, menopausal hot flashes (Brisdelle)	10, 20, 30, 40 tabs; 10/5mL; 12.5, 25, 37.5 mg XR; 7.5 (Brisdelle)	20 mg QHS–50 QHS CR: 25 QD–62.5 QD Increase by 10 mg/d Qweek; CR: 12.5 mg/d Qweek	None	Paroxetine: $11.80; $151.25 (ER) Paxil: $232.45 Paxil CR: $291.76 Pexeva: $505.57
Sertraline (Zoloft)	MDD, OCD (6+ yrs), panic disorder, PTSD, PMDD, social anxiety	25, 50, 100 tabs; 20/mL	50 QD–200 QD Increase by 50 mg/d Qweek	GAD	Sertraline: $11.26 Zoloft: $351.52

Table 3.1: Pharmacokinetics and Drug Interactions of SSRIs

SSRI	Metabolized by (major pathways in bold)	Inhibits (potent inhibition in bold)	Elimination half life
Citalopram	**2C19, 3A4**	2D6 (weak)	35 h
Escitalopram	**2C19, 2D6, 3A4**	2D6 (weak)	27–32 h
Fluoxetine	**2D6**	**2C9/19, 2D6,** 3A4	4–6 days fluoxetine; 9 days norfluoxetine (metabolite)
Fluvoxamine	**1A2, 2D6**	**1A2, 2C19, 3A4**	15 h
Paroxetine	**2D6**	**2D6**	21 h
Sertraline	**2C19**, 2D6, 3A4	2D6 (weak), 3A4 (weak)	26 h

SELEGILINE TRANSDERMAL (EMSAM) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Supplied as 6 mg, 9 mg, 12 mg/24 hour patch (total selegiline 20 mg, 30 mg, 40 mg, respectively) as **EMSAM** (Dey Pharma).
- Start 6 mg/24 hours QD; may ↑ in increments of 3 mg/24 h every 2 weeks up to a maximum of 12 mg/24 hours.
- Apply to clean, dry, intact skin to upper torso (below neck and above waist), upper thigh, or outer surface of upper arm; apply at the same time each day and rotate application sites; wash hands with soap and water after handling; avoid touching sticky side of patch.
- Cost (for one month supply at 9 mg/24 hour patch per day, priced Jan 2014):
  - Emsam: $1,053.05

Side Effects:

- Most common (most bothersome in bold): headache, **insomnia, application site reaction,** hypotension, **diarrhea,** dry mouth, weight loss.
- Serious but rare: orthostatic hypotension; caution in patients at risk (elderly, cerebrovascular disease, cardiovascular disease, hypovolemia).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2B6 to active (N-desmethylselegiline, amphetamine, methamphetamine) and inactive metabolites; t ½: 18–25 hours.
- Avoid with other antidepressants, serotonergic agents, stimulants, sympathomimetics, dextromethorphan, disulfiram, meperidine. Do not use within 5 weeks of fluoxetine discontinuation or 2 weeks of other antidepressant discontinuation. Discontinue at least 10 days prior to elective surgery. Antihypertensives may exaggerate hypotensive effects. Avoid use with foods or supplements high in tyramine, tryptophan, phenylalanine, or tyrosine.
- Wait 2 weeks after discontinuing transdermal selegiline before initiating therapy with serotonergic or any other contraindicated drug.

Clinical Pearls:

- Oral selegiline (Eldepryl) used in Parkinson's disease (≤10 mg/day) is a selective inhibitor of MAO-B, which metabolizes dopamine. When used transdermally as EMSAM, selegiline achieves higher blood levels and non-selectively inhibits both MAO-A and MAO-B. Its antidepressant effect is thought to be due to its MAO-A inhibition, which blocks the breakdown of other centrally-active neurotransmitters (norepinephrine, serotonin).
- When using 6 mg/day patch, no special diet required. When using higher doses, tyramine-restricted diet should be followed.
- Patch may contain conducting metal (eg, aluminum); avoid exposure of application site to external heat source, which may increase the amount of drug absorbed.

Fun Fact:

Named "EmSam" after Emily and Samuel, the children of the CEO of Somerset Pharmaceuticals (original manufacturer).

Bottom Line:

The only commercially available transdermal antidepressant; may be appropriate in those rare patients who cannot tolerate oral administration. Generally better tolerated than older MAOIs, and dietary concerns pose a somewhat lesser risk, but caution must still be exercised regarding drug interactions. When MAOI indicated, this may be least risky and easiest to try.

TRAZODONE (Oleptro) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Supplied as:
  - 50 mg, 100 mg, 150 mg, 300 mg scored tablets as generic only (Desyrel brand no longer available).
  - 150 mg, 300 mg scored ER tablets as **Oleptro** (Angelini Labopharm).
- Depression:
  - IR formulation: start 50 mg TID; ↑ by 50 mg/day every 3–4 days to response (usually 300–400 mg/day); maximum dose 600 mg/day.
  - ER formulation: start 150 mg QHS, ↑ by 75 mg/day every 3 days; maximum dose 375 mg/day.
- Insomnia (off-label): start 25 mg–50 mg QHS; may ↑ by 50 mg increments up to 200 mg QHS.
- Cost (for one month supply at 300 mg/day, priced Nov 2013):
  - Trazodone (generic): $16
  - Oleptro: $208, Target Pharmacy

Side Effects:

- Most common (most bothersome in bold): **drowsiness,** dry mouth, **dizziness** or lightheadedness, orthostatic hypotension, headache, blurred vision, nausea, or vomiting.
- Serious but rare: reports of priapism (painful erection >6 hours in duration); may require surgical or pharmacologic (eg, epinephrine) intervention and may result in impotence or permanent impairment of erectile function. Orthostatic hypotension and syncope reported (less at hypnotic doses). Concomitant administration of antihypertensive therapy may require dose reduction of antihypertensive(s).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4 to active metabolite (mCPP); Induces P-glycoprotein; t ½: 7–10 hours.
- Avoid use with MAOIs; dabigatran (Pradaxa): P-glycoprotein inducers (like trazodone) may decrease the serum concentration of dabigatran. Caution with inhibitors or inducers of CYP3A4: potential for altered trazodone concentrations.

Clinical Pearls:

- If daytime drowsiness occurs, administer the majority of dosage at bedtime or ↓ dose.
- Trazodone's hypnotic effects are not due to anticholinergic nor antihistaminergic effects.
- IR formulation rarely used as antidepressant due to risk for oversedation and orthostasis at therapeutic doses; majority of IR use currently is for insomnia.
- ER tablet: swallow whole or separate tablet along the score line; do not crush or chew.

Fun Fact:

As a consequence of the production of mCPP as a metabolite, patients taking trazodone may test positive on urine tests for the presence of MDMA (ecstasy).

Bottom Line:

Fewer sexual side effects and less weight gain compared to other serotonergic antidepressants make this drug appealing for depression. But significant daytime somnolence and dizziness (even with ER formulation), as well as questionable efficacy for depression at doses ≤375 mg/day limit utility of trazodone in depression. Trazodone continues to be a go-to drug for many patients with insomnia.

VENLAFAXINE (Effexor XR) Fact Sheet

FDA Indication:

major depression; social anxiety disorder; GAD; panic disorder.

Dosing:

- Supplied as:
  - 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg scored tablets as generic.
  - 37.5 mg, 75 mg, 150 mg, 225 mg XR capsules as **Effexor XR** (Pfizer) and generic.
- Depression:
  - Start 75 mg/day in 2–3 divided doses or as XR once daily; ↑ dose by 75 mg/day at intervals of 4 or more days; maximum 375 mg/day (divided TID) or 225 mg/day of XR given once daily. IR may be switched to nearest equivalent daily dose of XR QD.
- Anxiety:
  - XR: start 75 mg QD, ↑ by 75 mg/day at weekly intervals; maximum 225 mg/day; for panic disorder, to minimize exacerbation of panic, start 37.5 mg QD, ↑ to 75 mg QD after one week then by 75 mg/day at weekly intervals; max 225 mg/day.
- Cost (for one month supply at 150 mg/day, priced Mar 2014):
  - Venlafaxine (generic): $25.38; $19.25 (XR)
  - Effexor XR: $242.98

Side Effects:

- Most common (most bothersome in bold): anorexia, constipation, dizziness, dry mouth, **nausea**, **nervousness**, somnolence, sweating, **sexual side effects**, headache, insomnia.
- Serious but rare: sustained, dose-related hypertension reported. May cause hyponatremia or SIADH; use with caution in patients who are volume-depleted, elderly, or taking diuretics.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2D6 to O-desmethylvenlafaxine (ODV), major active metabolite (an SNRI, marketed as Pristiq) and also by CYP3A4; t ½: 5 hrs (11 hrs for ODV).
- Avoid use with MAOIs, other serotonergic agents. Caution with CYP2D6 or 3A4 inhibitors, which may increase venlafaxine levels. Inhibits CYP2D6.

Clinical Pearls:

- Used off-label for diabetic neuropathy and menopause-associated hot flashes.
- Do not divide, crush, or chew XR capsule. Can open and sprinkle on small amount of applesauce; swallow immediately and drink water to ensure all pellets are swallowed.
- For patients with nausea, start at lower dose, titrate more slowly and give with food.
- May cause false-positive PCP in urine drug screen.
- Because of possibility of modest increase in systolic BP, control preexisting hypertension before starting venlafaxine and regularly monitor BP.
- Significant discontinuation syndrome, even with XR formulation.
- Theoretically functions as an SSRI in low doses (75 mg/day), an SNRI in moderate doses (150 mg–225 mg/day), and affects all monoamines in high doses (>225 mg/day).
- No additional benefit seen with doses >225 mg/day in moderately depressed outpatients, but patients with more severe depression may respond to higher doses (350 mg/day).

Fun Fact:

Venlafaxine is structurally related to the atypical opioid analgesic tramadol (Ultram) (itself a serotonergic agent), but not to any other antidepressant drugs.

Bottom Line:

May be a good alternative for patients who have failed or not tolerated an SSRI; good choice for patients with comorbid anxiety disorder or severely depressed patients who may respond to a high dose of venlafaxine.

VILAZODONE (Viibryd) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Supplied as 10 mg, 20 mg, 40 mg unscored tablets as **Viibryd** (Forest).
- Start 10 mg QD for 7 days; ↑ to 20 mg QD for 7 days, then to recommended dose of 40 mg QD (with food). Purpose of dose titration is to minimize GI effects. 20 mg/day may not be effective so it is important to get patients to the target dose of 40 mg/day.
- Cost (for one month supply at 40 mg/day, priced Nov 2013):
  - Viibryd: $156, Sam's Club

Side Effects:

- Most common (most bothersome in bold): **diarrhea, nausea,** vomiting, dry mouth, insomnia, dizziness.
- Serious but rare: possible hyponatremia or SIADH; use with caution in patients who are volume-depleted, elderly, or taking diuretics.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 25 hours.
- Avoid use with MAOIs, other serotonergic agents. More P450 drug interactions possible with vilazodone than some other SSRIs: 3A4 inhibitors (may require dose reduction of 50%) or inducers can affect vilazodone metabolism. Vilazodone inhibits 2D6 moderately: may increase levels of 2D6 substrates (eg, stimulants, aripiprazole, duloxetine, atomoxetine, paroxetine, fluoxetine, risperidone, beta blockers, many others).

Clinical Pearls:

- Giving with food minimizes GI effects and doubles levels compared to taking on empty stomach.
- Mechanism of action suggests vilazodone will act like SSRI in combination with buspirone (5-HT1A partial agonist); benefit of this, if any, over existing antidepressants remains to be seen.

Fun Fact:

In an unprecedented move, the FDA published an article in the *Journal of Clinical Psychiatry* essentially warning practitioners not to believe the marketing hype about vilazodone. In reviewing the data submitted to the FDA, they dispelled two myths: vilazodone does not work faster and it does not have a lower sexual side effect burden.

Bottom Line:

This really just appears to be another SSRI (with a little buspirone thrown in). It has no proven advantages over other SSRIs, and it has special dosing and titration issues that present challenges that are absent in other SSRIs and may have a drug interaction burden that other SSRIs do not. For these reasons, we recommend that you relegate vilazodone to second-line status in your quiver of remedies.

VORTIOXETINE (Brintellix) Fact Sheet

FDA Indication:

major depression.

Dosing:

- Supplied as 5 mg, 10 mg, 15 mg, 20 mg immediate-release tablet as **Brintellix** (Lundbek/Takeda).
- Start at 10 mg QD; ↑ to 20 mg QD as tolerated. Consider 5 mg/day for those unable to tolerate higher doses.
- Cost (for one month supply at 20 mg/day, priced Feb 2014):
  - Brintellix: $235.36

Side Effects:

- Most common (most bothersome in bold): **nausea,** constipation, vomiting, sexual side effects, dry mouth, headache.
- Serious but rare: serotonergic antidepressants have been rarely associated with bruising or bleeding; caution in patients at risk.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP 2D6 and, to a lesser extent, via 3A4/5, 2C9/19, 2A6, 2C8 and 2B6; t ½: 66 hours.
- Avoid use with MAOIs, other serotonergic medications. Use lower doses (no more than 10 mg/d) in presence of potent 2D6 inhibitors.

Clinical Pearls:

- The most recently approved antidepressant, this is a "multimodal" antidepressant or a "serotonin modulator and stimulator." This means it has effects on more than one receptor site (like several other antidepressants). Mostly, it works as a serotonin reuptake inhibitor with agonism at 5-HT1A receptors (think buspirone and aripiprazole). The partial agonism at 5-HT1B receptors and antagonism at 5-HT3A, 5-HT1D and 5-HT7 receptors are of unknown clinical significance. Theoretically (based on animal data), 5-HT7 antagonism may produce pro-cognitive effects but there are no adequate clinical data to support such a claim.
- Negative findings in some studies were attributed to dose being too low (5–10mg/d). Higher dose studies showed vortioxetine to be as effective as duloxetine and as effective as agomelatine, a European antidepressant not approved by the FDA for use in the US due to difficulties in convincingly showing efficacy.

Fun Fact:

Brintellix received the FDA's approval without deliberation by a scientific advisory panel, the usual public review of an investigational drug's safety and effectiveness.

Bottom Line:

More experience will give us a better understanding of this drug's place in therapy and if it really is different than other serotonergic antidepressants. Until then, consider it a second line agent due to higher cost and less experience.

Antipsychotics: "New" is the New Old

At last count, there were 10 atypical antipsychotics on the market, and more than a dozen older, "typical" agents. Until very recently, antipsychotics have been churned out at the rate of about one per year. All antipsychotics, new and old, have essentially the same primary mechanism of action: they block dopamine type 2 (D2) receptors. The atypical antipsychotics also block the serotonin 2A receptor, 5HT2A, so they're sometimes called D2/5HT2A blockers (or serotonin-dopamine antagonists, SDAs) for short.

The first-generation antipsychotics like haloperidol and perphenazine are relatively pure D2 blockers. The problem with indiscriminate blockade of D2 is that this can cause movement disorders (labeled "extrapyramidal symptoms" to distinguish these involuntary movements from the voluntary movements arising from the pyramidal tract). Similar to what is seen in Parkinson's disease, extrapyramidal symptoms result from D2 blockade in the nigrostriatal pathway, where dopamine is required for fluid movement.

Movement problems are—in theory, at least—less of a problem with the atypicals because, in addition to blocking D2, they also block the 5HT2A receptor. And what does serotonin have to do with anything? The theory is that serotonin and dopamine (DA) have a seesaw relationship with one another: when serotonin goes up, DA levels fall via feedback inhibition. Thus, blocking serotonin receptors causes extra DA release, partly compensating for the DA blockade. When this happens in the nigrostriatal pathway, the negative effects of antipsychotics on movement are prevented. Of course, this same thing may happen in mesolimbic pathways, but this appears not to substantially interfere with the antipsychotic properties of these drugs, for as-yet unclear reasons.

A different, although related, explanation for the more beneficial effect of atypicals on movement is that they appear to bind much more loosely to the dopamine D2 receptor. In other words, they transiently bind to D2 receptors and then rapidly dissociate to allow for normal dopamine signaling to take place. This "fast-off" theory of atypical action may explain why atypicals show fewer extrapyramidal side effects at doses that still confer antipsychotic efficacy (Seeman P, *Can J Psychiatry* 2002;47:27–38).

There are no differences in clinical efficacy between atypicals and typicals, though there are rather dramatic side effect differences, one of the main conclusions from the CATIE trial (Lieberman JA, et al, *N Engl J Med* 2005;353(12):1209–1233). Although manufacturers of the newest agents may tout advantages for negative symptoms, the field has recently pretty much put to rest the myth that atypicals are more effective than older antipsychotics for negative symptoms. This apparent effect was an artifact of the methodology of clinical trials, and the fact that untreated extrapyramidal effects can look a bit like negative symptoms.

Nevertheless, if you are like most American psychiatrists, more than 90% of your antipsychotic prescriptions are for atypicals (vs less than 50% for your British colleagues). This may be due to our concern over the remote possibility of tardive dyskinesia (TD)—more of a hazard with the first-generation antipsychotics—rather than side effects more commonly seen with atypicals, such as weight gain and hyperlipidemia. Moreover, many atypicals have been approved for disorders such as bipolar disorder, depression, and a smattering of others (see table 6 for FDA indications), and, not surprisingly, have been marketed aggressively.

All of the atypical antipsychotics carry the same FDA class warnings. Rather than repeating all of these concerns on each fact sheet, we will mention the warnings here. Again, be aware that these apply to all atypical antipsychotic agents.

In 2003, the FDA required all manufacturers of atypical antipsychotics to revise their package labeling to reflect the potential risks for weight gain, hyperglycemia, new onset or worsening diabetes, and hyperlipidemias. While this has become a class warning, it's clear that there are a handful of really bad actors here: clozapine and olanzapine are the worst, quetiapine and risperidone less so. Patient-specific factors may also play a role. In general, the incidence and severity of weight gain and metabolic effects appear to be greater in the pediatric population.

A 2004 consensus statement from the American Psychiatric Association and American Diabetes Association recommends the following monitoring protocol for patients on atypical agents. These are the minimal recommendations for monitoring; obviously, more frequent monitoring—for example, in individuals with elevated triglycerides or blood sugar—may be more appropriate for your patients.

TABLE 4: APA/ADA Monitoring Protocol for Patients on SGAs

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	x					x	
Weight (BMI)	x	x	x	x	x		
Waist circumference	x					x	
Blood pressure	x			x		x	
Fasting plasma glucose	x			x		x	
Fasting lipid profile	x			x			x

- A black-box warning for all agents in this class suggests a substantially **higher mortality rate in geriatric patients with dementia-related psychosis** receiving atypical antipsychotics (4.5%) compared with those receiving placebo (2.6%). Although most fatalities resulted from cardiac-related events (eg, heart failure, sudden death) or infections (mostly pneumonia) as opposed to a clearly direct effect of medication, atypical antipsychotics are *not* approved for the treatment of dementia-related psychosis and such use should be avoided or minimized when possible.
- **Adverse cerebrovascular events** (eg, stroke, TIA), sometimes fatal, have been reported in geriatric patients (73–97 years of age) with dementia-related psychosis. The FDA has issued a black-box warning on atypical antipsychotics to reflect this risk; several studies have shown that cerebrovascular event risk is elevated with typical antipsychotics, as well.

Other warnings that should be considered for all antipsychotic agents (atypicals as well as typical agents) include the following:

- **Neuroleptic malignant syndrome (NMS),** a potentially fatal syndrome characterized by fever, severe muscle rigidity, and autonomic instability, has been reported in patients receiving antipsychotic agents. Treatment requires immediate discontinuation of the drug and intensive symptomatic treatment in a hospital setting.
- **Tardive dyskinesia (TD),** a syndrome of potentially irreversible, involuntary dyskinetic movements, has been reported. TD is more common with first-generation antipsychotics than with atypical agents.
- **Extrapyramidal and withdrawal symptoms** in the newborn have been reported with maternal use of typical antipsychotics during third trimester. Symptoms in the newborn may include agitation, feeding disorder, hypertonia or hypotonia, respiratory distress, and somnolence. These effects vary in severity and may be self-limiting (subsiding within hours or days) or require hospitalization.

Table 5: TYPICAL ANTIPSYCHOTICS

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg)	Dosage Equivalents	Usual Dosage Range (starting–max) (mg)	EPS and Akathisia	Anticholinergic	Relative Sedation and Orthostasis	Notes
Chlorpromazine (Thorazine) 1957	Psychosis, mania, nausea/vomiting	10, 25, 50, 100, 200	100	50–600	Low	Moderate	High	Injectable available; photosensitivity
Fluphenazine (Prolixin, Prolixin Decanoate) 1960	Psychosis	1, 2.5, 5, 10	2	2–20	Very high	Low	Low	Oral solution; injectables (short and LAI) available
Haloperidol (Haldol, Haldol Decanoate) 1967	Psychosis	0.5, 1, 2, 5, 10, 20	2	2–20	Very high	Very low	Low	Oral solution; injectables (short and LAI) available
Loxapine (Adasuve, Loxitane) 1975	Schizophrenia	5, 10, 25, 50	10	20–100	High	Low	Moderate	10 mg oral inhalation powder available as Adasuve since 2012; available only in enrolled health care facilities
Perphenazine (Trilafon) 1957	Psychosis, severe nausea/vomiting	2, 4, 8, 16	8	8–64	High	Low	Low	Mid-potency agent studied and compared to atypicals in CATIE (see Fact Sheet)
Thioridazine (Mellaril) 1962	Psychosis	10, 15, 25, 50, 100, 150, 200, 100 mg/ml	100	50–600	Low	High	High	Oral solution available; QT prolongation; irreversible retinal pigmentation at >800mg/d
Thiothixene (Navane) 1967	Psychosis	1, 2, 5, 10, 20	4	5–40	High	Low	Low	High-potency agent
Trifluoperazine (Stelazine) 1959	Psychosis, non-psychotic anxiety	1, 2, 5, 10	5	5–40	High	Low	Low	High-potency agent

TABLE 6: ATYPICAL ANTIPSYCHOTICS

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s) (pediatric ages specified where relevant)	Available Strengths (mg)	Usual Dosage Range (starting–max) (mg)*	Weight Gain and Metabolic Effects	EPS and Akathisia	QT Prolongation	Notes
Aripiprazole (Abilify, Abilify Discmelt) 2002 generic not available	Schizophrenia (13+) Bipolar mania, monotherapy and adjunctive (10+) Bipolar maintenance, monotherapy and adjunctive Depression adjunct Irritability in autism (6–17) Agitation in schizophrenia or bipolar (IM only)	Tablet: 2, 5, 10, 15, 20, 30 ODT: 10, 15 Liquid: 1 mg/ml IM: 9.75 mg/1.3ml LAI: 300 and 400 extended release injectable suspension (see Fact Sheet)	10–15 QD	Low	High (mainly akathisia)	Low	Probably most "activating"
Asenapine (Saphris) 2009 generic not available	Schizophrenia Bipolar mania, monotherapy and adjunctive	Tablet: 5, 10 (sublingual only)	5–10 BID	Moderate	Moderate	Low	Avoid food or drink for 10 minutes after taking; sedating
Clozapine (Clozaril, FazoClo) 1989	Treatment-resistant schizophrenia Recurrent suicidal behavior in schizophrenia or schizoaffective disorders	Tablet: 12.5, 25, 50, 100, 200 ODT: 12.5, 25, 100, 150, 200	150–300 BID	High	Low	Low	Probably most effective AP
Iloperidone (Fanapt) 2009 generic not available	Schizophrenia	Tablet: 1, 2, 4, 6, 8, 10, 12	6–12 BID	Moderate	Low	Moderate/High	Orthostatic dizziness
Lurasidone (Latuda) 2010 generic not available	Schizophrenia Bipolar depression	Tablet: 20, 40, 60, 80, 120	40–160 QD	Low/Moderate	Moderate	Low	Sedating; take with food
Olanzapine (Zyprexa, Zyprexa Zydis) 1996	Schizophrenia (13+) Bipolar mania, monotherapy and adjunctive (13+) Bipolar maintenance, monotherapy Agitation in schizophrenia or bipolar (IM only)	Tablet: 2.5, 5, 7.5, 10, 15, 20 ODT: 5, 10, 15, 20 IM Injection: 10 mg/vial LAI: Relprevv (see Fact Sheet)	10–20 QD	High	Low/Moderate	Low	

Paliperidone (Invega) 2006 generic not available	Schizophrenia (12+) Schizoaffective disorder	ER Tablet: 1.5, 3, 6, 9 LAI: Sustenna (see Fact Sheet)	6–12 QD	Moderate	High	Moderate	Good for those with hepatic impairment; increases prolactin
Quetiapine (Seroquel) 1997 (Seroquel XR) 2007 generic not available in ER formulation	Schizophrenia (13+) Bipolar mania, monotherapy and adjunctive (10+) Bipolar disorder maintenance Bipolar depression Depression adjunct (approved in ER form)	Tablet: 25, 50, 100, 200, 300, 400 ER Tablet: 50, 150, 200, 300, 400	150–750 QD; divided BID to TID 400–800 QHS for XR	Moderate	Low	Low	Sedating
Risperidone (Risperdal, Risperdal M-Tab) 1993	Schizophrenia (13+) Bipolar mania, monotherapy and adjunctive (10+) Irritability in autism (ages 5–16)	Liquid: 1 mg/ml Tablet: 0.25, 0.5, 1, 2, 3, 4 ODT: 0.25, 0.5, 1, 2, 3, 4 LAI: Consta (see Fact Sheet)	2–6 divided QD to BID	Moderate	High	Low	Increases prolactin
Ziprasidone (Geodon) 2001 generic not available in IM or oral suspension formulations	Schizophrenia Bipolar mania, monotherapy Bipolar maintenance adjunctive Agitation in schizophrenia (IM injection)	Capsule: 20, 40, 60, 80 Liquid: 10 mg/ml IM Injection: 20 mg/ml	120–160 divided BID	Low	Low	High	Take with food

ODT = orally disintegrating tablet LAI = long-acting injectable ER, XR = extended release *For schizophrenia indication

ARIPIPRAZOLE (Abilify, Abilify Discmelt) Fact Sheet

FDA Indications:

schizophrenia (adults, adolescents 13–17 years); bipolar disorder, acute treatment of manic and mixed episodes (adults, children 10–17 years); bipolar disorder, maintenance treatment (adults); major depression, as adjunct (adults); irritability in autism spectrum disorder (children 6–17 years); acute agitation in schizophrenia or bipolar disorder (IM).

Dosing:

- Supplied as 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg unscored tablets as **Abilify** (Bristol Myers Squibb/Otsuka); 1 mg/ml oral solution; 10 mg, 15 mg oral disintegrating tablets as **Abilify Discmelt** (Bristol Myers Squibb/Otsuka); 9.75 mg/1.3 ml IM injection; 300 mg and 400 mg extended release injectable suspension as **Abilify Maintena** (Bristol Myers Squibb/Otsuka) (see table on page 50).
- Schizophrenia and bipolar disorder (adults): Start and target dose is 10 mg–15 mg/day (maximum 30 mg/day).
- Depression (adults): start 2 mg/day–5 mg/day, ↑ to 15 mg/day, if necessary, as adjunct. Titrate gradually to prevent agitation/akathisia and at intervals >2 weeks.
- Oral solution and tablet equivalent up to 25 mg; for 30 mg tablets, give 25 mg oral solution.
- Orally disintegrating tablets and tablets bioequivalent; place tablet in mouth immediately; tablet dissolves rapidly in saliva; may be swallowed with or without liquid; do not split.
- Dosing of IM formulation: 9.75 mg as a single dose (range: 5.25 mg–15 mg); repeated doses may be given at ≥2 hour intervals to a maximum of 30 mg/day. If ongoing therapy is necessary, transition to oral therapy as soon as possible.
- Cost (for one month supply at 30 mg/day, priced Nov 2013):
  - Abilify: $1,004.55

Side Effects:

- Most common (most bothersome in bold): headache, **sedation (dose-related)**, anxiety, agitation, **akathisia (dose-related)**, insomnia, and nausea.

Pharmacokinetics and Drug Interactions:

- Metabolized by CYP450 2D6 and 3A4; t ½: 3 to 6 days.
- Most potential drug interactions unlikely to be of significant clinical concern although carbamazepine may decrease levels and paroxetine, fluoxetine may increase levels.

Clinical Pearls:

- As a dopamine partial agonist, it has been suggested that aripiprazole works as a dopamine agonist at low doses and as an antagonist at higher doses, although this is purely speculative.
- The combination of aripiprazole with other antipsychotics was shown to be no more effective than monotherapy in psychosis.
- Some prescribers use low-dose aripiprazole to counteract antipsychotic-induced prolactinemia, given its partial agonist properties, but there is little evidence for this strategy.

Fun Fact:

Otsuka is already studying brexpiprazole, another dopamine partial agonist, in clinical trials for depression, schizophrenia, and ADHD.

Bottom Line:

Good choice for minimizing risk of weight gain and metabolic side effects, but beware of akathisia. The large number of FDA-approved indications and anecdotal reports of success at a variety of doses make it difficult to predict how each patient will respond at a given dose and for a given indication.

ASENAPINE (Saphris) Fact Sheet

FDA Indications:

schizophrenia; bipolar disorder, acute treatment of manic or mixed episodes.

Dosing:

- Supplied as 5 mg, 10 mg sublingual tablets as **Saphris** (Merck), regular and black cherry flavors.
- Schizophrenia: Start at 5 mg SL BID. Target dose = 5 mg SL BID.
- Bipolar (adults): Start at 5 mg SL BID. Target dose = 10 mg SL BID. Max dose = 10 mg SL BID.
- Administered sublingually due to low bioavailability (<2%) and extensive first-pass metabolism with swallowing of tablets; SL administration increases bioavailability to 35%.
- Avoid food or drink for 10 minutes after taking (they reduce absorption and bioavailability significantly). Do not cut, crush, swallow, or chew.
- Use dry hands when handling tablets; do not remove sublingual tablet from blister pack until just prior to administration; peel back colored tab to expose the tablet; do *not* push tablet through blister pack; gently remove tablet and place *under* tongue, then allow to dissolve completely (usually takes about 10 seconds).
- Cost (for one month supply at 10 mg BID, priced Nov 2013):
  - Saphris: $738.44

Side Effects:

- Most common (most bothersome in bold): **akathisia** (seems to be dose-related), oral hypoesthesia (numbing of the tongue or decreased oral sensitivity), **somnolence**, dizziness, extrapyramidal symptoms other than akathisia, weight gain.
- Serious but rare: hypersensitivity reactions including anaphylaxis, angioedema, low blood pressure, rapid heart rate, swollen tongue, difficulty breathing, wheezing, or rash; orthostatic hypotension and syncope, particularly early in treatment (FDA warning, 9/2011).

Pharmacokinetics and Drug Interactions:

- Metabolized by glucuronidation and CYP450 1A2; inhibitor of 2D6; t ½: 24 hours.
- Caution with antihypertensive agents and other drugs that can cause additive hypotension or bradycardia. May double paroxetine levels.

Clinical Pearls:

- Has a receptor-binding profile similar to clozapine, although asenapine has very little anticholinergic activity. Weight gain does seem to be a problem in many patients.

Fun Fact:

Black cherry flavor developed after patients complained about original tablets.

Bottom Line:

No clear, distinct advantage over other atypical antipsychotics. For most patients, SL administration and twice daily dosing make this agent less easy to use than other agents. Mouth numbness, sedation, dizziness, akathisia, weight gain, and potential for allergic reaction are significant liabilities. Not recommended for first-line use.

CLOZAPINE (Clozaril, FazaClo) Fact Sheet

FDA Indications:

treatment-resistant schizophrenia; reduction in risk of suicide in schizophrenia and schizoaffective disorder.

Dosing:

- Supplied as:
  - 25 mg, 100 mg scored tablets as **Clozaril** (Novartis).
  - 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg scored generic tablets.
  - 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg orally disintegrating tabs as **FazaClo** (Azur) and generic (12.5 mg, 25 mg, 100 mg only).
- Start 12.5 mg once or twice daily; ↑ gradually, in increments of 25–50 mg/day to target dose of 300–450 mg/day; may ↑ further in increments ≤100 mg and no more frequently than once or twice weekly. May require doses as high as 600–900 mg/day; maximum is 900 mg/day (usually in 2–3 divided doses). May take 4–6 weeks, or as long as 3–6 months, for response.
- If dosing is interrupted for ≥48 hours, must be retitrated from 12.5mg/day–25 mg/day; may be increased more rapidly than initial titration, as tolerated.
- Cost (for one month supply at 400 mg/day, priced Jan 2014):
  - Clozapine (generic): $132.93
  - Clozaril: $1,343.56

Side Effects:

- Most common (most bothersome in bold): **sedation**, orthostatic hypotension, **hypersalivation** (place towel on pillow), **weight gain** (15–30 pound average weight gain after one year), **constipation** (risk of toxic megacolon if untreated), tachycardia (can treat with propranolol).
- Serious but rare: potentially life-threatening agranulocytosis (1%–2%); periodic WBC testing (see prescribing information for monitoring details) must occur. Anticholinergic effects. Myocarditis, pericarditis, pericardial effusion, cardiomyopathy, and heart failure. Dose-related seizures. Rare cases of thromboembolism, including pulmonary embolism.

Pharmacokinetics and Drug Interactions:

- Metabolized by several CYP450 1A2, 2D6 and 3A4; t ½: 12 hours.
- Avoid use with drugs that may cause bone marrow suppression (eg, carbamazepine) and lower seizure threshold. Collapse, respiratory arrest, and cardiac arrest reported during initial clozapine treatment in patients taking benzodiazepines. Inhibitors of 1A2 (eg, fluvoxamine), 2D6 (eg, paroxetine, fluoxetine, quinidine) and 3A4 (eg, erythromycin) may increase clozapine levels. Inducers of 1A2 (eg, smoking) and 3A4 (eg, St. John's wort) may decrease.

Clinical Pearls:

- Not first-line treatment; should fail at least two trials of other antipsychotic treatment.
- Risk of agranulocytosis greatest within first 6 months, then incidence declines but can still occur. Register patients with Clozaril National Registry to ensure no prior agranulocytosis.
- Divided doses may minimize some adverse effects (eg, hypotension, seizures, sedation).
- To discontinue, reduce dose gradually over one to two weeks or longer to minimize rebound cholinergic effects (eg, headache, nausea, vomiting, diarrhea) and rebound psychosis.

Fun Facts:

The Quiet Room is a compelling memoir written by a patient, Lori Schiller, who was one of the early users of clozapine.

Bottom Line:

The only drug with convincing evidence, and years of clinical experience, to help treatment-resistant schizophrenia. It should probably be considered earlier in such patients' treatment course rather than subjecting them to endless trials of "me too" atypicals or complicated and ineffective combinations of antipsychotics.

ILOPERIDONE (Fanapt) Fact Sheet

FDA Indication:

schizophrenia.

Dosing:

- Supplied as 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg unscored tablets as **Fanapt** (Novartis).
- Start 1 mg BID; ↑ to 2 mg BID on day 2 and then daily by 4 mg/day to a target dose of 6 mg–12 mg BID daily; maximum dose is 12 mg BID.
- Cost (for one month supply at 10 mg BID, priced Nov 2013):
  - Fanapt: $746.04

Side Effects:

- Most common (most bothersome in bold): **dizziness (dose-related)**, dry mouth, fatigue, nasal congestion, **orthostatic hypotension** (can minimize by gradual dose titration), **somnolence**, tachycardia (dose-related), moderate weight gain.
- Serious but rare: relatively moderate to high risk of QTc prolongation (risk is increased in patients taking potent CYP2D6 or 3A4 inhibitors, or at higher doses); avoid use in patients with bradycardia, history of MI, hypokalemia, hypomagnesemia, or comcomitant use of other drugs which prolong QTc. Relatively modest elevations in prolactin concentrations reported. Priapism reported rarely.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP 2D6 (major) and 3A4 (minor); t ½: 18 hours (33 hours in poor metabolizers).
- Avoid concomitant use of other drugs known to prolong the QTc interval.
- Potent inhibitors of CYP 2D6 (eg, paroxetine, fluoxetine, quinidine) or 3A4 (eg, ketoconazole, clarithromycin) may increase iloperidone levels; in such cases, decrease iloperidone dose by 50%.

Clinical Pearls:

- Must follow initial titration schedule if treatment has been interrupted for >3 days.
- Minimal data regarding uses other than schizophrenia.

Fun Fact:

Iloperidone was initially on track for FDA approval in 2002 but its approval was delayed to 2009 due to multiple company mergers and out-licensing deals as well as the FDA's request for more data.

Bottom Line:

Not recommended as first-choice agent due to twice daily dosing, need for titration, QT prolongation (at least as much as ziprasidone), dizziness, moderate weight gain, and increases in blood sugar and because it appears less efficacious than other antipsychotics.

LONG-ACTING INJECTABLE (LAI) Antipsychotics

See LAI table on the following page for **FDA indication(s), medication names, costs, available as, dosing information, pharmacokinetics, clinical pearls,** and **notes**.

General Notes on LAIs:

- Establish efficacy and tolerability with corresponding oral agent prior to initiation of long-acting IM therapy.
- Avoid use (absolute contraindication) in patients with history of neuroleptic malignant syndrome (NMS) on any antipsychotic.
- Full therapeutic effect may not be seen for several months; caution to not adjust LAI dose prematurely.
- Cost-effective, especially for patients who fail to adhere to oral treatment; for patients stabilized on long-acting antipsychotic, may see decreased relapse rates, fewer/shorter hospitalizations for acute exacerbations.

Clinical Pearls:

- **Fluphenazine—**Watch for hypotension; long history of use; good choice for patients who tolerate and respond to oral but do not adhere to medication. Less favored than haloperidol decanoate due to less predictable pharmacokinetics and twice monthly injections.
- **Haloperidol—**Monthly injection preferable to others which require twice monthly dosing. Low cost, long history of use make this a first line LAI in patients who tolerate and respond to oral but do not adhere to medication.
- **Aripiprazole—**Newest LAI on market; monthly dosing and minimal oral overlap make it appealing choice.
- **Olanzapine—**Post-injection delirium/sedation syndrome: sedation (including coma) and delirium (agitation, anxiety, confusion, disorientation) observed; associated with rapid rise in serum levels; administer at registered healthcare facility where patients continuously monitored (≥3 hours) for symptoms; highest risk in first hour but may occur after 3 hours; risk is cumulative with each injection; recovery expected by 72 hours. After 3-hour monitoring, patient must be escorted; no driving for remainder of the day. Restricted use requires registration, paperwork with Eli Lilly's program. High cost, restriction of use, monitoring requirement and risk of adverse outcome limit use severely.
- **Paliperidone—**Full effect not seen for several months; more difficult to use with two separate loading injections; however no oral overlap is an advantage. Less painful injection than Consta or Relprevv. Expensive; difficult to justify using over less costly alternatives.
- **Risperidone—**Vehicle used in injectable has rarely been associated with retinal artery occlusion in patients with abnormal arteriovenous anastomosis (eg, patent foramen ovale). 3-week oral overlap and requirement for refrigeration make this LAI more difficult to use.

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TABLE 7: LONG-ACTING INJECTABLE ANTIPSYCHOTICS

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths	Dosing Initiation	Oral Overlap	Maintenance Dose	Pharmacokinetics	Administration Notes	Cost for Monthly Supply at Average Dose (March 2014)
Typical Antipsychotics								
Fluphenazine decanoate (Prolixin Decanoate) 1972	Schizophrenia	25 mg/ml in sesame oil suspension	1.25x total daily oral dose Q2–3 weeks	For 2–3 days, then ↓ by 50% every 2–3 days until discontinued	Dose adjustments should be made in increments of 12.5 mg; do not exceed 100 mg per dose	t ½ = 7–14 days; peak = 2–3 days	Deltoid or dorsal gluteal; can be painful; advise patient to remain recumbent for 30 min to prevent hypotension	1 vial, 5 ml of 25 mg/ml Generic: $99.33 Relative monthly cost for 25 mg Q2 weeks: $40
Haloperidol decanoate (Haldol Decanoate) 1986	Schizophrenia	50 mg/ml and 100 mg/ml in sesame oil suspension	10–20x total oral daily dose Q4 weeks First dose should be ≤100 mg; if higher dose needed, give remainder in 1–2 weeks	With usual oral dose and by 50% weekly	10–15x total oral daily dose Q4 weeks	t ½ = 21–30 days; peak = 7 days	Deltoid or dorsal gluteal; can be painful; do not exceed 3 ml per injection site or 450 mg per month	150 mg/month Generic: $54.65 Haldol Deconoate: $231.29
Atypical Antipsychotics								
Aripiprazole (Abilify Maintena) 2013 generic not available	Schizophrenia	300 mg and 400 mg vials of ER injectable suspension	400 mg Q4 weeks	For 14 days	400 mg Q4 weeks; decrease to 300 mg Q4 weeks if side effects	t ½ = 30–46 days; peak = 5–7 days	Gluteal	400 mg/month Abilify Maintena: $1,582.43
Olanzapine (Zyprexa Relprevv) 2009 generic not available	Schizophrenia	210, 300, and 405 mg vials of ER suspension in powder	10 mg/day oral: 210 mg Q2 weeks x 4 doses or 405 mg Q4 weeks x 2 doses; 15 mg/day oral: 300 mg Q2 weeks x 4 doses; 20 mg/day oral: 300 mg Q2 weeks	No overlap	10 mg/day oral: 150 mg Q2 weeks or 300 mg Q4 weeks; 15 mg/day oral: 210 mg Q2 weeks or 405 mg Q4 weeks; 20 mg/day oral: 300 mg Q2 weeks; Maximum dose: 300 mg Q2 weeks or 405 mg Q4 weeks	t ½ = 30 days; peak = 7 days	Gluteal; must be reconstituted according to manufacturer's directions (on kit); must obtain a new kit if aspiration of blood occurs	300 mg Q2 weeks $1,979.98

Paliperidone palmitate (Invega Sustenna) 2009 generic not available	Schizophrenia	Prefilled syringes of 39, 78, 117, 156, and 234 mg of ER suspension	234 mg IM in deltoid, then 156 mg one week later	No overlap	117 mg 3 weeks after 2nd dose then Q month (maintenance given deltoid or gluteal) Approx. equivalence: 3 mg oral: 39–78 mg 6 mg oral: 117 mg 12 mg oral: 234 mg	t 1/2 = 25–49 days; peak = 13 days	First 2 injections deltoid; then deltoid or gluteal; prior to injection, shake syringe for >10 seconds to ensure homogenous suspension	117 mg/month Invega Sustenna: $967.74
Risperidone (Risperdal Consta) 2003 generic not available	Schizophrenia; bipolar, manic/mixed	12.5, 25, 37.5, and 50 mg of ER polymeric microspheres in powder	25 mg Q2 weeks Dose adjustments should not be made more frequently than Q4 weeks	With usual oral dose for 3 weeks	Approx. equivalence: <4 mg/day oral: 25 mg 4–6 mg/day oral: 37.5 mg >6 mg/day oral: 50 mg Maximum dose: 50 mg Q2 weeks	t ½ = 3–6 days	Deltoid or gluteal; alternate sides Q2 weeks; use needle provided in kit. Kit must be stored in refrigerator; bring to room temperature prior to reconstitution. Reconstitute with provided diluent only; use within 6 hours. Shake vigorously for ≥10 seconds to ensure a homogeneous suspension.	25 mg Q2 weeks Risperdal Consta: $649.81

LURASIDONE (Latuda) Fact Sheet

FDA Indications:

schizophrenia; bipolar depression.

Dosing:

- Supplied as 20 mg, 40 mg, 80 mg, 60 mg, 120 mg unscored tablets as **Latuda** (Sunovion).
- Schizophrenia: start 40 mg QD, with food (at least 350 calories); no titration required. Maximum dose 160 mg QD.
- Bipolar depression: start 20 mg QD, with food (at least 350 calories); no titration required. Maximum dose 120 mg QD, although doses >80 mg/day rarely more effective.
- Cost (for one month supply at 80 mg/day, priced Nov 2013):
  - Latuda: $1,258

Side Effects:

- Most common (most bothersome in bold): **sedation (dose-related)**, **akathisia (dose-related)**, nausea, parkinsonism, agitation.
- Serious but rare: orthostatic hypotension and syncope reported (rarely).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP450 3A4; t ½: 18 hours.
- Avoid use with medications which cause orthostasis, potent 3A4 inhibitors (eg, ketoconazole) or inducers (eg, rifampin). Exercise caution/monitor when using in combination with moderate 3A4 inhibitors (eg, diltiazem); use maximum dose of 40 mg/day in patients taking moderate 3A4 inhibitors.

Clinical Pearls:

- Administration with food (at least 350 calories) increases bioavailability roughly threefold; fat content of meal is not important.
- Appears to be relatively weight-neutral and cardiometabolic parameters little affected in company-sponsored trials, although post-marketing observations have been limited.

Fun Fact:

One unique feature of Latuda is its high affinity for the 5-HT7 receptor, which has been linked to depression, learning/memory, cognition, anxiety, and pain. Unfortunately, to date, Latuda has shown no clear benefit over other atypical antipsychotics on these measures.

Bottom Line:

This drug offers some advantages including no need for titration, once daily dosing, relatively low-moderate metabolic profile, and relatively low QTc prolongation risk. However, need to administer with ≥350 calories of food, potential for drug interactions, and side effects including sedation, akathisia, and EPS limit its use. In clinical practice, you might lump lurasidone with the other atypicals that cause little weight gain, such as aripiprazole and ziprasidone.

OLANZAPINE (Zyprexa, Zyprexa Zydis) Fact Sheet

FDA Indications:

schizophrenia (adults and children >13 years); acute or mixed bipolar I manic episodes, as monotherapy or adjunct (adults and children >13 years); maintenance treatment of bipolar disorder; bipolar depression (with fluoxetine, sold as Symbyax); treatment-resistant unipolar depression (with fluoxetine); acute agitation in schizophrenia and bipolar mania (injectable form).

Dosing:

- Supplied as:
  - 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg tablets (unscored) as **Zyprexa** (Eli Lilly) and generic.
  - 5 mg, 10 mg, 15 mg, 20 mg orally disintegrating tablets as **Zyprexa Zydis** (Eli Lilly) and generic.
  - 10 mg IM injection as **Zyprexa IM** (Eli Lilly) and generic.
  - 210 mg, 300 mg, 405 mg long-acting injection as **Zyprexa Relprevv** (Eli Lilly) (see table on page 50).
  - Fixed combination capsules with fluoxetine: 3/25 mg, 6/25 mg, 6/50 mg, 12/25 mg, 12/50 mg olanzapine/fluoxetine, as **Symbyax** (Eli Lilly) and generic.
- Schizophrenia, bipolar disorder, depression: Start most patients at 5 mg–10 mg QD, may ↑ by 5 mg QD, in weekly increments, to target dose of 10 mg–20 mg QD.
- Acute mania (adults and adolescents): Start 10 mg–15 mg QD, may ↑ by 5 mg daily, in 24 hour increments, to target dose of 10 mg–20 mg QD.
- Maximum approved dose: 20 mg/day although doses up to 30 mg/day–50 mg/day have been used.
- Bipolar depression (Symbyax, fixed combination with fluoxetine): Start 6/25 mg QPM, ↑ as indicated to target dose of 6–12/25–50 mg olanzapine/fluoxetine.
- Cost (for one month supply at 20 mg/day, priced Nov 2013):
  - Olanzapine (generic): $21.25, CVS Pharmacy
  - Zyprexa: $1,173.58

Side Effects:

- Most common (most bothersome in bold): **somnolence (dose-related)**, dry mouth (dose-related), constipation, **weight gain** (up to 40% incidence; may be substantial; 10 to 30 pounds weight gain is common), increased appetite, EPS (dose-related).

Pharmacokinetics and Drug Interactions:

- Metabolized by CYP 450 1A2, 2D6 (minor) and direct glucuronidation; t ½: 1 to 2 days.
- CYP1A2 inducers (eg, carbamazepine, ritonavir, smoking) may reduce levels significantly.

Clinical Pearls:

- Use in adolescents ≥13 years of age may result in increased weight gain and sedation, as well as greater increases in LDL cholesterol, total cholesterol, triglycerides, prolactin, and liver transaminase levels when compared to adults.

Fun Fact:

Olanzapine has been studied for chemotherapy-induced nausea and vomiting (helpful).

Bottom Line:

Good efficacy, particularly in acute schizophrenia and bipolar mania, once daily dosing and low risk of QTc interval prolongation make this an appealing drug. However, its high risk for weight gain and metabolic complications make this a second line choice for many.

PALIPERIDONE (Invega) Fact Sheet

FDA Indications:

schizophrenia in adults and children ≥12 years; schizoaffective disorder.

Dosing:

- Supplied as:
  - 1.5 mg, 3 mg, 6 mg, 9 mg osmotic controlled-release tablets (not breakable) as **Invega** (Janssen).
  - 39 mg, 78 mg, 117 mg, 156 mg and 234 mg long-acting injection as **Invega Sustenna** (Janssen) (see table on page 50).
- Schizophrenia/schizoaffective disorder: start 6 mg QAM, which may be the effective dose; if required, may ↑ by 3 mg/day at intervals of >5 days to maximum of 12 mg/day.
- Cost (for one month supply at 12 mg/day, priced Nov 2013):
  - Invega: $1,410.27

Side Effects:

- Most common (most bothersome in bold): **akathisia, EPS (dose-related), tremor, tachycardia**, insomnia, somnolence (especially adolescents), weight gain, orthostatic hypotension, headache, prolactin elevation.
- Serious but rare: modest increase in QTc interval. Orthostatic hypotension and syncope reported. Rarely, controlled-release tablet may get caught in GI tract and cause obstructive symptoms in patients with known strictures; avoid use in patients with severe, preexisting GI narrowing (either pathologic or iatrogenic). Esophageal dysmotility and aspiration possible; use caution in patients at risk for aspiration pneumonia (eg, those with advanced Alzheimer's dementia).

Pharmacokinetics and Drug Interactions:

- Not metabolized by liver; t ½: 23 hours.
- Avoid use with drugs known to prolong the QT interval. Paliperidone is the principal active metabolite of risperidone; therefore avoid use with risperidone. Minimal drug interactions.

Clinical Pearls:

- Invega (and Concerta, see page 18) is an extended release tablet based on the OROS osmotic delivery system: water from GI tract enters through a semipermeable membrane coating the tablet, solubilizing the drug into a gelatinous form which is then expelled through laser-drilled holes in the coating. Shell is nonabsorbable and will be expelled in the stool. Swallow whole, with fluids; do not chew, divide, or crush.
- Studies suggest paliperidone is not highly effective in acute mania either as monotherapy or in combination with lithium or valproate.
- Along with risperidone, causes the most EPS and hyperprolactinemia of all the atypicals.

Fun Fact:

First drug with FDA approval for schizoaffective disorder, allowing Janssen to carve out a new marketing niche and separate this drug from its competitors (at least from a commercial and marketing perspective).

Bottom Line:

Invega looks like risperidone without drug-drug interactions, but with more QT interval prolongation, more tachycardia, possibly more EPS, and the same amount of hyperprolactinemia. Significant disadvantages, including higher cost, make use of this drug difficult to justify.

PERPHENAZINE (Trilafon) Fact Sheet

FDA Indications:

schizophrenia; severe nausea and vomiting.

Dosing:

- Supplied as 2 mg, 4 mg, 8 mg, 16 mg tablets, formerly as **Trilafon** (Schering); now generic only.
- Schizophrenia: start at 4 mg–8 mg TID (8 mg–16 mg BID–QID for hospitalized patients); adjust to lowest effective dose. Dose range 8 mg–16 mg BID–QID; maximum FDA-approved dose for non-hospitalized patients is 24 mg/day, but hospitalized psychotic patients can be dosed up to 64 mg/day.
- Cost (for one month supply at 16 mg/day, priced Nov 2013):
  - Perphenazine (generic): $34.01

Side Effects:

- Most common (most bothersome in bold): **EPS**, headache, **drowsiness**, dry mouth, prolactin elevation (sexual side effects, amenorrhea, galactorrhea).
- Serious but rare: tachycardia (especially with sudden marked increase in dose).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily by CYP2D6; may inhibit CYP2D6. Poor metabolizers of CYP2D6 metabolize the drug more slowly; may have increased effects; t ½: 9 to 12 hours.
- CYP2D6 inhibitors (eg, fluoxetine, paroxetine, quinidine) may increase perphenazine levels. Caution with substrates of 2D6 as perphenazine may increase their levels and effects.

Clinical Pearls:

- Perphenazine is an intermediate-potency conventional (typical) antipsychotic; this leads to less EPS compared to high-potency agents (eg, haloperidol, fluphenazine) and to less anticholinergic side effects compared to low-potency agents (eg, chlorpromazine).
- Fewer metabolic effects (weight gain, glucose, lipids) than some antipsychotics.
- Based on 18-month, randomized trial of 1493 patients with schizophrenia (CATIE trial), perphenazine appears similar in efficacy and EPS compared to atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone). For this reason, we include perphenazine as a representative of the first-generation antipsychotic medications.

Fun Fact:

Perphenazine has long been available in a formulation with amitriptyline (a tricylic antidepressant) called Triavil. This combination antipsychotic/antidepressant was first available in 1965, foreshadowing the next such combination drug (Symbyax) by 38 years.

Bottom Line:

Effective, well-tolerated, and inexpensive alternative to atypical antipsychotics.

QUETIAPINE (Seroquel, Seroquel XR) Fact Sheet

FDA Indications:

schizophrenia (adults and children ≥13 years); bipolar, manic/mixed (adults and children >10 years); bipolar depression; maintenance treatment for bipolar; major depression, as adjunct.

Dosing:

- Supplied as:
  - 25 mg, 50, mg 100 mg, 200 mg, 300 mg, 400 mg unscored tablets as **Seroquel** (Astra Zeneca) and generic.
  - 50 mg, 150 mg, 200 mg, 300 mg, 400 mg unscored extended release tablets as **Seroquel XR** (Astra Zeneca).
- Schizophrenia: Start 25 mg BID or 300 mg XR QD.
- Mania: Start 50 mg BID or 300 mg XR QD.
- Depression: Start 50 mg QD.
- For all Indications: may ↑ dose by 50 mg–100 mg/day increments, given in divided doses, every 1–4 days (or up to 300 mg/day XR increments in intervals of >1 day), to target dose.
- Recommended target dose ranges: schizophrenia: 300–800 mg/day; bipolar mania: 400–800 mg/day; bipolar depression: 300 mg/day; bipolar maintenance: 400–800 mg/day; major depression (adjunct): 300 mg/day (XR). Maximum daily dose in adults: 800 mg/day.
- Consider dosing slower and lower in pediatric, elderly, or debilitated patients.
- Cost (for one month supply at 300 mg/day, priced Nov 2013):
  - Quetiapine (generic): $34.30
  - Seroquel: $794.74, CVS Pharmacy
  - Seroquel XR: $583.07

Side Effects:

- Most common (most bothersome in bold): **somnolence**, hypotension, dry mouth, dizziness, constipation, **weight gain.**
- Serious but rare: orthostatic hypotension, particularly at high dose or with rapid titration.

Pharmacokinetics and Drug Interactions:

- Metabolized by CYP3A4; t ½: 6 hours (XR: 7 hours).
- Avoid use with agents which may cause additional orthostasis. CYP3A4 inducers (eg, carbamazepine) may lower quetiapine levels; CYP3A4 inhibitors (eg, erythromycin, ketoconazole) may increase.

Clinical Pearls:

- Swallow XR tablet whole; do not break, crush, or chew; switch between IR and XR at the same total daily dose; dose adjustments may be necessary based on response and tolerability.
- If patient discontinues drug >1 week, retitrate dose as with initial therapy.
- Quetiapine abuse has been reported, particularly in incarcerated populations.

Fun Fact:

Cataracts developed in initial studies with beagle dogs; human studies have not shown an association. However, the label still recommends a slit-lamp exam every six months.

Bottom Line:

Low risk for EPS and a broad spectrum of efficacy make this an appealing first choice agent. However, sedation,and orthostasis may limit use. Dosing at bedtime, or switching to XR, may help reduce daytime sedation.

RISPERIDONE (Risperdal, Risperdal M-Tab) Fact Sheet

FDA Indications:

schizophrenia (adults and children >13 years); bipolar disorder, manic/mixed (adults and children >10 years); irritability symptoms of autism (children >5 years).

Dosing:

- Supplied as:
  - 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg unscored tablets as **Risperdal** (Janssen) and generic.
  - 1 mg/ml oral solution as **Risperdal** (Janssen) and generic.
  - 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg orally disintegrating tablets as **Risperdal M-Tabs** (Janssen) and generic.
  - 12.5 mg, 25 mg, 37.5 mg, 50 mg long-acting injection as **Risperdal Consta** (Janssen) (see table on page 50).
- Schizophrenia, bipolar (adults): Start 1 mg BID; may ↑ by 1 mg/day–2 mg/day at intervals ≥24 hours to a recommended dosage range of 4 mg/day–6 mg/day; may be given as a single daily dose once maintenance dose achieved. Daily dosages >6 mg provide no additional benefit, only higher risk for EPS, which is dose-dependent.
- Children, elderly, first-episode psychosis: Lower initial dosages (eg, 0.5 mg–1 mg daily) and slower titration to initial target dose of 2 mg daily.
- Autism (children ≥5 years): if <15 kg (33 lbs), use with caution. For 15 kg–20 kg (33 lbs to 44 lbs), start 0.25 mg/day, ↑ to 0.5 mg/day after ≥4 days. If response insufficient, may ↑ by 0.25 mg/day in ≥2 week intervals; give QD or BID. For ≥20 kg (44 lbs), start 0.5 mg/day; may ↑ to 1 mg/day after ≥4 days. If response insufficient, may ↑ dose by 0.5 mg/day in ≥2-week intervals; give QD or BID.
- Bipolar mania or schizophrenia (children): Start 0.5 mg QD; ↑ in increments of 0.5 mg–1 mg/day at intervals ≥24 hours to target dose of 2 mg–3 mg/day; doses >3 mg/day do not confer additional benefit and are associated with increased side effects.
- Cost (for one month supply at 4 mg/day, priced Nov 2013):
  - Risperidone (generic): $21.58
  - Risperdal: $1,141.84

Side Effects:

- Most common (most bothersome in bold): **EPS**, somnolence (particularly in children), anxiety, constipation, nausea, dyspepsia, dizziness, rhinitis, prolactin elevation, **weight gain.**
- Serious but rare: orthostatic hypotension may occur, particularly at higher doses or with rapid titration. Hyperprolactinemia with clinical symptoms (galactorrhea, amenorrhea).

Pharmacokinetics and Drug Interactions:

- Metabolized by CYP2D6; t ½: 20 hours.
- CYP2D6 inhibitors (eg, fluoxetine, paroxetine, quinidine) may increase effects of risperidone. Carbamazepine reduces levels and effects of risperidone.

Clinical Pearls:

- Along with paliperidone, causes the most EPS and hyperprolactinemia of all the atypicals.
- When reinitiating after discontinuation, initial titration schedule should be followed.

Fun Fact:

Risperdal M-tabs are marketed in other countries as Risperdal Quicklets.

Bottom Line:

Risperidone has been widely used and is often used first line. At higher doses (>4 mg/day), risperidone may not provide some of the putative advantages of other atypical antipsychotics, particularly with regard to side effects.

ZIPRASIDONE (Geodon) Fact Sheet

FDA Indications:

schizophrenia; bipolar disorder, acute treatment of manic/mixed episode; maintenance treatment of bipolar disorder as adjunct; acute agitation in patients with schizophrenia (IM only).

Dosing:

- Supplied as:
  - 20 mg, 40 mg, 60 mg, 80 mg capsules (not breakable) and 10 mg/ml oral solution as **Geodon** (Pfizer) and generic (capsules only).
  - 20 mg/ml single-dose vials for injection as **Geodon IM** (Pfizer).
- Schizophrenia, bipolar disorder: Start 20 mg BID (40 mg BID for acute mania) with meals for 2 to 3 days; ↑ by 40 mg/day increments; can usually ↑ rather quickly to target dose of 60 mg–80 mg BID. Maximum approved dose is 160 mg/day though can go higher in some patients; there are some safety data for doses up to 320 mg/day.
- Schizophrenia, acute agitation: (IM injection) 10 mg Q2 hours or 20 mg Q4 hours; maximum 40 mg/day. Replace with oral therapy as soon as possible.
- Cost (for one month supply at 80 mg BID, priced Jan 2014):
  - Ziprasidone (generic): $136.90
  - Geodon: $831.59

Side Effects:

- Most common (most bothersome in bold): **somnolence**, dizziness, **akathisia**, rash (5%).
- Serious but rare: may result in minor QTc prolongation (dose related; 10 msec at 160 mg/day). Clinically-relevant prolongation (>500 msec) rare (0.06%) and less than placebo (0.23%). Significant QTc prolongation has been associated with the development of malignant ventricular arrhythmias (torsade de pointes) and sudden death. Avoid in patients with hypokalemia, hypomagnesemia, bradycardia, persistent QTc intervals >500 msec or those receiving other drugs which prolong QTc interval. Patients with symptoms of dizziness, palpitations, or syncope should receive further cardiac evaluation.

Pharmacokinetics and Drug Interactions:

- Metabolized in liver principally by aldehyde oxidase; less than one-third of clearance mediated by CYP450: CYP3A4 (major), and CYP1A2 (minor); t ½: 7 hours.
- Avoid use with other drugs that prolong QTc interval.

Clinical Pearls:

- Administer twice daily, ideally with meals; ingestion of several hundred calories necessary to increase absorption up to twofold.
- Causes less weight gain than clozapine, olanzapine, quetiapine, or risperidone. Significant disadvantages, including higher cost, make use of this drug difficult to justify.
- Average increase in QTc greater than any other atypical, although not much more than for quetiapine. Post-marketing surveillance has shown one or two instance of torsade possibly related to ziprasidone use.

Fun Fact:

The brand name Geodon has been suggested to bring to mind the phrase “down (don) to earth (geo)” referring to the goals of the medication.

Bottom Line:

Appealing weight and metabolic profile but dosage titration and range for target dose make this agent more cumbersome to use. QTc interval prolongation risk not clinically important for the majority of patients, but use caution if risk factors exist (bradycardia, low potassium, or magnesium).

Dementia Medications

Drugs currently available for the treatment of dementia include three acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and one N-methyl-D-aspartate (NMDA) receptor antagonist (memantine). Fact sheets for each of these agents follow. The first cholinesterase inhibitor (CI), tacrine, was introduced in 1993 but is no longer used due to its poor bioavailability, need for frequent dosing, and considerable side effects (including nausea, diarrhea, and hepatotoxicity). Its successors are much better tolerated.

Although these medications can sometimes temporarily improve other symptoms of dementia (including apathy, disinhibition, anxiety), they work primarily by slowing the decline of cognition. It is important to explain this point to family members, who might otherwise expect to see actual improvement in cognition, which is unusual. Moreover, not only is symptomatic improvement modest, but there may be a delay of six to 12 weeks in seeing benefits.

All of the CIs are approved for use for the symptomatic treatment of mild to moderate Alzheimer's disease. Donepezil and rivastigmine are also approved, at higher dose, for the treatment of severe Alzheimer's dementia. In addition, rivastigmine is approved for treating dementia associated with Parkinson's disease. All three of the commonly used CIs perform equally well, according to a meta-analysis of 13 randomized double blind placebo-controlled trials (Birks J, *Cochrane Database Syst Rev* 2006). While they may be equivalently effective, each has its own advantages and disadvantages (see fact sheets for details).

All CIs commonly cause nausea, vomiting, and dizziness, and this is why the recommended dosing schedule is excruciatingly slow, generally no faster than one increment every four weeks. How long should patients be treated with these agents? A report in the *Archives of Neurology* compared two ultra-long-term studies of donepezil (lasting about three years), both of which started as standard placebo-controlled trials. In one study, after six months of donepezil treatment, patients were switched to placebo for six weeks before being allowed to resume donepezil in an open label extension of the study. Cognitive scores plummeted in these patients, right down to the level of those who had been on placebo since day one. And even when these patients were "rescued" with open-label donepezil, cognitive decline continued. This effect also occurred in the group that was more mercifully washed out for only three weeks, but it was not nearly as dramatic. The moral of this story? Once a patient is on a cholinesterase inhibitor, don't stop it.

TABLE 8: DEMENTIA MEDICATIONS

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg except where noted)	Usual Dosage Range (starting–max) (mg)
Donepezil (Aricept, Aricept ODT) 1996	Mild to moderate Alzheimer's dementia, severe Alzheimer's dementia	5, 10, 23; 5, 10 ODT	5 QAM–23 QAM
Galantamine (Razadyne) 2001	Mild to moderate Alzheimer's dementia	4, 8, 12; 4 mg/ml sol	4 BID–12 BID
Galantamine ER (Razadyne ER) 2004	Mild to moderate Alzheimer's dementia	8, 16, 24	8 ER QAM–24 ER QAM
Memantine (Namenda) 2003 generic not available IR formulation to be discontinued in August 2014	Moderate to severe Alzheimer's dementia	5, 10; 2 mg/ml sol	5 QAM–10 BID
Memantine ER (Namenda XR) 2010 generic not available	Moderate to severe Alzheimer's dementia	7, 14, 21, 28	7–28 QD
Rivastigmine (Exelon) 2000	Mild to moderate Alzheimer's dementia, dementia associated with Parkinson's disease	1.5, 3, 4.5, 6; 2 mg/ml sol	1.5 BID–6 BID
Rivastigmine (Exelon Patch) 2007 generic not available	Mild to moderate Alzheimer's dementia, dementia associated with Parkinson's disease	4.6, 9.5, 13.3/24 hr	4.6 mg/24 hr QD–13.3 mg/24hr QD

DONEPEZIL (Aricept, Aricept ODT) Fact Sheet

FDA Indications:

mild to moderate Alzheimer's dementia; severe Alzheimer's dementia (23 mg).

Dosing:

- Supplied as:
  - 5 mg, 10 mg, 23 mg unscored tablets as **Aricept** (Eisai) and generic.
  - 5 mg, 10 mg orally disintegrating tablets as **Aricept ODT** (Eisai) and generic.
- Dementia: start 5 mg QD and ↑ to 10 mg QD after four weeks.
- Moderate to severe dementia: may ↑ further to 23 mg QD after ≥3 months (range 10 mg–23 mg/day).
- Cost (for one month supply at 10 mg/day, priced Nov 2013):
  - Donepezil (generic): $18.20
  - Aricept: $756

Side Effects:

- Most common (most bothersome in bold): dose-related **diarrhea, nausea**, vomiting, weight loss, anorexia, **insomnia,** abnormal dreams.
- Serious but rare: cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease; syncope reported.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP 2D6 and 3A4; t ½: 70 hours.
- Avoid use with anticholinergic agents as they will diminish therapeutic effects; avoid beta blockers due to risk of bradycardia. P450 interactions not usually clinically important.

Clinical Pearls:

- The first to be approved, it is also the most prescribed of the three CIs. Recently received additional FDA approval for use in severe dementia (in addition to its current mild to moderate dementia approval).
- The manufacturer recommends bedtime dosing, but giving it in the morning may prevent the insomnia and vivid dreams some patients report with Aricept.
- Once a day dosing, easy titration makes this agent easiest to use.
- GI side effects usually resolve in one to two weeks.
- Based on a Cochrane Review, donepezil causes fewer side effects than rivastigmine.
- Be mindful of other medications which may have intrinsic anticholinergic activity; these will counteract donepezil's therapeutic effects.
- Donepezil may also be effective in the treatment and prevention of delirium, which has been hypothesized to be due to an overall deficiency of cholinergic tone in the brain.

Fun Fact:

Donepezil has been studied in children. These minimal data in autism, pervasive developmental disorders, ADHD, and tic disorders, however, do not support such use.

Bottom Line:

First-line agent, but don't expect big improvements.

GALANTAMINE (Razadyne, Razadyne ER) Fact Sheet

FDA Indication:

mild to moderate Alzheimer's dementia.

Dosing:

- Supplied as:
  - 4 mg, 8 mg, 12 mg unscored tablets as **Razadyne** (Janssen) and generic.
  - 8 mg, 16 mg, 24 mg ER capsules as **Razadyne ER** (Janssen) and generic.
  - 4 mg/ml oral solution as **Razadyne** (Janssen) and generic.
- Dementia:
  - IR: start 4 mg BID (breakfast and dinner), ↑ by 4 mg BID increments every 4 weeks.
  - ER: start 8 mg QAM (breakfast), ↑ by 8 mg/day every 4 weeks.
  - For both, maximum of 24 mg/day (usual target dose: 16 mg–24 mg/day).
- If using oral solution, mix dose with three to four ounces of any nonalcoholic beverage; mix well and drink immediately.
- If therapy is interrupted for ≥3 days, restart at the lowest dose and increase to current dose.
- Cost (for one month supply at 16 mg/day, priced Jan 2014):
  - Galantamine (generic): $85
  - Galantamine ER (generic): $84.65
  - Razadyne: $294.30
  - Razadyne ER: $290.98

Side Effects:

- Most common (most bothersome in bold): **diarrhea, nausea**, vomiting, weight loss, anorexia, **insomnia,** abnormal dreams.
- Serious but rare: cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease; syncope reported.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2D6 and 3A4; t ½: 7 hours.
- Avoid use with anticholinergic agents as they will diminish therapeutic effects; avoid beta blockers due to risk of bradycardia. P450 interactions not usually clinically important.

Clinical Pearls:

- Razadyne's claim to fame is that it has a "dual" mechanism of action, modulating cholinergic nicotinic receptors in addition to inhibiting acetylcholinesterase. The manufacturer may use this factoid to argue that Razadyne is more effective than the other CIs. However, accumulating evidence seems to show no difference in efficacy (Loy C et al, Galantamine in Alzheimer's Disease. *Cochrane Database of Systematic Reviews* 2002. Updated 2006).
- ER formulation seems to be used more often due to ease of once daily dosing.

Fun Fact:

Razadyne was approved in 2001 with its original name, Reminyl. Pharmacists were sometimes confusing written scripts for Reminyl with Amaryl, a diabetes medication. In April 2005, the trade name was changed to Razadyne to avoid future dispensing errors.

Bottom Line:

No appreciable benefit over donepezil, which has a longer time on market and greater range of experience given additional indication for severe dementia; consider this a second-line agent.

MEMANTINE (Namenda, Namenda XR) Fact Sheet

FDA Indication:

moderate to severe Alzheimer's dementia.

Dosing:

- Supplied as:
  - 5 mg, 10 mg unscored tablets and 2 mg/ml oral solution as **Namenda** (Forest).
  - 7 mg, 14 mg, 21 mg, 28 mg ER capsules as **Namenda XR** (Forest).
- IR: 5 mg QD week 1; 5 mg BID week 2; 10 mg QAM and 5 mg QHS week 3; 10 mg BID week 4 and beyond.
- XR: start 7 mg QD, ↑ by 7 mg/day in increments ≥1 week to target maximum dose of 28 mg/day (10 mg BID equivalent to 28 mg XR QD). Can be opened and sprinkled on food.
- Cost (for one month supply at 28 mg/day, priced Mar 2014):
  - Namenda XR: $294

Side Effects:

- Most common (most bothersome in bold): dizziness, **transient confusion**, headache, constipation, sedation.

Pharmacokinetics and Drug Interactions:

- Metabolism primarily hepatic, but not P450; t ½: 60–80 hours.
- Pharmacokinetic interactions unlikely.

Clinical Pearls:

- Unlike other agents, not a cholinesterase inhibitor; memantine functions as an N-methyl-D-aspartate (NMDA) receptor antagonist.
- FDA-approved for moderate to severe AD only; may also be effective as augmentation added to donepezil in patients with moderate to severe AD.
- Data comparing 10 mg BID and 20 mg QD of IR formulation, as well as pharmacokinetic profile, support use of once daily IR dosing; used QD in Europe.

Fun Fact:

Forest has announced they are discontinuing sales of the IR formulation as of August 15, 2014, in order to "focus on" XR formulation….just ahead of the IR patent expiration.

Bottom Line:

Memantine's indication (moderate to severe dementia only) may limit its use, but it does boast a unique mechanism of action and has some data to support its usefulness as an augmenter of donepezil. Many prescribers put the majority of their dementia patients on a combination of one of the CIs and memantine; we recommend adding memantine when dementia has progressed to the moderate or severe level. Launch of XR formulation seemingly delayed to a time close to the patent expiration of the IR product; no clinical benefit that we can see to using XR.

RIVASTIGMINE (Exelon, Exelon Patch) Fact Sheet

FDA Indications:

mild to moderate and severe Alzheimer's dementia; dementia associated with Parkinson's disease.

Dosing:

- Supplied as:
  - 1.5 mg, 3 mg, 4.5 mg, 6 mg capsules and 2 mg/ml oral solution as **Exelon** (Novartis) and generic.
  - 4.6 mg/24 hour, 9.5 mg/24 hour, 13.3 mg/24 hour transdermal patches as **Exelon Patch** (Novartis), containing rivastigmine 9 mg, 18 mg, and 27 mg, respectively.
  - Start 1.5 mg BID with meals for 4 weeks, ↑ by 1.5 mg BID increments every 4 weeks, up to maximum of 6 mg BID with meals.
  - Patch: for mild to moderate dementia, start 4.6 mg/24 hours; if tolerated, ↑ after ≥4 weeks to 9.5 mg/24 hours (target and maximum dose). For severe dementia, titrate to 13.3 mg/24 hour (effective and maximum dose).
  - Converting oral to patch: <6mg/day: use 4.6 mg/24 hour patch; 6 mg–12 mg/day: use 9.5 mg/24 hour patch; apply patch on next day following last oral dose.
- Cost (for one month supply at 4.5 mg BID, priced Feb 2014):
  - Rivastigmine (generic): $153.94
  - Exelon: $308.74
  - Exelon patch (9.5 mg/day): $333.64

Side Effects:

- Most common (most bothersome in bold): dizziness, headache, diarrhea, **anorexia, nausea, vomiting.**
- Serious but rare: cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease; syncope reported.

Pharmacokinetics and Drug Interactions:

- Metabolized extensively although CYP enzymes minimally involved; t ½: 1.5 hours (oral), 3 hours (after patch removal).
- Avoid use with anticholinergic agents as they will diminish therapeutic effects; avoid beta blockers due to risk of bradycardia. P450 interactions not likely.

Clinical Pearls:

- Only CI with additional indication for Parkinson's-related dementia; in a placebo-controlled trial of 541 patients, clinically meaningful improvement occurred in 5% more patients on rivastigmine than placebo, and worsening occurred in 10% more placebo patients.
- Rivastigmine inhibits both acetylcholinesterase and the nonspecific butyrylcholinesterase (also known as pseudocholinesterase or BuChE), which is mostly found in the liver and GI tract; this may explain why rivastigmine causes significant GI side effects.
- Rivastigmine transdermal patches may cause less nausea and vomiting.

Fun Fact:

Exelon is also the name of a corporation that provides energy services (electric and natural gas) and is the largest nuclear operator in the United States.

Bottom Line:

Since all CIs are equally effective, we recommend starting with donepezil, which offers once daily dosing, generic availability, and good tolerability profile. Rivastigmine remains second-line due to BID dosing, cost, and unacceptably high rates of nausea and vomiting.

Hypnotics

Insomnia is one of the most common complaints in psychiatry, and there are multiple drugs available to treat it. But before reaching for the prescription pad, one should always first ensure insomnia is not secondary to underlying psychiatric disorder (eg, depression, mania, anxiety, psychosis) or medical disorder (eg, thyroid, peptic ulcer, pain). Lifestyle causes (eg, shift work, poor sleep hygiene, substance use) or drug-induced causes (eg, sympathomimetics, decongestants, diuretics, theophylline, bupropion) are also common. Treat any underlying causes when possible.

If you decide that a medication is indicated, note that hypnotics should generally be used for limited time periods. Tolerance to sedating effects can occur as early as two weeks of use; therefore most agents are approved only for the short-term management of insomnia (some, like ramelteon and eszopiclone, have longer-term data). Continuous, long-term treatment is not recommended, but it may be required in some cases.

The fact sheets include hypnotic drugs from various classes of medications. **Antihistamines** (diphenhydramine and doxylamine) are over-the-counter agents that induce sedation by blocking histamine H1 receptors. **Benzodiazepines** (clonazepam, lorazepam, temazepam, triazolam) bind to subtypes of GABA receptors to induce hypnotic effects as well as anxiolytic, anticonvulsant, and muscle relaxant effects. They are very frequently used (some would say "overused") for anxiety disorders, and we have included FDA indications where they exist. The non-benzodiazepine **"Z drugs"** (eszopiclone, zaleplon, zolpidem) bind selectively to specific subunits of the GABA receptors that induce sleep, but not other pharmacologic effects associated with the benzodiazepines. Unlike most other hypnotics which act on the histamine or GABA system, ramelteon is a **melatonin agonist.**

Other drugs also fit into the above categories, based on the mechanism by which they induce sleep. Doxepin (Silenor) was recently approved by the FDA for use as a hypnotic; it is an old drug in new clothing—a tricyclic antidepressant being used for its antihistamine properties. Trazodone, another antidepressant, is commonly used for insomnia thanks to its various pharmacologic properties (5HT2A antagonism as well as alpha 1 and histamine 1 blockade); see page 35 for the fact sheet on trazodone.

Hypnotics remain a high-risk class of medications, particularly for the elderly, who are at greater risk for confusion, memory problems, and gait disturbances (sometimes leading to falls). Their use should be minimized in the older population and the lowest effective dose should be used for the shortest duration of time.

Certain precautions apply to most of these agents and they will be listed here to minimize repetition in the fact sheets.

- **Daytime grogginess or hangover effect:** most likely to occur with antihistamines or with longer acting benzodiazepines; use a lower dose or an alternative hypnotic.
- **Anterograde amnesia:** most likely to occur with benzodiazepines, particularly high potency agents such as triazolam; use lower dose or alternate agent.
- **CNS depression:** Hypnotics may impair physical or mental abilities and alertness; alert patients to use caution when performing tasks which require alertness (eg, driving).
- **Respiratory depression:** benzodiazepines in particular may depress respiration; avoid in patients at risk including those with COPD or apnea, or those taking other depressants such as opiates.
- **Paradoxical reactions,** including hyperactive or aggressive behavior, have been reported, and are particularly seen with benzodiazepines; younger patients, elderly, and those with head injury or organic brain syndromes at greatest risk.
- **Tolerance** to sedating effects of benzodiazepines generally occurs after several weeks of continuous use (⅓ of patients will experience tolerance after 4 weeks of use). Tolerance to anxiolytic effects occurs more slowly, and to anti-seizure effects very little or not at all. Psychological and physical dependence occurs with prolonged use.
- **Discontinuation syndrome:** withdrawal effects occur with most hypnotics and include rebound insomnia, agitation, anxiety, and malaise. Discontinuation syndromes from benzodiazepines are most severe with longer term use, higher doses, and with shorter-acting agents; in severe cases, discontinuation may include seizures. Use of hypnotics should not be abruptly discontinued; doses should be tapered gradually.
- **Recreational use and abuse** may occur with many hypnotics, particularly the benzodiazepines. Avoid or minimize use in patients who have addiction risk or when abuse is suspected.

TABLE 9: HYPNOTICS

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg except where noted)	Usual Dosage Range (starting–max) (mg)	Equivalent Dose to 1 mg Lorazepam (for Benzodiazepines)	Onset of Action*	Half Life (hours)	Duration of Action (hours)*
Clonazepam (Klonopin, Klonopin Wafers) 1975	Panic disorder	0.5, 1, 2; ODT: 0.125, 0.25, 0.5, 1, 2	0.25 to 0.5–2	0.25-0.5	1 h	20–50	6–8
Diphenhydramine (Benadryl, others) 1946 available OTC	Insomnia	25	25–50	NA	1 h	3.5–9	4–6
Doxepin (Silenor) 2010/1969 generic not available in 3 mg, 6 mg	Insomnia (sleep maintenance)	3, 6, 10, 25, 50, 75, 100, 150, 10 mg/ml oral concentrate	6 (use 10 generic)	NA	1 h	15	4–6
Doxylamine (Unisom, others) 1978 available OTC	None	25	25–50	NA	1 h	10	4–6
Eszopiclone (Lunesta) 2004	Insomnia (sleep onset and sleep maintenance)	1, 2, 3	2–3	NA	30 min	6	6–8
Lorazepam (Ativan) 1977	Anxiety	0.5, 1, 2, 2 mg/ml solution	1–4	1	30–60 min	10–20	4–6
Ramelteon (Rozerem) 2005 generic not available	Insomnia (sleep onset)	8	8	NA	30 min	1–2.6	Unknown
Temazepam (Restoril) 1981	Insomnia (short-term)	7.5, 15, 22.5, 30	15–30	15	30–60 min	9–18	4–6
Trazodone 1981	None	50, 100, 150, 300; ER: 150, 300	25 to 50–200	NA	1 h	7–10	Unknown
Triazolam (Halcion) 1982	Insomnia (short-term)	0.125, 0.25	0.25–0.5	0.25	15–30 min	1.5–5	Unknown

Zaleplon (Sonata) 1999	Insomnia (short-term, sleep onset)	5, 10	10–20	NA	30 min	1	4
Zolpidem (Ambien, Ambien CR, Edluar, Zolpimist) 1992 generic not available for Elduar and Zolpimist	Insomnia (IR: short-term, sleep onset; CR: sleep onset and maintenance)	5, 10; ER: 6.25, 12.5; SL: 5, 10; 5mg/spray	10, 12.5 CR (5, 6.25 in women)	NA	30 min	2.5–3	6–8
Zolpidem low dose (Intermezzo) 2011 generic not available	Difficulty falling asleep after middle of the night awakening	1.75, 3.5	1.75 women; 3.5 men	NA	30 min	2.5	4

*onset and duration vary from person to person, dose to dose, and preparation to preparation

ANTIHISTAMINES (diphenhydramine, doxylamine) Fact Sheet

Diphenhydramine:

Benadryl, Compoz, Nytol, Simply Sleep, Sleep-Eze D, Sominex, Unisom SleepGels, Unisom SleepMelts and generic.

Doxylamine:

NyQuil, Unisom SleepTabs, and generic.

FDA Indications:

insomnia; allergies; motion sickness; antiparkinsonism.

Dosing:

- Generally supplied as 25 mg (tablets, chewable tablets, caplets, capsules, and oral solutions, varies by brand); generics available; over the counter (OTC) availability.
- Insomnia: start 25 mg, 30 minutes before bedtime. The dose required to induce sleep can be as low as 6.25 mg, but is usually dosed at 25 mg. Some patients may require 50 mg at bedtime.
- Cost (for 100, 25 mg pills, priced Jan 2014):
  - Diphenhydramine (generic): $4
  - Benadryl: 14.99, Walgreens

Side Effects:

- Most common (most bothersome in bold): **dry mouth**, ataxia, urinary retention, constipation, **drowsiness**, memory problems.
- Serious but rare: blurred vision, tachycardia.

Pharmacokinetics and Drug Interactions:

- Metabolized by liver, CYP2D6; t ½: for diphenhydramine, 3.5–9 hours; for doxylamine, 10 hours (12–15 in elderly).
- Avoid use with other antihistamines or anticholinergics (additive effects).

Clinical Pearls:

- These antihistamines non-selectively antagonize central and peripheral histamine H1 receptors. They also have secondary anticholinergic effects which can cause side effects including dry mouth and urinary retention, as well as cognitive impairment in susceptible populations.
- Be aware that anticholinergic drugs are often used to treat or prevent extrapyramidal symptoms in patients taking antipsychotics; diphenhydramine is often chosen and dosed at night to take advantage of its sedative effect.

Fun Facts:

The name NyQuil is a portmanteau (combination of words) of “night” and “tranquil.”

Bottom Line:

Antihistamines can be very effective sleepers for many patients; although some patients may experience too much grogginess (“hangover”) in the morning. Good first-line agents due to low risk of drug tolerance, dependence, or abuse, but exercise caution in the elderly who may not tolerate peripheral effects.

CLONAZEPAM (Klonopin, Klonopin Wafers) Fact Sheet

FDA Indications:

seizure disorders; panic disorder.

Dosing:

- Supplied as:
  - 0.5 mg, 1 mg, 2 mg scored and unscored tablets as **Klonopin** (Roche) and generic.
  - 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg orally disintegrating tablets as **Klonopin Wafers** (Roche) and generic.
  - C-IV controlled substance.
- Dose varies based on patient characteristics (eg, age) and tolerance to benzodiazepines. Generally, start at 0.25mg–0.5 mg QHS as needed for insomnia. Maximum dose for insomnia: 2 mg at bedtime. Usually dosed BID or TID for anxiety. Use lower doses for elderly.
- Cost (for one month supply at 1 mg/day, priced Nov 2013):
  - Clonazepam (generic): $6.13
  - Klonopin: $72.84

Side Effects:

- Most common (most bothersome in bold): **somnolence,** daytime grogginess, confusion; ataxia.
- Serious but rare: anterograde amnesia, increased fall risk, paradoxical reaction (irritability, agitation).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 20–50 hours.
- Avoid concomitant use with other CNS depressants, including alcohol (additive effects). Potent CYP3A4 inhibitors (eg, fluvoxamine, erythromycin) may increase clonazepam levels; CYP3A4 inducers (eg, carbamazepine) may decrease clonazepam levels.

Clinical Pearls:

- High potency, long-acting benzodiazepine with active metabolites that may accumulate.
- Tolerance to sedative effect may develop more rapidly (within two to four weeks of use) than tolerance to anti-anxiety effect. Benzodiazepines affect the normal sleep architecture; thus, long-term use is discouraged.
- Withdrawal effects may not be seen until three to five days after abrupt discontinuation and may last 10 to 14 days due to long half-life and active metabolites of clonazepam.
- Full effects of a particular dose may not be evident for a few days since active metabolites will accumulate with continual use (versus PRN use). Wait several days before increasing dose if patient is taking clonazepam nightly.

Fun Fact:

Klonopin tablets (or “K-pins”) have a street value of $2–$5 per tablet, depending on dose and geographic region.

Bottom Line:

May work as a good hypnotic for the short-term, although dependence and long half-life limit its use. If a benzodiazepine is prescribed, we prefer a “cleaner” agent like lorazepam, with its shorter half-life, no active metabolites, and no potential P450 drug interaction, although admittedly, other prescribers’ preferences vary widely.

DOXEPIN (Silenor) Fact Sheet

FDA Indications:

insomnia (sleep maintenance). Generic doxepin (at higher doses) approved for depression, anxiety disorders.

Dosing:

- Supplied as:
  - 3 mg, 6 mg unscored tablets as **Silenor** (Somaxon).
  - 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg capsules and 10 mg/ml oral concentrate as generic (for depression and anxiety).
- Insomnia: start 6 mg QHS (this is the starting, target, and maximum dose). Use 3 mg/day in elderly. Avoid meals within three hours of taking doxepin.
- Cost (for one month supply at 10 mg/day generic or 6 mg/day Silenor, priced Jan 2014):
  - Doxepin (generic): $7
  - Silenor: $243.09

Side Effects:

- Most common (most bothersome in bold): **somnolence**, nausea, dry mouth, constipation.
- Serious but rare: orthostasis (more likely at higher doses).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2D6; t ½: 15 hours.
- Clinically significant drug interactions not likely at the low doses used for hypnotic effects.

Clinical Pearls:

- Silenor's manufacturer took an old, off-patent and cheap drug (doxepin), gave it a new name (Silenor) and obtained FDA-approval for a new indication (insomnia). The use of tiny doses (3 mg or 6 mg) is theoretically to avoid daytime sleepiness, but possibly also to thwart pharmacy substitution or compounding. The manufacturer advises against splitting generic 10 mg tabs in half, but there seems to be no good reason other than to preserve Silenor sales. Don't fall for it!

Fun Fact:

Somaxon Pharmaceuticals was founded in 2003, but its only product is Silenor, a compound which has been available since 1969 and was approved in low-dose form in 2010.

Bottom Line:

Clinically and pharmacologically, Silenor at 3 mg–6 mg/nightly differs very little from 10 mg/nightly of the generic doxepin, available at a fraction of the price. However, its approval and availability serves as a good reminder that low-dose TCAs may be used as sedatives for their antihistaminic and anticholinergic activity. Silenor/doxepin may be a good agent to put in your arsenal, particularly for those patients in whom you want to avoid benzodiazepines or Z drugs. There appears to be no good reason to use the much more expensive branded product; stick to the low dose generic.

ESZOPICLONE (Lunesta) Fact Sheet

FDA Indication:

insomnia (sleep onset and sleep maintenance).

Dosing:

- Supplied as 1 mg, 2 mg, 3 mg unscored tablets as **Lunesta** (Sunovion) and generic.
- C-IV controlled substance.
- Insomnia: start 2 mg QHS; may ↑ to maximum of 3 mg QHS. Use lower doses in elderly (1 mg to start; 2 mg maximum). Take immediately before falling asleep. Avoid administering with high-fat meal (delays onset of effect).
- Cost (for one month supply at 3 mg/day, priced April 2014):
  - Eszopiclone (generic): $269.93
  - Lunesta: $353.53

Side Effects:

- Most common (most bothersome in bold): **somnolence, headache, unpleasant taste,** dizziness, dry mouth.
- Serious but rare: anaphylaxis; complex sleep-related behavior (sleep-driving, cooking, eating, making phone calls).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4 and CYP2E1; t ½: 6 hours (9 hours in elderly).
- Avoid concomitant use with other CNS depressants, including alcohol (additive effects). Potent CYP3A4 inhibitors (eg, fluvoxamine, erythromycin) may increase effects of eszopiclone significantly, whereas CYP3A4 inducers (eg, carbamazepine) may decrease eszopiclone levels; eszopiclone dose adjustments may be necessary.

Clinical Pearls:

- Non-benzodiazepine in structure, but binds to the GABA-benzodiazepine receptor complex like benzodiazepines; selective for the alpha receptor subtype (causing hypnotic effects but none of the other pharmacologic effects of benzodiazepines); one of the "Z drugs." Eszopiclone is the *S*-enantiomer of zopiclone (a hypnotic agent available in other countries).
- Unlike benzodiazepines, eszopiclone does not disrupt normal sleep architecture (stages).
- Taking after a large, high fat meal will delay its onset of action (by about an hour). Because of its rapid onset of action, eszopiclone should be taken immediately before bedtime or once difficulty falling asleep has occurred.

Fun Fact:

The longest, largest phase 3 trial of eszopiclone has been criticized in the *New England Journal of Medicine (NEJM)* because even though it concluded that eszopiclone was more effective than placebo, patients in the eszopiclone group reported falling asleep an average of only 15 minutes faster and sleeping an average of 37 minutes longer than those in the placebo group.

Bottom Line:

Like other "Z-drugs," eszopiclone is an effective sedative with less potential for dependence than the benzodiazepines. Dosing is simple and, apart from the bitter aftertaste, its rapid onset and long duration of action make it well accepted among patients. As with all sedative/hypnotics, nightly use should be discouraged.

LORAZEPAM (Ativan) Fact Sheet

FDA Indications:

anxiety; status epilepticus (IV route).

Dosing:

- Supplied as 0.5 mg, 1 mg, 2 mg scored and unscored tablets and 2 mg/ml oral solution as **Ativan** (Valeant) and generic; IM/IV formulation also available.
- C-IV controlled substance.
- Insomnia: start 0.5 mg–1 mg QHS, 20–30 minutes before bedtime; maximum 4 mg nightly. Use lower doses in elderly.
- Cost (for one month supply at 2 mg/day, priced Mar 2014):
  - Lorazepam (generic): $8.02
  - Ativan: $359.48

Side Effects:

- Most common (most bothersome in bold): **somnolence,** dizziness, weakness, ataxia.
- Serious but rare: anterograde amnesia; increased fall risk; paradoxical reaction (irritability, agitation).

Pharmacokinetics and Drug Interactions:

- Metabolism primarily hepatic (non-CYP450) to inactive compounds; t ½: 10–20 hours.
- Avoid concomitant use with other CNS depressants, including alcohol (additive effects). No risk for CYP450 drug interactions.

Clinical Pearls:

- Lorazepam does not have a long half-life or active metabolites which could accumulate, and poses no CYP450 drug interaction risk.
- Withdrawal symptoms usually seen on the first day after abrupt discontinuation and last 5–7 days in patients receiving short-intermediate half-life benzodiazepines such as lorazepam. A gradual taper is highly recommended, particularly if prolonged treatment on a high dose.
- Tolerance to sedative effect may develop within two to four weeks of use and benzodiazepines affect the normal sleep architecture; thus, long-term use is discouraged.

Fun Fact:

Early Ativan marketing efforts included clever direct-to-consumer advertising campaigns. These included: “Now it can be yours—The Ativan Experience” in 1977 and “In a world where certainties are few...no wonder Ativan is prescribed by so many caring clinicians” in 1987.

Bottom Line:

When a benzodiazepine is appropriate for use (short-term; minimal risk of abuse), we consider this and temazepam to be first-line agents.

RAMELTEON (Rozerem) Fact Sheet

FDA Indication:

insomnia (sleep onset).

Dosing:

- Supplied as 8 mg unscored tablets as **Rozerem** (Takeda).
- Start, target and maximum dose is 8 mg QHS, 30 minutes before bedtime. Avoid administering with high fat meal (delays therapeutic effect by 45 minutes).
- Cost (for one month supply at 8 mg/day, priced Nov 2013):
  - Rozerem: $218, Target

Side Effects:

- Most common: headache, somnolence, fatigue dizziness.
- Serious but rare: anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls), increased prolactin, abnormal cortisol or testosterone levels.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP1A2 (major), CYP2C9, and CYP3A4; t ½: 1–2.6 hours.
- Avoid concomitant use with CNS depressants (additive effects). Exercise caution in patients taking potent CYP1A2 inhibitors (eg, fluvoxamine) which could increase ramelteon effects.

Clinical Pearls:

- Mechanism of action unrelated to other hypnotics. Ramelteon is a melatonin receptor agonist which binds to melatonin MT1 (induces sleepiness) and MT2 (influences regulation of circadian rhythms) receptors to induce sleep.
- No evidence of abuse potential or physical dependence was detected following administration of doses up to 20 times the recommended hypnotic dose in patients with a history of drug abuse or dependence.
- Hormonal alterations occur very rarely and usually with high dose (16 mg in one study) and longer-term use (6–12 months). If unexplained amenorrhea, galactorrhea, decreased libido, or fertility problems occur, consider evaluating patient's prolactin or testosterone levels.
- Another melatonin receptor agonist, Hetlioz (tasimelteon) (Vanda Pharmaceuticals), was approved by the FDA in January 2014 to treat non-24-hour sleep-wake disorder ("non-24") in totally blind individuals.

Fun Fact:

Another melatonin agonist, agomelatine, has been studied as an antidepressant, partly because circadian rhythms are disrupted in depression (it is approved overseas but the manufacturer shelved it in the US).

Bottom Line:

A good alternative to benzodiazepines and "Z drugs" for patients in whom dependence, withdrawal, and abuse potential are clinical concerns. Compared to other hypnotics, lower risk for respiratory depression and hangover effect (morning grogginess). A good agent to have in your bag of tricks, but consider the possibility of rare hormonal effects, particularly when using for extended periods of time. Also consider that over-the-counter melatonin (which ramelteon mimics) may do the same job, at a lower price.

TEMAZEPAM (Restoril) Fact Sheet

FDA Indication:

insomnia (short-term).

Dosing:

- Supplied as 7.5 mg, 15 mg, 22.5 mg, 30 mg capsules as **Restoril** (Mallinckrodt) and generic.
- C-IV controlled substance.
- Start 15 mg QHS. Maximum dose 30 mg nightly. Use lower doses in elderly.
- Cost (for one month supply at 15 mg/day, priced Nov 2013):
  - Temazepam (generic): $8.08
  - Restoril: $389.03

Side Effects:

- Most common (most bothersome in bold): **somnolence,** dizziness, weakness, ataxia.
- Serious but rare: anterograde amnesia, increased fall risk, paradoxical reaction (irritability, agitation).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through liver but no CYP450 involvement; t ½: 9–18 hours.
- Avoid concomitant use with other CNS depressants, including alcohol (additive effects). No risk for CYP450 drug interactions.

Clinical Pearls:

- Temazepam does not have a long half-life or active metabolites which could accumulate and poses no CYP450 drug interaction risk.
- Withdrawal symptoms usually seen on the first day after abrupt discontinuation and lasts five to seven days in patients receiving short-intermediate half-life benzodiazepines such as lorazepam.
- Tolerance to sedative effect may develop within two to four weeks of use and benzodiazepines affect the normal sleep architecture; thus, long-term use is discouraged.

Fun Facts:

The US Air Force uses temazepam as one of the hypnotics approved as “no-go pills” to help aviators and special duty personnel sleep in support of mission readiness; “ground tests” are required prior to authorization being issued to use the medication in an operational situation.

Bottom Line:

When a benzodiazepine is appropriate for use (short-term; minimal risk of abuse), we consider this and lorazepam to be first-line agents.

TRAZODONE (Oleptro) Fact Sheet

See page 35

TRIAZOLAM (Halcion) Fact Sheet

FDA Indication:

insomnia (short-term).

Dosing:

- Supplied as 0.125 mg (unscored) and 0.25 mg (scored) tablets as **Halcion** (Pfizer) and generic.
- C-IV controlled substance.
- Start 0.25 mg QHS; maximum 0.5 mg nightly. Take immediately before bedtime. Use lower doses in elderly.
- Cost (for one month supply at 0.25 mg/day, priced Nov 2013):
  - Triazolam (generic): $9.09, Sams Club
  - Halcion: $90.48, Kroger Pharmacy

Side Effects:

- Most common (most bothersome in bold): **drowsiness,** headache, dizziness, ataxia.
- Serious but rare: anterograde amnesia, increased fall risk, paradoxical reaction (irritability, agitation).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 1.5–5.5 hours.
- Avoid concomitant use with other CNS depressants, including alcohol (additive effects). Avoid use with potent 3A4 inhibitors (eg, erythromycin, ketoconazole, fluvoxamine) as they may increase triazolam levels significantly.

Clinical Pearls:

- Rapid onset of effect; best to take when already in bed.
- Due to its short half-life, triazolam is not effective for patients that suffer from frequent awakenings or early wakening; mostly useful for sleep onset.
- Rebound insomnia and other withdrawal symptoms are more likely and more severe with a short-acting benzodiazepine such as triazolam.
- Tolerance to sedative effect may develop within two to four weeks of use and benzodiazepines affect the normal sleep architecture; thus, long-term use is discouraged.
- May induce more anterograde amnesia than other benzodiazepines; concomitant use of alcohol or use of higher dose (0.5 mg) increases risk.
- Due to studies that suggest the frequency of severe psychiatric disturbances is higher with triazolam compared to other benzodiazepines, the United Kingdom and Brazil have banned it.

Not-So-Fun Fact:

Serial killer Jeffrey Dahmer used triazolam to sedate his victims.

Bottom Line:

There are far better benzodiazepines to use for sleep (lorazepam, temazepam) in patients who are appropriate for benzodiazepine treatment. We cannot recommend using triazolam; some have even suggested that it be banned from the US market given the higher likelihood for adverse effects (anterograde amnesia, psychiatric disturbances).

ZALEPLON (Sonata) Fact Sheet

FDA Indication:

insomnia (short-term, sleep onset).

Dosing:

- Supplied as 5 mg, 10 mg capsules as **Sonata** (King Pharmaceuticals) and generic.
- C-IV controlled substance.
- Start 10 mg QHS. Maximum dose 20 mg nightly. Avoid administering with high fat meal (delays onset of effect). Use lower doses in elderly.
- Cost (for one month supply at 10 mg/day, priced Nov 2013):
  - Zaleplon (generic): $18.75, Kmart
  - Sonata: $167.67

Side Effects:

- Most common (most bothersome in bold): somnolence, dizziness, **headache.**
- Serious but rare: anaphylaxis, complex sleep-related behavior (sleep-driving, cooking, eating, making phone calls).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through aldehyde oxidase and also CYP3A4; t ½: 1 hour.
- Avoid concomitant use with other CNS depressants, including alcohol (additive effects). Potent CYP3A4 inhibitors (eg, fluvoxamine, erythromycin) may increase effects of zaleplon significantly, whereas CYP3A4 inducers (eg, carbamazepine) may decrease zaleplon levels; adjust zaleplon dosing.

Clinical Pearls:

- Non-benzodiazepine in structure, but binds to the GABA-benzodiazepine receptor complex like benzodiazepines; selective for the alpha receptor subtype (causing hypnotic effects but none of the other pharmacologic effects of benzodiazepines); one of the "Z drugs."
- Administer immediately before going to bed or after in bed and experiencing difficulty falling asleep; use only when able to get ≥4 hours of sleep (to minimize amnesic episodes).
- Because of zaleplon's very short half-life, it rarely causes next day impairment.
- Unlike benzodiazepines, zaleplon does not disrupt normal sleep stages.
- Most useful for sleep initiation disorders; does not substantially increase total sleep time or decrease number of awakenings.
- Classified as a Schedule IV drug; but, at therapeutic doses, abuse potential is somewhat less than benzodiazepines. However, abuse potential of high doses (2.5–7.5 times recommended dose) similar to that of benzodiazepines.
- Fewer withdrawal effects than with benzodiazepines but abrupt discontinuation, particularly from higher doses, can cause withdrawal symptoms (mostly rebound insomnia).

Fun Fact:

The name "Sonata" calls to mind the classical music composition, often for one or two instruments, with three or four movements, much like the phases of sleep.

Bottom Line:

Great for inducing sleep, not great for sleep maintenance throughout the night. The only sleeping pill that can be taken at 3 or 4 am without causing functional impairment when the patient gets out of bed at 7 or 8 am, although patients should always use caution the next day.

ZOLPIDEM (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) Fact Sheet

FDA Indication:

insomnia (IR: short-term, sleep onset; CR: sleep onset and maintenance; Intermezzo: difficulty falling asleep after middle-of-the-night awakening).

Dosing:

- Supplied as:
  - 5 mg, 10 mg unscored tablets as **Ambien** (Sanofi-Aventis) and generic.
  - 6.25 mg, 12.5 mg ER unscored tablets as **Ambien CR** (Sanofi-Aventis) and generic.
  - 5 mg, 10 mg SL tablets as **Edluar** (Meda Pharmaceuticals).
  - 1.75 mg, 3.5 mg SL tablets as **Intermezzo** (Purdue Pharma and Transcept Pharmaceuticals)
  - 5 mg/oral spray as **Zolpimist** (ECR Pharma).
  - C-IV controlled substance.
- Start 10 mg QHS (5 mg in women). ER: start 12.5 mg QHS (6.25 mg in women). Take immediately before bed. Dose may be increased to 10 mg (or 12.5 mg ER) QHS if no daytime grogginess. Higher doses may lead to greater abuse potential. Dose lower in elderly.
- Intermezzo: 1.75 mg (women), 3.5 mg (men) SL QHS, with ≥4 hours remaining before wake time.
- Cost (for one month supply at 10 mg/day, priced Nov 2013):
  - Zolpidem (generic): $6.91
  - Ambien: $269, Walgreens
  - Intermezzo (3.5 mg/day): $240

Side Effects:

- Most common (most bothersome in bold): **headache, somnolence,** dizziness.
- Serious but rare: complex sleep-related behavior (sleep-driving, eating, making phone calls).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 2.5–3 hours.
- Avoid concomitant use with other CNS depressants, including alcohol (additive effects). Potent CYP3A4 inhibitors may increase effects of zolpidem, whereas CYP3A4 inducers (eg, carbamazepine) may decrease zolpidem levels.

Clinical Pearls:

- Binds to the GABA-benzodiazepine receptor complex like benzodiazepines; selective for the alpha receptor subtype (causing hypnotic effects but no other effects of benzodiazepines).
- Use only when able to get ≥7 hours of sleep (to minimize amnesic episodes).
- Unlike benzodiazepines, zolpidem does not disrupt normal sleep stages.
- At therapeutic doses, abuse potential is somewhat less than with benzodiazepines.
- Less withdrawal effects than with benzodiazepines but abrupt discontinuation, particularly from higher doses, can cause withdrawal symptoms (mostly rebound insomnia).
- CR formulation: The dual layer allows some medication to be released immediately, with the rest released gradually, resulting in higher levels through the night.

Fun Fact:

Purdue, the maker of Intermezzo, successfully defended their $2 billion/year blockbuster OxyContin from generic challenges.

Bottom Line:

Good hypnotic that can also help with sleep maintenance, particularly in the ER formulation. “New” lower-dose version is simply a patent extender and we find it difficult to justify the higher cost (use generic zaleplon instead for middle-of-the-night awakening).

Mood Stabilizers

The term "mood stabilizer" suggests an agent effective not only in treating acute episodes of mania or depression, but an agent that also prevents cycling (maintenance treatment of bipolar disorder). In fact, some of the agents that we casually may refer to as "mood stabilizers" really are mostly effective for the treatment of acute mania and are not fully deserving of the title "mood stabilizer" (which has, historically, been used to describe valproate, lithium, and carbamazepine alone).

In managing bipolar disorder, manic episodes are usually the most straightforward to treat. In fact, many medications qualify as anti-manic agents: lithium, valproic acid (VPA), carbamazepine, oxcarbazepine, most atypical antipsychotics, typical antipsychotics (in 1974, chlorpromazine was the second drug approved for acute mania after lithium), and benzodiazepines are all effective, owing to their sedative effect.

Bipolar depression, on the other hand, is more challenging as we have fewer proven strategies. Using antidepressants alone may increase cycling by inducing a "switch" into mania, even though, for better or for worse, it is a strategy often employed. A recent rigorous study (Systematic Treatment Enhancement Program for Bipolar Disorder or STEP-BD) found that adding bupropion or paroxetine to a mood stabilizer provided no additional benefit. The medications that have received FDA indications for the treatment of bipolar depression include the combination of fluoxetine and olanzapine (Symbyax), quetiapine (Seroquel), and more recently, lurasidone (Latuda). In addition, there are data supporting the use of aripiprazole (Abilify) as well as lithium in bipolar depression.

Lamotrigine initially showed promise in one placebo controlled trial; however, four subsequent trials failed to show any benefit to using lamotrigine in bipolar depression. Some experts recommend that patients with bipolar depression should be treated with a mood stabilizer plus quetiapine or lithium. If this combination proves ineffective, then an antidepressant (in combination with mood stabilizer) should be considered.

Maintenance treatment of bipolar disorder should include a mood stabilizer with a proven record of reducing cycling and increasing the time period between acute episodes. Only a few medications have such a record. These include lithium (more effective at preventing mania than depression), lamotrigine (more effective at preventing depression than mania), and some atypical antipsychotics (olanzapine, aripiprazole, quetiapine, and ziprasidone; all more effective at preventing mania than depression). The anticonvulsants valproic acid and carbamazepine are commonly used as maintenance treatment. Although they are not indicated by the FDA for this purpose, APA treatment guidelines permit them as first-line agents for maintenance treatment of bipolar disorder.

Several mood stabilizers are also routinely used as anticonvulsants. The reader should note that the FDA recently issued a black-box warning regarding suicide for anticonvulsants as a class. The warning is based on pooled analysis of 199 trials involving various antiepileptics (regardless of indication) that showed an increased risk of suicidal thoughts/behavior (incidence rate: 0.43% treated patients compared to 0.24% of patients receiving placebo). The risk was observed as early as one week after initiation and continued through duration of trials (most trials ≤24 weeks). The risk was higher for patients with seizure disorders compared to those receiving anticonvulsants for other indications. Nevertheless, the FDA recommends that you monitor all patients for notable changes in behavior that might indicate suicidal thoughts, although it's also important to balance the risk of suicidality with the risk of untreated illness.

Another class warning for the anticonvulsants regards a potentially serious, sometimes fatal, multiorgan hypersensitivity reaction syndrome (drug rash with eosinophilia and systemic symptoms, or DRESS) which has been reported with some antiepileptic drugs (rare). Symptoms may include fever, rash, and/or lymphadenopathy; monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems. Early symptoms of hypersensitivity reaction (eg, lymphadenopathy, fever) may occur without rash. If this occurs, discontinuation and conversion to alternate therapy may be required.

Table 10: MOOD STABILIZERS

Generic Name (Brand Name) Year FDA Approved for Bipolar Disorder or Mania *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg)	Usual Dosage Range (starting–max) (mg)
Carbamazepine (Carbatrol, Equetro, Tegretol) 2004	Bipolar disorder (Equetro: acute mania)	CH: 100; IR: 200; ER: 100, 200, 300 and 400; oral solution: 100/5ml	200 BID–800 BID
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR) 2003 generic not available for ODT and ER formulations	Bipolar disorder (maintenance)	25, 100, 150, 200, 250 and 300; CH: 2, 5 and 25; ODT: 25, 50, 100 and 200 mg; ER: 25, 50, 100, 200, 250 and 300	25 QD–200 QD 25 QD–100 QD if on VPA
Lithium (Lithobid) 1970	Acute mania, bipolar maintenance	150, 300, 600; ER: 300, 450; oral solution: 300/5mL	300–600 QHS–2400 QD
Oxcarbazepine (Trileptal, Oxtellar XR) Not approved for this indication	None	150, 300 and 600; oral suspension: 300/5mL	300 BID–2400 QD
Valproic Acid (Depakene, Depakote, Depakote ER, Depakote Sprinkles, Stavzor) 1995	Bipolar disorder (acute mania)	250; 250/5ml syrup; DR: 125, 250 and 500; ER: 250 and 500	250–500 QHS–4000 QD

CARBAMAZEPINE (Carbatrol, Equetro, Tegretol, Tegretol XR) Fact Sheet

FDA Indications:

seizures; trigeminal neuralgia; bipolar disorder (Equetro: acute mania).

Dosing:

- Supplied as:
  - 100 mg scored chewable, 200 mg scored tablets as **Tegretol** (Novartis) and generic.
  - 100 mg, 200 mg, 400 mg ER tablets as **Tegretol XR** (Novartis) and generic.
  - 100 mg, 200 mg, 300 mg ER capsules as **Carbatrol** (Shire) and generic.
  - 100 mg, 200 mg, 300 mg ER capsules as **Equetro** (Shire).
  - 100mg/5ml oral solution as **Tegretol** (Novartis) and generic.
- Bipolar disorder: Start 200 mg BID and gradually ↑ by 200 mg/day every three to four days, to target dose of 400 mg–600 mg BID (guided by clinical response). Maximum 800 mg BID.
- Cost (for one month supply at 400 mg BID, priced Nov 2013):
  - Carbamazepine (generic): $8
  - Tegretol: $91.46, Kroger Pharmacy
  - Equatro: $283.35

Side Effects:

- Most common (most bothersome in bold): **dizziness, somnolence,** nausea, headache.
- Serious but rare: hematologic abnormalities including agranulocytosis, aplastic anemia, neutropenia, leukopenia, thrombocytopenia, and pancytopenia reported, hepatic complications including slight increases in hepatic enzymes, cholestatic, and heptocellular jaundice, hepatitis and, rarely, hepatic failure, hyponatremia, SIADH; rash (5%–10%), including exfoliation reported. Severe reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome are rare but can be fatal.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 15 hours (initially 25–65 hours, but induces its own metabolism within two to four weeks and then stabilizes).
- High potential for significant interactions: potent inducer of CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP3A4, P-glycoprotein; use caution with medications significantly metabolized through these pathways as their levels may become subtherapeutic; caution in patients taking strong CYP3A4 inducers or inhibitors which can affect carbamazepine levels.
- Avoid concomitant use with oral contraceptives (possibility of unplanned pregnancy) and with clozapine (additive risk of agranulocytosis).

Clinical Pearls:

- Therapeutic levels: 4 mcg/mL–12 mcg/mL in seizure disorders. Studies in bipolar haven't shown correlation between levels and clinical response, so it's best dosed clinically.
- Lab monitoring: Baseline and periodic (at six weeks and every three months) CBC and LFTs.
- Patients of Asian descent should be screened for the variant HLA-B*1502 allele prior to starting carbamazepine; associated with significantly increased risk of developing Stevens-Johnson syndrome and/or toxic epidermal necrolysis. Avoid use in such patients.

Fun Fact:

Carbamazepine may cause false-positive serum TCA screen and, indeed, its chemical structure contains the familiar tricyclic nucleus common to all TCAs.

Bottom Line:

Equetro is the only FDA-approved formulation for bipolar disorder; however, use of other formulations would result in the same effects, at a much lower price. We still would not recommend carbamazepine as a first-line treatment for bipolar disorder due to its side effect profile and high likelihood of significant interactions.

LAMOTRIGINE (Lamictal, Lamictal ODT, Lamictal XR) Fact Sheet

FDA Indications:

bipolar disorder (maintenance) in adults; seizures in adults and children.

Dosing:

- Supplied as:
  - 25 mg, 100 mg, 150 mg, 200 mg scored tablets as **Lamictal** (GSK) and generic.
  - 2 mg, 5 mg, 25 mg chewable tablets as **Lamictal** (GSK) and generic.
  - 25 mg, 50 mg, 100 mg, 200 mg orally disintegrating tablets as **Lamictal ODT** (GSK).
  - 25 mg, 50 mg, 100 mg, 250 mg, 300 mg ER tablets as **Lamictal XR** (GSK) and generic.
- Bipolar disorder:
  - Start 25 mg QD for 2 weeks, ↑ to 50 mg QD for 2 weeks, then 100 mg QD; maximum dose 200 mg/day.
  - Patients on valproate: Start 25 mg QOD (every other day) for 2 weeks, ↑ to 25 mg QD for 2 weeks, then 50 mg QD; maximum 100 mg/day (VPA doubles lamotrigine levels).
- Cost (for one month supply at 100 mg/day, priced Nov 2013):
  - Lamotrigine (generic): $6.64, Kroger Pharmacy
  - Lamictal: $237.16

Side Effects:

- Most common (most bothersome in bold): dizziness, headache, **nausea,** sedation, benign rash (7%).
- Serious but rare: skin reactions (black box warning): severe, potentially life-threatening skin rashes requiring hospitalization reported, incidence is higher in pediatric patients, risk increased by coadministration with valproic acid, higher than recommended starting doses, and exceeding recommended dose titration. The majority of cases occur in the first eight weeks, but isolated cases may occur beyond eight weeks or in patients without risk factors. Discontinue at first sign of rash and do not reinitiate unless rash is clearly not drug related; rare cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema reported.

Pharmacokinetics and Drug Interactions:

- Metabolism primarily hepatic (non-P450); t ½: 25–33 hours (with VPA 48–70 hours; with carbamazepine 13–14 hours).
- Caution with enzyme inducing medications (eg, carbamazepine), which may decrease lamotrigine levels. Caution with hormonal contraceptives which may decrease lamotrigine levels; lamotrigine maintenance dose may need to be increased (twofold). Gradual increases of lamotrigine levels may occur during the inactive "pill-free" week. Lamotrigine may decrease levels of hormonal contraceptives; alternative birth control methods should be considered.

Clinical Pearls:

- Lamotrigine is useful for the maintenance treatment of bipolar disorder, with best efficacy in the prophylaxis of depressive episodes. Not useful in acute episodes.
- If lamotrigine has been stopped/missed >5 half-lives (see above), consider restarting according to initial dosing recommendations to minimize rash risk.

Fun Fact:

The first FDA-approved drug for bipolar disorder (not just acute mania) since lithium, a drug approved more than 30 years earlier (2003 for lamotrigine; 1970 for lithium).

Bottom Line:

Use of lamotrigine should be reserved for maintenance treatment in patients with predominantly bipolar depressive episodes or bipolar type II.

LITHIUM (Lithobid) Fact Sheet

FDA Indications:

acute mania; bipolar disorder (maintenance) in children and adults.

Dosing:

- Supplied as:
  - 150 mg, 300 mg, 600 mg capsules as lithium (generic).
  - 300 mg ER tablets as **Lithobid** (Noven) and generic.
  - 450 mg ER scored tablets (formerly **Eskalith CR**) as generic only.
  - 300 mg/5 mL as lithium citrate oral solution.
- Bipolar: start 300 mg–600 mg QHS, gradually ↑ to target lithium level of 0.8 mEq/L (usually 900 mg–1200 mg/day). Can be dosed BID–TID or all QHS. Maximum dose 2400 mg/day.
- Cost (for one month supply at 900 mg/day, priced Nov 2013):
  - Lithium (generic): $29.94, Rite-Aid
  - Lithobid: $268.83

Side Effects:

- Most common (most bothersome in bold): **nausea/**diarrhea (take with meals, split dosing, switch to ER), fine tremor (lower dose or use propranolol), polyuria/excessive thirst (dose all at bedtime), memory problems, weight gain, hypothyroidism (7%–8%; 9 times more common in women), acne or worsening psoriasis, benign increase in WBC.
- Serious but rare: chronic use may result in diminished renal concentrating ability (nephrogenic diabetes insipidus); usually reverses when discontinued or treat with hydrochlorothiazide 25 mg–50 mg/day or amiloride 5 mg–10 mg twice daily. Cardiac: bradycardia, cardiac arrhythmia, flattened or inverted T waves, sinus node dysfunction may occur rarely.

Pharmacokinetics and Drug Interactions:

- Eliminated by kidneys; t ½: 18–24 hours.
- Drugs that ↑ lithium levels: "**N**o **ACE** in the **H**ole" (**N**SAIDs, **ACE** inhibitors and **H**CTZ); excess sweating can ↑ levels; low-sodium diet may ↑ lithium levels. Caffeine may ↓ levels.

Clinical Pearls:

- Check lithium level, TSH/T4, BUN/Cr, electrolytes after one week of treatment, at one to two months, then every six to 12 months. Target levels for acute mania: 0.8–1.2 mEq/L; maintenance: 0.6–1.0 mEq/L; toxicity >1.5 mEq/L but may see signs at lower levels.
- An increase or decrease of 300 mg/day will change serum level by roughly 0.25±0.1 mEq/L.
- Dehydration: Use with caution in patients with significant fluid loss (protracted sweating, diarrhea, or prolonged fever); temporary reduction or discontinuation may be necessary.

Fun Facts:

The soft drink 7-UP was originally called "Bib-Label Lithiated Lemon-Lime Soda" and contained lithium until 1950.

Bottom Line:

Lithium remains the gold standard for bipolar disorder and is likely underutilized today. It is more useful for euphoric mania than for mixed and rapid-cycling types of bipolar disorder, but it is effective for depressive episodes and maintenance treatment of bipolar disorder. It is also known for its anti-suicide effects in bipolar and unipolar mood disorders. Although it is not free from side effects, most common effects can be managed quite well.

OXCARBAZEPINE (Trileptal, Oxtellar XR) Fact Sheet

FDA Indication:

seizure disorders in adults and children. Use in bipolar disorder is off label.

Dosing:

- Supplied as 150 mg, 300 mg, 600 mg scored tablets as **Trileptal** (Novartis) and generic; 300 mg/5 mL oral suspension as **Trileptal** and generic; 150 mg, 300 mg, 600 mg ER tablets as **Oxtellar XR** (Supernus).
- Bipolar disorder (off-label): Start 300 mg BID, ↑ by 300 mg/day every 3 days or 600 mg/day weekly to target dose of 600–1200 mg BID. Maximum dose 2400 mg/day. No data on use of XR product for bipolar disorder; caution as higher doses of XR likely needed when converting from IR to XR.
- Cost (for one month supply at 600 mg/day, priced Jan 2014):
  - Oxcarbazepine (generic): $22.18
  - Trileptal: $283.71

Side Effects:

- Most common (most bothersome in bold): **dizziness; somnolence,** headache, ataxia, nausea, vomiting.
- Serious but rare: potentially serious, sometimes fatal, dermatologic reactions (eg, Stevens-Johnson, toxic epidermal necrolysis) reported, monitor for skin reactions. Rare cases of anaphylaxis and angioedema reported, even after initial dosing, permanently discontinue should symptoms occur.
- Use caution in patients with previous hypersensitivity to carbamazepine (cross-sensitivity occurs in 25% to 30%). Clinically significant hyponatremia (serum sodium <125 mmol/L) may develop (1%–3%; higher rate than with carbamazepine), monitor serum sodium, particularly during first three months of therapy especially in patients at risk for hyponatremia.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP450; potent inducer of CYP3A4 and inhibitor of CYP2C19; t ½: 2 hours (nine hours for active metabolite).
- No auto-induction of metabolism and fewer interactions than with carbamazepine. However, there is still potential for interactions. Avoid concomitant use with medications metabolized by CYP3A4 since oxcarbazepine may reduce their levels. Oxcarbazepine may reduce efficacy of oral contraceptives; nonhormonal measures recommended.

Clinical Pearls:

- Oxcarbazepine is the 10-keto analog of carbamazepine (its "chemical cousin"); it is thought of as a "kinder, gentler" carbamazepine due to its more favorable side effect and drug interaction profile.
- Not bioequivalent to carbamazepine. Increase total daily dose by 20%–30% if switching from carbamazepine to oxcarbazepine.

Fun Fact:

While first synthesized in 1965, oxcarbazepine first appeared on US market in 2000. In 2010, Novartis pled guilty to marketing oxcarbazepine for neuropathic pain and bipolar disorder in 2000 and 2001.

Bottom Line:

Compared to carbamazepine, oxcarbazepine poses less concern for drug interactions, hepatic or hematologic toxicities and no need for serum level monitoring. However, due to the paucity of efficacy data in bipolar disorder, it is reserved for second-line use after lithium and valproic acid.

VALPROIC ACID (Depakene, Depakote, Depakote ER, Depakote Sprinkles, Stavzor) Fact Sheet

FDA Indications:

seizures; bipolar disorder (acute mania); migraine prophylaxis.

Dosing:

- Supplied as:
  - 250 mg capsules and 250 mg/5 ml syrup as **Depakene** (Abbott) and generic.
  - 125 mg, 250 mg, 500 mg DR divalproex sodium (sodium valproate and valproic acid in a 1:1 ratio) tablets as **Depakote** (Abbott) and generic.
  - 125 mg DR capsules as **Depakote Sprinkles** (Abbott) and generic.
  - 125 mg, 250 mg, 500 mg DR gel capsules as **Stavzor** (Noven).
  - 250 mg, 500 mg ER tablets as **Depakote ER** (Abbott) and generic.
- Acute mania: start 250 mg–500 mg QHS, ↑ rapidly to effective dose (serum level 50 mcg/ml–125 mcg/ml, usual dose 1000 mg–1500 mg/day); max 4000 mg/day, or 60 mg/kg.
- When converting from regular Depakote to Depakote ER, be aware that patients will get about 20% less valproic acid with the ER formulation.
- Cost (for one month supply at 1,000 mg/day, priced Jan 2014):
  - Valproic acid (generic): $25.66
  - Depakene: $480.32
  - Divalproex (generic): $16.30
  - Depakote: $311.28

Side Effects:

- Most common (most bothersome in bold): **somnolence, nausea,** fatigue, dizziness, hair loss, tremor, thrombocytopenia (up to 24% of patients; dose-related).
- Serious but rare: **hepatotoxicity** rare idiosyncratic reaction, not dose related; most cases occur within 3 months; risk factors: age <2 years, multiple anticonvulsants, and presence of neurologic disease in addition to epilepsy. Asymptomatic elevations of liver enzymes may occur, not necessarily associated with hepatic dysfunction. **Pancreatitis** (rare but potentially fatal). Polycystic ovary syndrome (PCOS) in about 10% of women. Hyperammonemia, encephalopathy (sometimes fatal) reported and may present with normal liver enzymes.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily by liver but by non-CYP450 enzymes; t ½: 9 to 16 hours.
- VPA causes ↑ levels of lamotrigine and risk for rash. Taking with topiramate can lead to encephalopathy.

Clinical Pearls:

- ER tablets have 10% to 20% less fluctuation in serum concentration than delayed release tablets. Divalproex sodium ER and DR tablets are *not* bioequivalent; increase total daily dose by 10%–20% if switching from DR to ER.
- Monitoring: LFTs and CBC with platelets at baseline and Q6 month intervals, PT/PTT (especially prior to surgery), ammonia (with symptoms of lethargy, mental status change).
- Once steady state levels reached (within two to four days of initiation or dose adjustment), trough serum levels should be drawn just before the next dose (ER/DR preparations) or before the morning dose (for immediate-release preparations).

Fun Fact:

Valproic acid was first synthesized in 1882 by B.S. Burton as an analogue of valeric acid, found naturally in valerian.

Bottom Line:

Go-to antimanic agent for acute manic episodes with faster onset of response and better adverse effect profile compared to lithium, fewer drug interactions than carbamazepine, and efficacy for rapid cycling and relapse prevention.

Natural Treatments

Natural products have been used by many cultures to treat a variety of psychiatric illnesses. Very few such products have been subjected to the scientific scrutiny of standardized research methods reserved for standard drug products. As a result, the data to determine a particular product's safety or efficacy profile are minimal. Or, when there are data to suggest safety or efficacy, we are limited in our ability to interpret a product's place in therapy as there are usually no (or very few) active comparator trials.

Another difficulty in utilizing these agents is that these products remain unregulated. This results in a lack of quality control of natural products. Preparations are not standardized from brand to brand, the amount of active constituents can vary not only from brand to brand, but also from batch to batch, and some products may be adulterated with other herbs, chemicals, drugs, or toxins.

Lastly, for those patients who present with significant symptomatology or who have more severe and recurring illness, the use of natural products may delay the use of treatments known to be safe and effective.

All that said, there are some natural products which we deem worth considering in the appropriate patient. To minimize potential for variability or contaminants, we recommend that patients stick to well-known brands sold by trusted retailers.

TABLE 11: NATURAL TREATMENTS

Name (Brand Name, if applicable)	Commonly Available Strengths	Reported Uses in Psychiatry	Usual Dosage Range (starting–max) (mg)
L-methylfolate (Deplin and others)	3, 7.5, 15 mg	Depression (adjunct)	15
Melatonin	0.5, 1, 2.5, 3, 5, and 10 mg	Insomnia	1–10
Omega-3 Fatty Acids (Fish Oil)	500, 1000, and 1200 mg	Depression (unipolar, bipolar)	1000–2000
S-Adenosyl-L-Methionine (SAMe)	100, 200, and 400 mg	Depression	800 BID
St. John's Wort	100, 300, and 450 mg	Depression	300 TID

L-METHYLFOLATE (Deplin, Metafolin, Metanx, others) Fact Sheet

FDA Indications:

"Medical food product" (not FDA-approved drug product); prescription only (Deplin, Metanx); reported use: adjunctive treatment for depression.

Dosing:

- **Deplin:** supplied as L-methylfolate 7.5 mg tablets and 15 mg caplets (Pamlab).
- **Metanx:** supplied as L-methylfolate 3 mg + pyridoxal 5'-phosphate (vitamin B6) 35 mg + methylcobalamin (vitamin B12) 2 mg (Pamlab).
- **Metafolin:** supplied as L-methylfolate 800 mcg (0.8 mg) (Merck).
- Depression (Deplin only): start 7.5 mg QD; target and maximum dose is 15 mg/day.
- Cost (for one month supply at target dose, priced Nov 2013):
  - Deplin (15 mg/day): $123.25, Kmart
  - Metanx (35 mg/day): $62.88, Kroger Pharmacy

Side Effects:

- Most common: not well known; likely well tolerated.
- Serious but rare: folic acid supplementation may mask symptoms of vitamin B12 deficiency (administration of folic acid may reverse the hematological signs of B12 deficiency, including megaloblastic anemia, while not addressing neurological manifestations). L-methylfolate may be less likely than folic acid to mask B12 deficiency though the possibility should be considered. May not be a concern with Metanx.

Pharmacokinetics and Drug Interactions:

- No typical drug metabolism pathway as it is naturally stored and used by body; t ½: 3 hours.
- Drug interactions generally unlikely although L-methylfolate may decrease anticonvulsant levels (including carbamazepine, valproic acid). Drugs that lower folate, such as anticonvulsants (including carbamazepine, valproic acid, lamotrigine), may necessitate higher doses of L-methylfolate.

Clinical Pearls:

- L-methylfolate (Deplin), also known as methyltetrahydrofolate (MTHF), is the active form of folate in the body. L-methylfolate is necessary for the synthesis of monoamines (serotonin, norepinephrine, dopamine). In about 50% the population, genetic variations impair the function of this enzyme (MTHFR) to a greater or lesser degree. A recent review of the data on one of these genetic polymorphisms (called "C677T") found that overall, it did not put people at any higher risk of depression (in fact, schizophrenia was more common).
- A few small studies over the years have shown that both folate (over-the-counter) and L-methylfolate may be somewhat helpful as adjunctive agents in the treatment of depression, particularly in those with low baseline folate levels.

Fun Fact:

"Medical foods" are foods that are specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone. These include total parenteral nutrition as well as nasogastric tube feeds and oral rehydration products. Depression has no accepted "distinctive nutritional needs."

Bottom Line:

Though the data are not robust, folate supplementation *might* be effective for some patients with depression, but we recommend that patients try the cheap stuff (folic acid) before springing for Deplin (L-methylfolate).

MELATONIN Fact Sheet

FDA Indications:

not regulated; reported uses: insomnia, jet lag, and work-shift sleep disorder.

Dosing:

- Supplied over the counter (OTC) in various forms including liquid, tablets, capsules, sublingual, and time-release formulations; usually in 0.5 mg, 1 mg, 2.5 mg, 3 mg, 5 mg, and 10 mg.
- Insomnia (adults): 0.5 mg to 20 mg in the early evening. Emerging data suggest lower doses are effective; start low (0.5 mg–1 mg), gradually increase to desired effect ("normal" melatonin levels vary widely among individuals and same dose can induce different levels depending on age or health).
- For jet lag, usual dose is 1 mg–3 mg on day of departure at a time that corresponds to the anticipated bedtime at arrival destination, followed by 1 mg–3 mg at bedtime for next three to five days.
- Cost (for one month supply at 3 mg/day, priced Nov 2013):
  - Nature Made brand: $1 (240 capsules: $8.12)

Side Effects:

- Most common (most bothersome in bold): generally well tolerated in the short-term. Drowsiness, headaches and dizziness most common but at similar rates to placebo; next-day grogginess or irritability (higher doses); vivid dreams or nightmares (higher doses).
- Serious but rare: no serious side effects reported; however, long-term human studies have not been conducted. Theoretically, melatonin may alter other hormones (inhibiting ovulation in women and gonadal development in children and adolescents); avoid use in women who are pregnant or are attempting to become pregnant and use caution in children.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP1A2, may inhibit CYP1A2; t ½: 35–50 minutes.
- Some suggest melatonin may reduce glucose tolerance and insulin sensitivity and may ↑ efficacy of calcium channel blockers for blood pressure.

Clinical Pearls:

- Melatonin is secreted from the pineal gland in a 24-hour circadian rhythm. It rises at sunset and peaks in middle of night, regulating the normal sleep/wake cycle.
- Melatonin should only be taken in its synthetic form; the "natural" form comes from ground-up cow pineal glands and may spread disease (eg, Mad Cow disease).
- Melatonin taken at bedtime doesn't seem to affect nocturnal sleep. Taken in the early evening, it appears to be similar to temazepam in hypnotic effect.
- Although melatonin products have been available over the counter in the US since the mid-1990s, many other countries do not permit its sale or require a prescription.

Fun Fact:

Foods containing melatonin include cherries, bananas, grapes, rice, cereals, herbs, olive oil, wine, and beer.

Bottom Line:

Short-term melatonin treatment appears to only modestly reduce the time it takes to fall asleep (about 12 minutes, might not be considered clinically relevant) and does not appear to significantly improve sleep. However, some patients report minor improvement in subjective feelings of sleep quality. It may be something to consider using in the short-term, particularly in older patients (whose endogenous melatonin levels are lower). It is cheaper than ramelteon (Rozerem); however, like ramelteon, we are lacking good long-term safety data, especially with regard to effects on hormones.

OMEGA-3 FATTY ACIDS (Fish Oil, Lovaza) Fact Sheet

FDA Indications:

not regulated; reported uses in unipolar and bipolar depression, and other conditions; effective for high triglycerides (Lovaza is FDA-approved for this indication), likely effective in heart disease and possibly hypertension.

Dosing:

- Supplied over the counter (OTC) in various dosages and formulations; 500 mg, 1000 mg, and 1200 mg softgel capsules most common.
- By prescription only: **Lovaza:** 1000 mg softgel capsules (GSK). Dosage on label usually reflects fish oil dosage, which is not the same as omega-3 fatty acid dosage (eg, 1000 mg fish oil in some brands may provide 300 mg of omega-3 fatty acids, including EPA and DHA). Dosing recommendations are based on mg of fish oil.
- Effective dose unclear, but studies have used 300 mg to 6 grams QD. For depression, start 500 mg/day, increase as tolerated (usual target dose 1 gram–2 grams/day); doses >3 g/day should be used cautiously. Dividing dose BID–TID helps with side effect tolerability.
- Cost (for one month supply at 4 g/day, priced Jan 2014):
  - OTC Omega-3 Nordic Naturals brand: $25.46, The Vitamin Shoppe
  - Lovaza: $227.63

Side Effects:

- Most common: well tolerated up to 4 grams/day. Nausea, loose stools, fishy aftertaste.
- Serious but rare: caution in those who are allergic to seafood. Increased risk of bleeding, particularly at higher doses.

Pharmacokinetics and Drug Interactions:

- Metabolism is hepatic, primarily through CYP450; t ½: unknown.
- For most patients, drug interactions not likely an issue; however, may prolong bleeding time. Fish oils may lower blood pressure and have additive effects when used with antihypertensives.

Clinical Pearls:

- Fish oils contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); both are omega-3 fatty acids (which form the lipid bilayers of cell membranes). Although the body can synthesize these fats from alpha-linolenic acid (ALA), this is believed to be inefficient in many people.
- EPA and DHA are derived from fish; ALA is derived from flax seed and other vegetable matter. Mercury accumulates in fish meat more than in fish oil, which might explain the lack of detectable mercury in most fish oil supplements. Also, the manufacturing process used to deodorize fish oil supplements seems to lower levels of PCBs and other contaminants.

Fun Fact:

Inuit people have been reported to ingest up to 16 grams/day (via fish) with no dangerous side effects.

Bottom Line:

The evidence on efficacy in depression is conflicting and the ideal dose has not been established. However, since omega-3 fatty acids are fairly benign and may offer other health benefits, you may consider using it from time to time. Based on the limited data available, we recommend the best use of omega-3 fatty acids (particularly 1 gram–2 grams with at least 60% EPA) is as an adjunct in the treatment of unipolar and bipolar depression in less severely ill patients, but there is not enough evidence to recommend omega-3 fatty acids in other disorders at this time.

S-ADENOSYL-L-METHIONINE (SAMe) Fact Sheet

FDA Indications:

not regulated; reported use in depression as well as osteoarthritis.

Dosing:

- Supplied over the counter most often as 100 mg, 200 mg, and 400 mg tablets, usually enteric coated.
- Effective dose is variable but most antidepressant studies have used doses of about 400 mg–1600 mg/day (1600 mg most common), usually divided BID.
- Cost (for 36, 400 mg pills, priced Jan 2014):
  - Nature Made brand: $25

Side Effects:

- Most common: well tolerated. Higher doses may result in flatulence, nausea, vomiting, diarrhea, constipation, dry mouth, headache, mild insomnia, anorexia, sweating, dizziness, and nervousness. Anxiety and tiredness have occurred in people with depression, and hypomania in people with bipolar disorder.
- Serious but rare: safe. Theoretical concern of elevated homocysteine since SAMe is converted to this during normal metabolism. No reports to date but some recommend taking folate and vitamin B supplements anyway.

Pharmacokinetics and Drug Interactions:

- Metabolism similar to endogenous SAMe (transmethyltion, trans-sulphuration and amino-propylation); t ½: 100 minutes.
- No drug interactions reported. Theoretically, serotonin syndrome possible but no reports.

Clinical Pearls:

- SAMe is produced by our bodies as a derivative of the amino acid methionine. It functions as a methyl donor and is necessary for the production of serotonin and norepinephrine (and in more than 100 other biochemical reactions) throughout virtually all body tissues and fluids. Concentrations are highest in childhood and decrease with age.
- SAMe is difficult to formulate as a stable oral salt, and the FDA halted trials of an investigational prescription product in 1993 due to concerns about tablet dissolution; concerns have been raised that some supplements may also have these problems.

Fun Facts:

SAMe has been available as a dietary supplement in the US since 1999, but it has been used as a prescription drug in Italy since 1979, in Spain since 1985, and Germany since 1989. Patients in trials of SAMe for depression noted improvement in their arthritis symptoms, suggesting another possible use.

Bottom Line:

Several clinical studies (lasting up to 42 days) have shown that taking SAMe is more effective than placebo and appears to be as effective as TCAs. However, some of these studies are limited by small numbers of patients, inconsistent diagnostic criteria, and short treatment periods. It may have a role as an adjunctive agent in patients who do not respond to antidepressants. Consider using this for those patients with mild to moderate depression who are interested in using alternative therapies, or as an augmentation strategy in partial responders.

St. John's Wort Fact Sheet

FDA Indications:

not regulated; reported use: depression.

Dosing:

- Supplied over the counter most commonly as 100 mg, 300 mg, and 450 mg tablets and capsules.
- For mild to moderate depression, most clinical trials have used St. John's wort extract containing 0.3% hypericin and/or 3% hyperforin; most common dose is 300 mg TID. Doses of 1200 mg QD have also been used. Some studies have also used a 0.2% hypericin extract dosed at 250 mg BID. A St. John's wort extract standardized to 5% hyperforin and dosed at 300 mg TID has also been used.
- Cost (for one month supply at 350 mg/day, priced Nov 2013):
  - Nature's Way brand: $5.49

Side Effects:

- Most common: well tolerated at recommended doses. Insomnia (decrease dose or take in morning), vivid dreams, restlessness, anxiety, agitation, irritability, gastrointestinal discomfort, diarrhea, fatigue, dry mouth, dizziness, and headache reported. Sexual dysfunction may occur but less often than with SSRIs.
- Serious but rare: risk of severe phototoxic skin reactions and photosensitivity at high doses (2–4 grams/day).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through the liver; t ½: 24–48 hours.
- Avoid concomitant use with serotonergic agents: rare cases of serotonin syndrome reported. Potent inducer of many CYP450 enzymes (3A4, 2C9, 1A2) and p-glycoprotein transporter, which results in increased metabolism and reduced plasma concentrations of a large number of drugs. St. John's wort can decrease oral contraceptive levels by 13% to 15%, resulting in bleeding or unplanned pregnancy; women should use an additional or nonhormonal form of birth control.

Clinical Pearls:

- Also known as *Hypericum perforatum*; active constituents (predominantly hypericin and hyperforin) are derived from the flowering buds. Thought to exert antidepressant effects by modulating effects of monoamines, and may inhibit reuptake of these neurotransmitters.
- St. John's wort is more effective than placebo, likely as effective as low-dose TCAs, and likely as effective as SSRIs in milder forms of depression; however, a study in *JAMA* found it no more effective than placebo or sertraline for moderate to severe depression.
- Avoid abrupt discontinuation due to the risk of withdrawal effects.

Fun Facts:

Although not indigenous to Australia and long considered a weed, St. John's wort is now grown as a cash crop and Australia produces 20 percent of the world's supply. The use of St. John's wort dates back to the ancient Greeks; Hippocrates documented the medical use of St. John's wort flowers. St. John's wort is so named because it blooms about June 24th, the birthday of John the Baptist. "Wort" is an old English word for plant.

Bottom Line:

St. John's wort can be considered an option along with conventional antidepressants for short-term treatment of mild depression; however, since it can cause many drug interactions, it would not be an appropriate choice for many patients, particularly those taking other medications.

Novel Anticonvulsants

Antiepileptic drugs affect various neurotransmitters (eg, GABA, glutamate), receptors (eg, GABAergic, glutamatergic), and ion channels (eg, for sodium or calcium). Such a broad spectrum of activity, combined with the fact that these pathways have been implicated in many psychiatric disorders, has led these agents to be tried in numerous other conditions. The newer anticonvulsants are appealing because they are generally less toxic than the older agents, do not require serum level monitoring, and in most cases have a lower risk of drug interactions. But do they work when used off-label in psychiatric disorders?

Gabapentin, pregabalin, tiagabine, and topiramate were all initially touted to have efficacy in bipolar disorder. The data that followed did not support such a claim. Still, data continue to emerge regarding the potential uses of these agents in anxiety disorders, including PTSD, alcohol dependence, and other conditions. We have yet to be convinced regarding efficacy. We also maintain a certain level of concern as the agents may cause significant adverse effects. Furthermore, the antiepileptics have a class warning for increased risk of suicidal thoughts and behavior; this warning stems from pooled analysis of trials (for seizure disorders as well as other indications) that showed a nearly doubling incidence of suicidal thought and behavior (0.43% for anticonvulsants vs 0.24% for placebo).

For now, we do not endorse their use except in the unusually treatment-refractory patient who has tried and failed medications with a more proven track record.

GABAPENTIN (Gralise, Horizant, Neurontin) Fact Sheet

FDA Indications:

partial seizures (Neurontin); post-herpetic neuralgia (Gralise, Neurontin); restless leg syndrome (Horizant).

Dosing:

- Supplied as:
  - 100 mg, 300 mg, 400 mg capsules, 600 mg, 800 mg tablets, 50 mg/ml oral solution as **Neurontin** (Pfizer) and generic.
  - 300 mg, 600 mg ER tablets as **Gralise** (Depomed).
  - 300 mg, 600 mg ER gabapentin enacarbil (a prodrug with better bioavailability) tablets as **Horizant** (GSK).
- For anxiety (off label use), start at 100 mg QHS and increase as tolerated to 300 mg TID. Maximum dose is 3600 mg/day (highest doses often used for pain indications). Use lower doses in patients with renal impairment.
- Cost (for one month supply at 300 mg TID, priced Jan 2014):
  - Gabapentin (generic): $13.78
  - Neurontin: $254.62

Side Effects:

- Most common (most bothersome in bold): **dizziness, somnolence**, ataxia, fatigue, weight gain.
- Serious but rare: potentially serious, sometimes fatal multiorgan hypersensitivity (also known as drug reaction with eosinophilia and systemic symptoms or DRESS, see page 79).

Pharmacokinetics and Drug Interactions:

- Not metabolized; excreted unchanged by kidneys; t ½: 5–7 hours.
- Few significant drug interactions; although you may see additive sedative effects with other sedating drugs. Analgesic control may be affected when gabapentin is added to opiates, including decreased levels of hydrocodone (Vicodin) or increased levels of morphine.

Clinical Pearls:

- Gabapentin is structurally related to GABA. However, it does not bind to GABAA or GABAB receptors, and it does not appear to influence synthesis or uptake of GABA.
- Controlled trials have shown no effect as monotherapy or adjunctive therapy for bipolar disorder.
- There have been reports of recreational use of gabapentin in correctional facilities, some of which have restricted its use.

Fun Facts:

Up to 90% of prescriptions for Neurontin have been for off-label uses. While off-label prescribing is not illegal, the promotion of off-label uses by a drug manufacturer is. A whistleblower lawsuit led to a $430 million settlement by Pfizer for the off-label marketing of Neurontin.

Bottom Line:

Studies have failed to find a role of gabapentin in the management of bipolar disorder. The same holds for its use in other off-label psychiatric conditions, such as insomnia and alcohol dependence. Gabapentin may have some utility in the treatment of anxiety symptoms, particularly when an antihistaminergic drug or benzodiazepine is not appropriate, or when neuropathic pain complaints are also present.

PREGABALIN (Lyrica) Fact Sheet

FDA Indications:

diabetic peripheral neuropathy; spinal cord injury-associated neuropathic pain; post-herpetic neuralgia; partial seizures; fibromyalgia.

Dosing:

- Supplied as 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg capsules as **Lyrica** (Pfizer).
- Start at 75 mg BID and ↑ as tolerated to a maximum of 300 mg BID (based on trials for generalized anxiety disorder, an off-label use). Use lower doses in renal impairment.
- Schedule V controlled substance (same category as cough suppressants containing codeine).
- Cost (for one month supply at 75 mg BID, priced Nov 2013):
  - Lyrica: $237.12

Side Effects:

- Most common (most bothersome in bold): peripheral edema, **dizziness, somnolence**, ataxia, weight gain.
- Serious but rare: hypersensitivity reactions, including skin redness, blistering, hives, rash, dyspnea, and wheezing. Angioedema, possibly life threatening, reported, use with caution in patients with a history of angioedema or patients on ACE Inhibitors. Increases in CPK and rare cases of rhabdomyolysis reported.

Pharmacokinetics and Drug Interactions:

- Negligible metabolism; mostly excreted unchanged by kidneys; t ½: 6 hours.
- No significant drug interactions, although you may see additive sedative effects with other sedating drugs.

Clinical Pearls:

- Pregabalin is related in structure to gabapentin but is more potent, has faster absorption and greater bioavailability.
- Controlled substance (C-V) because following abrupt withdrawal, insomnia, nausea, headache, or diarrhea may occur; this may be suggestive of physical dependence.
- For generalized anxiety disorder, pregabalin appears more effective than placebo but data comparing it to benzodiazepines are inconsistent.

Fun Facts:

Another drug related to gabapentin and pregabalin may follow; Pfizer is studying atagabalin for use in insomnia.

Bottom Line:

We may consider trying pregabalin in a patient with generalized anxiety disorder who has failed or not tolerated multiple SSRI trials, or when neuropathic pain is a concurrent symptom. However, when depression coexists with anxiety, we still believe an SSRI or SNRI is a better option.

TIAGABINE (Gabitril) Fact Sheet

FDA Indication:

partial seizures (as adjunctive treatment) in adults and children >12 years.

Dosing:

- Supplied as 2 mg, 4 mg, 12 mg, 16 mg unscored tablets as **Gabitril** (Cephalon) and generic.
- Dosing recommendations in PDR are applicable to epileptic patients already on other anticonvulsants which induce tiagabine's metabolism; not applicable to psychiatric dosing.
- Anecdotal reports suggest dosing by starting at 2 mg BID and ↑ by 2 mg BID increments as needed; maximum dose used in psychiatry trials is 16 mg/day.
- Cost (for one month supply at 4 mg/day, priced Nov 2013):
  - Tiagabine (generic): $75.80, CVS Pharmacy
  - Gabitril: $201.45

Side Effects:

- Most common (most bothersome in bold): **decreased concentration, dizziness**, nervousness, **somnolence**, nausea, tremor, weakness, difficulty speaking clearly, tingling in hands and fingers.
- Serious but rare: new-onset seizures and status epilepticus have been associated with tiagabine use for unlabeled indications, often these occurred shortly after initiation or shortly after dose increase. Seizures have also occurred with very low doses or after several months of therapy. In most cases, patients were using concomitant medications (eg, antidepressants, antipsychotics, stimulants, narcotics).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 7–9 hours (2–5 hours with enzyme inducers).
- Caution when administering with CYP3A4 inducers or inhibitors; may have additive sedative effects when given with CNS depressants.

Clinical Pearls:

- Based on three trials of over 1800 patients with generalized anxiety disorder, tiagabine did not show decrease in anxiety measures.
- No randomized trial evidence evaluating tiagabine for bipolar disorder. No randomized trials of tiagabine for acute mood episodes or for maintenance treatment of bipolar disorder.
- Used sometimes for substance abusers as a non-addictive alternative to benzodiazepines but evidence for this is lacking.

Fun Facts:

Gabitril is manufactured by Cephalon; the company's name comes from the adjective "cephalic" meaning "related to the head or brain," and it was established primarily to pursue treatments for neurodegenerative diseases. They also manufacture Provigil.

Bottom Line:

Off-label use is strongly discouraged as tiagabine has, ironically, been associated with new-onset seizures, including status epilepticus. Lack of efficacy data in psychiatric setting make this risk difficult to justify.

TOPIRAMATE (Topamax, Trokendi XR) Fact Sheet

FDA Indications:

seizure disorders for patients >2 years; migraine prophylaxis.

Dosing:

- Supplied as:
  - 25 mg, 50 mg, 100 mg, 200 mg tablets and 15 mg, 25 mg sprinkle capsules as **Topamax** (Janssen) and as generic.
  - 25 mg, 50 mg, 100 mg, 200 mg ER capsules as **Trokendi XR** (Supernus).
- Seizures/migraine: start 25 mg–50 mg QHS and ↑ by 50 mg/day in weekly increments. Doses used in psychiatry have typically been 50 mg–300 mg/day, divided BID.
- Cost (for one month supply at 50 mg/day, priced Jan 2014):
  - Topiramate (generic): $8.02
  - Topamax: $259.75

Side Effects:

- Most common (most bothersome in bold): **somnolence, dizziness, fatigue, nervousness,** ataxia, psychomotor slowing, speech problems, memory difficulties, confusion, anorexia.
- Serious but rare: decreases in serum bicarbonate (metabolic acidosis) relatively common but usually mild to moderate; more severe cases, including marked reductions to <17 mEq/L may occur more rarely. Watch for kidney stones, osteomalacia.

Pharmacokinetics and Drug Interactions:

- Not metabolized, excreted primarily unchanged; t ½: 21 hours; mild CYP3A4 inducer.
- Avoid concomitant use with hydrochlorothiazide: increased risk for hypokalemia; monitor potassium. Additive effects with sedatives or alcohol. Concurrent use with valproic acid may increase risk of hyperammonemia and associated encephalopathy. Higher doses (>200 mg/day) may decrease levels of some drugs, including contraceptives (P450 induction).

Clinical Pearls:

- Very limited anecdotal reports, case series and open trials published, *suggest* efficacy in a wide range of psychiatric disorders including bipolar disorder, PTSD, alcohol dependence, binge-eating disorder, and obesity. Available data do not support the increase in use of this drug by psychiatrists.
- Randomized controlled trials in bipolar disorder do not support the notion that topiramate is efficacious or that it should be considered for use over other agents with proven efficacy.
- Some patients may lose weight but this is not common; greatest decrease in weight seems to occur in heaviest patients (>100 kg). When weight loss occurs, it is often not a large effect (mean of 6 kg) nor is it a sustained effect (patients return to pretreatment weight after 12–18 months).
- A combination of extended release topiramate and phentermine was FDA-approved in 2012 for the long-term treatment of obesity as Qsymia (Vivus Pharmaceuticals).

Fun Facts:

Dose-related cognitive effects of topiramate have led some to refer to Topamax as "Dopamax."

Bottom Line:

Absence of evidence of efficacy, coupled with potential for adverse effects and drug interactions make it difficult for us to endorse use of this drug.

Sexual Dysfunction Medications

As with many physical complaints, sexual dysfunction (decreased libido in particular) may be secondary to psychiatric illness itself, a side effect of psychiatric medication, or unrelated to one's psychiatric condition entirely. A comprehensive evaluation and history is essential to determine the true cause. That said, antidepressant-associated sexual side effects may be underestimated, since clinical trials have traditionally relied on patient self-report of such adverse events, and clinicians often do not inquire about this side effect. Experience has shown that delayed orgasm or ejaculation may occur in more than 50% of patients on SSRIs, and anorgasmia in at least one-third.

Antidepressant-induced sexual side effects are one of the most common reasons for patients to discontinue treatment, but they can be successfully managed. One approach is to change to a different antidepressant without significant sexual effects, such as bupropion or mirtazapine; this may be the best approach in patients who are not adequately responding to their current antidepressant treatment. Some have suggested drug holidays, although this may be impractical; for example, fluoxetine has a long half-life, while shorter-acting SSRIs may cause a discontinuation syndrome or a recurrence of symptoms. Another effective approach for many patients is the use of adjunctive treatment with medications such as cyproheptadine, sildenafil, tadalafil, or vardenafil.

TABLE 12: SEXUAL DYSFUNCTION MEDICATIONS

Generic Name (Brand Name) Year FDA Approved *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg)	Starting Dose (mg)	Usual Dosage Range (starting–max) (mg)
Cyproheptadine 1961 brand name Periactin discontinued; generic only	None	4; 2/5 ml	4	4–12
Sildenafil (Viagra) 1998 generic only available as 20 mg tablet	Erectile dysfunction	25, 50, 100	25	25–100
Tadalafil (Cialis) 2003 generic not available	Erectile dysfunction	2.5, 5, 10, 20	5	5–20
Vardenafil (Levitra) 2003 generic not available	Erectile dysfunction	2.5, 5, 10, 20	10	10–20
Vardenafil ODT (Staxyn) 2010 generic not available	Erectile dysfunction	10 ODT	10	10

CYPROHEPTADINE Fact Sheet

FDA Indications:

allergic rhinitis; urticaria.

Dosing:

- Supplied as 4 mg scored tablets and 2mg/5 ml syrup as generic only; Pericatin brand discontinued.
- Cost (for one month supply at 4 mg/day, priced Nov 2013):
  - Cyproheptadine (generic): $8.31

Side Effects:

- Most common (most bothersome in bold): **sedation,** confusion, weight gain, anticholinergic effects.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through hepatic glucuronidation via UGT1A; t ½: 16 hours.
- Avoid concomitant use with MAOIs. Additive effects with other sedating agents.

Clinical Pearls:

- Cyproheptadine is a potent antihistamine and serotonin antagonist with several off-label uses including migraine prophylaxis, vascular headaches, spasticity in spinal cord injury, acute management of serotonin syndrome, anorexia nervosa, and the management of psychotropic-induced sexual side effects.
- There have been some reports of reversal of fluoxetine efficacy, presumably due to serotonin antagonist effects of cyproheptadine. Given the likely limited, sporadic use within the context of sexual side effect management, this is not likely a big cause for concern for most.

Fun Facts:

Cyproheptadine has been shown to be useful as part of the management of serotonin syndrome. It is also the most commonly used appetite stimulant for cats.

Bottom Line:

Cyproheptadine is effective in reversing SSRI-induced anorgasmia, but with continued use it could interfere with antidepressant efficacy. Occasional use of cyproheptadine can be recommended, but excessive sedation may negate its potential benefit in many patients.

SILDENAFIL (Viagra) Fact Sheet

FDA Indications:

erectile dysfunction; pulmonary arterial hypertension (Revatio brand name).

Dosing:

- Supplied as 25 mg, 50 mg, 100 mg unscored tablets as **Viagra** (Pfizer) and generic (20 mg tablets only).
- Avoid taking with high fat meal.
- Cost (for 10, 50 mg tablets, priced Nov 2013):
  - Viagra: $286.70

Side Effects:

- Most common (most bothersome in bold): **headache,** dyspepsia/heartburn, flushing.
- Serious but rare: may cause dose-related impairment of color discrimination. Sudden decrease or loss of hearing has been reported rarely, hearing changes may be accompanied by tinnitus and dizziness. Decreases in blood pressure may occur due to vasodilator effects, concurrent use with alpha-adrenergic antagonist or substantial alcohol consumption may cause symptomatic hypotension. Avoid use with nitrates (see below). Painful erection >6 hours in duration (priapism) may occur rarely.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 4 hours.
- Avoid concomitant use with nitrates in any form (eg, nitroglycerin, isosorbide dinitrate, amyl nitrate or "poppers"). Use with caution in patients taking alpha-adrenergic blockers; may cause symptomatic hypotension. Use with caution in patients taking strong CYP3A4 inhibitors which may increase or extend effects of sildenafil (maximum of 25 mg in 48 hours).

Clinical Pearls:

- Onset of effect is usually 15–20 minutes after a dose (but may be delayed 60 minutes by high fat meal) and usual duration is approximately two hours.

Fun Fact:

Sildenafil has been used recreationally. Some users mix it with methylenedioxymethamphetamine (MDMA, ecstasy), other stimulants, or opiates to try to compensate for the common side effect of erectile dysfunction; this combination is known as "sextasy."

Bottom Line:

Of the agents in this class, sildenafil has the best evidence to support its use, particularly in men, as an augmentation agent with SSRIs for managing sexual side effects.

TADALAFIL (Cialis) Fact Sheet

FDA Indications:

erectile dysfunction; benign prostatic hyperplasia; pulmonary arterial hypertension (Adcirca brand name).

Dosing:

- Supplied as 2.5 mg, 5 mg, 10 mg, 20 mg unscored tablets as **Cialis** (Lilly).
- Give 5 mg–20 mg, no more than once daily, 30–60 minutes prior to sexual activity.
- Cost (for 10, 20 mg tablets, priced Nov 2013):
  - Cialis: $339.29

Side Effects:

- Most common (most bothersome in bold): **headache,** dyspepsia/nausea, flushing, back pain, muscle aches.
- Serious but rare: may cause dose-related impairment of color discrimination. Sudden decrease or loss of hearing has been reported rarely, hearing changes may be accompanied by tinnitus and dizziness. Decreases in blood pressure may occur due to vasodilator effects, concurrent use with alpha-adrenergic antagonist or substantial alcohol consumption may cause symptomatic hypotension. Avoid use with nitrates (see below). Painful erection >6 hours in duration (priapism) may occur rarely.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 15–17.5 hours.
- Avoid concomitant use with nitrates in any form (eg, nitroglycerin, isosorbide dinitrate, amyl nitrate or "poppers"). Use with caution in patients taking alpha-adrenergic blockers; may cause symptomatic hypotension. Use with caution in patients taking strong CYP3A4 inhibitors which may increase or extend effects of tadalafil (maximum of 2.5 mg/day).

Clinical Pearls:

- Onset of effect of tadalafil is usually within one hour of a dose and its effects may last 36 hours.

Fun Fact:

Cialis's 36-hour effectiveness earned it the nickname, "The Weekend Pill."

Bottom Line:

Fewer data with tadalafil in psychiatric setting; however, compared to other agents in the class, tadalafil's long duration of action may improve spontaneity and the lack of interaction with meals may offer advantages.

VARDENAFIL (Levitra, Staxyn) Fact Sheet

FDA Indication:

erectile dysfunction.

Dosing:

- Supplied as 2.5 mg, 5 mg, 10 mg, 20 mg unscored tablets as **Levitra** (Bayer, GSK and Merck) and 10 mg orally disintegrating tablets as **Staxyn** (Bayer).
- Give 10 mg–20 mg, no more than once daily, one hour prior to sexual intercourse. For ODT (Staxyn), maximum is 10 mg/day. Avoid taking with high fat meal.
- Cost (20 mg tablets, priced Jan 2014):
  - Levitra (10 tablets): $298.33 (approx $30 per pill)
  - Staxyn (8 tablets): $154.54 (approx $19.30 per pill)

Side Effects:

- Most common (most bothersome in bold): flushing, **headache,** nasal congestion, heartburn.
- Serious but rare: may cause dose-related impairment of color discrimination. Sudden decrease or loss of hearing has been reported rarely, hearing changes may be accompanied by tinnitus and dizziness. Decreases in blood pressure may occur due to vasodilator effects, concurrent use with alpha-adrenergic antagonist or substantial alcohol consumption may cause symptomatic hypotension. Avoid use with nitrates (see below). Painful erection >6 hours in duration (priapism) may occur rarely.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 4–5 hours.
- Avoid concomitant use with nitrates in any form (eg, nitroglycerin, isosorbide dinitrate, amyl nitrate or "poppers"). Use with caution in patients taking alpha-blockers; may cause symptomatic hypotension. Use with caution in patients taking strong CYP3A4 inhibitors which may increase or extend effects of vardenafil (maximum of 5 mg/day).

Clinical Pearls:

- Taking with high fat meal may decrease serum vardenafil levels by as much as 50%.
- Usual onset of effect of vardenafil is within one hour of a dose; effects usually last two hours.

Fun Fact:

Staxyn, the orally disintegrating tablet form of vardenafil, is peppermint-flavored.

Bottom Line:

Vardenafil doesn't offer any benefits compared to sildenafil, which has more data in the psychiatric setting and more clinical experience.

Substance Abuse/Dependence Medications

Patients who present to the psychiatric setting should be assessed for substance use disorders. The successful treatment of substance use disorders often requires a multifactorial approach, and most experts recommend a combination of therapy (individual, group, family), medication management, treatment of comorbid conditions, and community support (eg, 12-step programs). In this section we will discuss currently available pharmacologic agents that may serve as part of your treatment strategy.

Opioid Dependence

Methadone was first approved by the FDA for use in opioid dependence in 1947. As a result of regulatory controls on methadone treatment facilities, treatment, while effective, has historically been isolated from conventional medical care and patients have been stigmatized. More recently, the availability of office-based treatment with the partial opioid agonist buprenorphine (previously sold as branded Subutex) and buprenorphine/naloxone combination (Suboxone), both approved in 2002, has made treatment for opioid dependence (whether for heroin or prescription opiates) more available and more acceptable to patients.

Using measurements such as treatment retention and negative urine samples, buprenorphine has been shown to be more effective than low-dose methadone (20 mg–40 mg/day) and equally effective as moderate- and high-dose methadone maintenance (up to 100 mg/day). However, unlike methadone, which displays better efficacy at higher doses compared to lower doses, buprenorphine seems to have a ceiling effect at 32 mg/day. Buprenorphine may also be more convenient for patients because a 30-day supply can be given to patients relatively soon after starting treatment, rather than requiring daily visits to a clinic. Patients on methadone maintenance treatment are not permitted such a take-home supply until a minimum of two years of compliance (five years in Florida) with a program.

These pharmacologic interventions are considered part of a harm reduction model with reduction in criminal activity and infections resulting from injection drug use. Particularly in patients who are not engaged in a recovery program or who have not made the necessary lifestyle changes, relapse rates can be high after treatment is discontinued. Unfortunately, while lifelong treatment is impractical, there has been no consensus on the preferred duration of buprenorphine treatment.

Alcohol Dependence

Psychiatric illness is highly associated with substance use, particularly alcoholism. Epidemiologic data suggest that as many as 45% of individuals with alcohol use disorders have a co-occurring psychiatric disorder. Other epidemiologic data suggest an even higher rate of lifetime comorbidity, with 78% of alcohol-dependent men and 86% of alcohol-dependent women meeting lifetime criteria for another psychiatric disorder.

Diagnosis can be difficult due to the fact that the relationship between alcohol use and psychiatric illness can be quite complex. Patients may use alcohol to self-medicate underlying psychiatric symptoms; conversely, chronic and excessive use of alcohol may unmask or worsen an underlying psychiatric disorder. In addition, alcohol intoxication or withdrawal symptoms may mimic psychiatric symptoms. Observing patients during a period of abstinence is ideal for accurate diagnosis but is often not possible.

Disulfiram was for a long time the only approved medication for treating alcohol dependence, and is still used today in patients with a high commitment to abstinence. Over the past 10 to 20 years, the FDA has approved several medications to assist in the treatment of alcoholism. Naltrexone blocks a specific type of opiate receptor in the brain, and is thought to act by reducing cravings and the rewarding effects of alcohol. Acamprosate has been found to be effective in maintaining abstinence post-detoxification. It is thought to "normalize" the brain glutamate system, which becomes unstable after many years of heavy alcohol use. Acamprosate may work best in those not abusing other substances, those who can stay alcohol-free prior to initiating, and those who have a strong commitment to abstinence.

As mentioned above, these medications are best used as part of a comprehensive treatment approach, but no single strategy has emerged as ideal. Naltrexone has been found to work best when combined with various forms of relapse-prevention counseling, including cognitive behavioral therapy. Trials with acamprosate, on the other hand, have been mixed.

Combining pharmacotherapies is another area of interest. The combination of acamprosate and disulfiram seems to be more effective than acamprosate alone; however, the combination of naltrexone and acamprosate

has not shown added benefit over using naltrexone alone. As with opioid dependence, relapse rates can be high and long-term maintenance treatment may be considered for many patients.

Smoking Cessation

We are all familiar with the toll of tobacco use and the enormous health and economic burden it imposes on individuals and society. In fact, 70% of smokers report wanting to quit and 44% make at least one quit attempt each year. Interestingly, smokers who are advised to quit by a physician are 50% more likely to make a quit attempt than those who do not receive such counseling.

In addition to the fact sheets that follow, you may want to consult the Public Health Service's *Treating Tobacco Use and Dependence 2008 Update*, found on the Surgeon General's website at www.surgeongeneral.gov/tobacco or by calling the Agency for Healthcare Research and Quality at 800-358-9295.

There are two non-nicotine medications, bupropion SR and varenicline, and five nicotine medications, including an inhaler, nasal spray, gum, lozenge, and patches (known collectively as *nicotine replacement therapy* or NRT). Abstinence rates vary from study to study, but basically any of these medications may double the patient's success rate compared to placebo (from about 13% to 25%). Some data have suggested that success rates with varenicline may be even higher (three times placebo) and better than those with NRT or bupropion SR, although significance values were only borderline in several studies.

NRT reduces the symptoms of withdrawal in smokers attempting to quit by replacing some of the nicotine usually obtained by smoking; it doesn't completely eliminate withdrawal symptoms because the delivery of nicotine via these medications doesn't replicate the very rapid and high levels of nicotine achieved via smoking. All forms of NRT have equivalent efficacy. The gum and lozenge provide oral sensations that are often missed when quitting smoking, while the inhaler most closely mimics the sensation of smoking. Patches release nicotine steadily over a prolonged period.

Some smokers may be 'peak seekers' who smoke irregularly, while others may be 'steady-state maintainers' who want to control withdrawal symptoms and therefore smoke more consistently and regularly. The NRT product(s) for a patient can be individualized based on such factors. In general, patients should quit smoking when NRT is initiated to avoid effects of nicotine toxicity. Regarding other medications, bupropion SR can reduce craving, may treat co-occurring depression, and may limit potential for weight gain in smoking cessation, while varenicline may reduce craving and the reinforcing effects of nicotine in continued smoking.

Pragmatic factors (insurance coverage, costs, likelihood of adherence, dentures when considering the gum, or dermatitis when considering the patch) may help influence medication selection. Prior successful smoking cessation with a particular agent may suggest subsequent success, especially if the patient found the medication to be tolerable and easy to use. Some evidence suggests that retreating relapsed smokers with the same medication produces small or no benefit, while other evidence suggests that it may be of substantial benefit. For patients particularly concerned with weight gain, data show that bupropion SR and NRT delay but do not prevent weight gain. For highly nicotine dependent patients, the higher dose preparations of nicotine gum, patch, and lozenge or combination NRT may be the best choices. The combinations shown to be effective and safe include patch plus gum, patch plus nasal spray, and patch plus inhaler. Another combination approach includes nicotine patch plus bupropion SR.

In addition, individual counseling, proactive telephone counseling, and group counseling are effective and should also be used in smoking cessation interventions.

TABLE 13: SUBSTANCE ABUSE AND DEPENDENCE MEDICATIONS

Generic Name (Brand Name) Year FDA Approved (Rx status) *Generic available unless otherwise noted*	Relevant FDA Indication(s)	Available Strengths (mg)	Usual Dosage Range (mg)
Acamprosate (Campral) 2004 (Rx)	Alcohol	333	666 TID
Buprenorphine (Buprenex, Butrans) 2002 (C-III)	Opiate	2, 8 SL; 0.3 mg/ml inj; 5, 10, 15, 20 mcg/h patch	8 QD–16 QD
Buprenorphine and Naloxone (Suboxone, Zubsolv) 2002 (C-III) generic available for 2/0.5, 8/2 mg SL tablets only	Opiate	2/0.5, 8/2, 12/3 SL strips; 2/0.5, 8/2 SL tabs (generic only); 1.4/0.36, 5.7/1.4 SL tabs	4–24 QD
Bupropion SR (Zyban) 1997 (Rx)	Smoking	150	150 QAM–150 BID
Disulfiram (Antabuse) 1951 (Rx)	Alcohol	250, 500	125 QPM–500 QPM
Methadone (Dolophine, Methadose) 1947 (C-II)	Opiate	5, 10, 40; 10 mg/ml	20 QD–120 QD
Naltrexone (ReVia) 1994 (Rx)	Alcohol, Opiate	50	25 QD–50 QD
Naltrexone ER (Vivitrol) 2006, 2010 (Rx) generic not available	Alcohol, Opiate	380	380 Q 4wk

Nicotine inhaled (Nicotrol Inhaler) 1997 (Rx) generic not available	Smoking	4 mg/ cartridge	6–16 cartridges per day
Nicotine nasal spray (Nicotrol NS) 1996 (Rx) generic not available	Smoking	0.5 mg/spray	1–2 sprays/hour PRN
Nicotine polacrilex (Nicorette Gum, others) 1992 (OTC)	Smoking	2, 4	1 piece PRN up to 24/day
Nicotine polacrilex (Nicorette Lozenge, others) 2009 (OTC)	Smoking	2, 4	1 piece PRN up to 20/day
Nicotine transdermal (Habitrol, Nicoderm CQ) 1991 (OTC)	Smoking	7, 14, 21 /24 hours	14–21 QD
Varenicline (Chantix) 2006 (Rx) generic not available	Smoking	0.5, 1	0.5 QD–1 BID

ACAMPROSATE (Campral) Fact Sheet

FDA Indication:

alcohol dependence.

Dosing:

- Supplied as 333 mg delayed release unscored tablets as **Campral** (Forest) and as generic.
- Start at 666 mg TID. Give 333 mg TID in patients with renal impairment.
- Cost (for one month supply at 333 mg/day, priced Jan 2014):
  - Acamprosate (generic): $30
  - Campral: $45.34

Side Effects:

- Most common (most bothersome in bold): **diarrhea** (dose related, transient), weakness, peripheral edema, insomnia, anxiety.
- Serious but rare: acute renal failure reported in a few cases, suicidal ideation, attempts, and completions rare but greater than with placebo in studies.

Pharmacokinetics and Drug Interactions:

- Not metabolized, cleared as unchanged drug by kidneys; t ½: 20–33 hours.
- There are no significant drug interactions.

Clinical Pearls:

- Approved by the FDA in 2004, but it has been used in France and other countries since 1989.
- Does not eliminate or treat symptoms of alcohol withdrawal. Usually prescribed for maintenance of abstinence; may continue even if patient relapses with alcohol.
- Mechanism of action is not fully defined; it appears to work by promoting a balance between the excitatory and inhibitory neurotransmitters, glutamate and GABA, respectively (GABA and glutamate activities appear to be disrupted in alcohol dependence).
- Clinically, acamprosate has demonstrated efficacy in more than 25 placebo-controlled trials, and has generally been found to be more effective than placebo in reducing risk of returning to any drinking and increasing the cumulative duration of abstinence. However, in reducing heavy drinking days, acamprosate appears to be no better than placebo.
- Acamprosate can be used with naltrexone or disulfiram (different mechanism of action) although the combination with naltrexone may not increase efficacy per available studies.
- Taking with food is not necessary but it may help compliance to take with meals.
- Minimal data or experience in elderly patients; use with caution.
- Compared to naltrexone and disulfiram, acamprosate is unique in that it is not metabolized by the liver and is not impacted by alcohol use, so it can be administered to patients with hepatitis or liver disease and to patients who continue drinking alcohol.

Fun Fact:

Each 333 mg tablet contains 33 mg of elemental calcium (because it is available as acamprosate calcium salt).

Bottom Line:

Acamprosate and naltrexone show similar reduced rates of relapse but acamprosate is associated with more diarrhea, while naltrexone is associated with more nausea, fatigue, and somnolence; acamprosate is preferred in patients with hepatic impairment.

BUPRENORPHINE (Buprenex, Butrans) Fact Sheet

FDA Indications:

opioid dependence, induction; moderate-severe pain (Buprenex, Butrans).

Dosing:

- Schedule III controlled substance. Prescribing of SL tablets for opioid dependence is limited to physicians who have met qualification criteria and have received a DEA number specific to buprenorphine. Information: www.buprenorphine.samhsa.gov.
- Supplied as:
  - 2 mg, 8 mg SL scored tablets as generic.
  - 0.3 mg/ml IM or IV injection as **Buprenex** (Reckitt Benckiser) and generic.
  - 5 mcg/h, 10 mcg/h, 15 mcg/h, 20 mcg/h transdermal patch as **Butrans** (Purdue Pharma).
- Start 2 mg–8 mg SL day 1; then 8 mg–16 mg SL QD (usual induction dose range is 12 mg–16 mg/day and accomplished over 3–4 days). Begin at least 4 hours after last use of heroin or other short-acting opioids and when first signs of withdrawal appear. In essence, if an opioid-dependent patient is not in sufficient withdrawal, introduction of buprenorphine may precipitate withdrawal due to its partial agonist effect. Not for maintenance treatment; patients should be switched to the buprenorphine/naloxone combination product for maintenance and unsupervised therapy.
- Cost (for one month supply at 16 mg/day, priced Nov 2013):
  - Buprenorphine (generic): $148.90

Side Effects:

- Most common (most bothersome in bold): **headache, pain, insomnia**, nausea, anxiety.
- Serious but rare: hepatitis reported rarely, ranging from transient, asymptomatic transaminase elevations to hepatic failure, in many cases, patients had preexisting hepatic dysfunction. QT prolongation with higher doses of transdermal patch.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 37 hours.
- Avoid concomitant use with opiate analgesics: diminished pain control. Additive effects with CNS depressants. CYP3A4 inhibitors and inducers may affect levels of buprenorphine.

Clinical Pearls:

- Binds to various opioid receptors, producing agonism at delta receptors, partial agonism at mu receptors and antagonism at kappa receptors (opioid agonist-antagonist).
- Initially, each approved doctor could treat only 10 patients but the law was modified to alleviate bottleneck treatment access; now each physician can treat up to 100 patients.

Fun Fact:

A subdermal implantable formulation of buprenorphine, Probuphine, using a polymer matrix sustained-release technology, is being developed to minimize risks of noncompliance and diversion. This formulation for maintenance therapy is capable of delivering continuous blood levels of buprenorphine for six months.

Bottom Line:

Buprenorphine alone was previously preferred for the initial (induction) phase of treatment, with buprenorphine/naloxone combination (Suboxone) preferred for maintenance treatment (unsupervised administration). Currently, the favored practice is use of the combination for both induction and maintenance as this decreases any abuse or diversion potential.

BUPRENORPHINE/NALOXONE (Suboxone, Zubsolv) Fact Sheet

FDA Indication:

opioid dependence (induction and maintenance).

Dosing:

- Schedule III controlled substance. Prescribing is limited to physicians who have met qualification criteria and have received a DEA number specific to buprenorphine. Information: www.buprenorphine.samhsa.gov.
- Supplied as:
  - 2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg SL strips as **Suboxone** (Reckitt Benckiser) and 2/0.5, 8/2 SL scored tablets as generic only.
  - 1.4/0.36 mg, 5.7/1.4 mg SL tablets as **Zubsolv** (Orexo AB).
- For induction, use strategy described in buprenorphine fact sheet. For maintenance, give combination product (Suboxone) daily in the equivalent buprenorphine dose on last day of induction; adjust dose in increments of 2 mg or 4 mg to a level which maintains treatment and suppresses opioid withdrawal symptoms (usually 4 mg–24 mg/day); maximum 32 mg/day.
- Cost (for one month supply at 8/2 mg dose/day, priced Mar 2014):
  - Buprenorphine/naloxone (generic): $185.22, CVS Pharmacy
  - Suboxone: $228.02
  - Zubsolv (5.7 mg/1.4 mg): $228.02

Side Effects:

- Most common (most bothersome in bold): **headache, pain,** vomiting, sweating.
- Serious but rare: hepatitis reported rarely, ranging from transient, asymptomatic transaminase elevations to hepatic failure; in many cases, patients had preexisting hepatic dysfunction.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP3A4; t ½: 37 hours (naloxone: 2–12 hours).
- Avoid concomitant use with opiate analgesics: diminished pain control. Additive effects with CNS depressants. CYP3A4 inhibitors and inducers may affect levels of buprenorphine.

Clinical Pearls:

- Naloxone is an opioid antagonist that is active only when injected; it is added to buprenorphine in order to reduce misuse via intravenous injection of a dissolved tablet.
- Sublingual film formulation is newer; manufacturer claims it dissolves faster and that it tastes better than SL tablets. Actually, it is more likely a way for the manufacturer to switch users to a "new" product (with patent protection until 2025) rather than lose patients to forthcoming generics.
- Prescribers should be aware of the high risk for diversion and sale of buprenorphine films and tablets. Some regular opioid abusers periodically buy buprenorphine "off the street" and use it to combat cravings and withdrawal symptoms when their drug of choice is not readily available.

Fun Fact:

The manufacturer of Suboxone, Reckitt Benckiser, gets most of its revenue from selling home and personal care products like Lysol cleaners and Durex condoms.

Bottom Line:

The combination product is preferred over buprenorphine alone for maintenance because the addition of naloxone affords it a lower potential for injection abuse. Although the SL film formulation is currently priced the same as the SL tablets, the SL film strips provide very little (if any) meaningful benefits, and generic SL tablets should be used as cost-saving measure.

BUPROPION SR (Zyban) Fact Sheet

FDA Indication:

smoking cessation.

Dosing:

- Supplied as 150 mg ER unscored tablets as **Zyban** (GSK) and generic (bupropion SR).
- Start at 150 mg QAM for 3 days, then 150 mg BID; separate doses by at least 8 hours and last dose no later than 6 pm to minimize insomnia. Target smoking quit dates are generally in the second week of treatment.
- Cost (for one month supply at 150 mg BID, priced Nov 2013):
  - Bupropion SR (generic): $36.08
  - Zyban: $204.45, CVS Pharmacy

Side Effects:

- Most common (most bothersome in bold): agitation, **insomnia, headache,** nausea, vomiting, tremor, tachycardia, dry mouth, weight loss.
- Serious but rare: seizures; risk higher with rapid and large dose increases and in patients at risk for seizures. Anaphylactoid reactions (eg, pruritus, urticaria, angioedema, dyspnea) reported rarely; reports include Stevens-Johnson syndrome, and anaphylactic shock. Class warning regarding suicide risk (see Antidepressants section).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2B6; may inhibit CYP2D6; t ½: 21 hours.
- Avoid use with MAOIs. Levels of drugs metabolized by CYP2D6 (eg, paroxetine, fluoxetine, aripiprazole, iloperidone, atomoxetine, beta blockers) may be increased. Successful cessation of smoking may alter pharmacokinetic properties of other medications (eg, clozapine, olanzapine, theophylline, warfarin, insulin).

Clinical Pearls:

- If patient successfully quits smoking after 7–12 weeks, may consider maintenance therapy based on individual patient risk-benefit. Efficacy of maintenance therapy (150 mg BID) has been shown for up to 6 months. But, if patient has not made significant progress by the seventh week of therapy, success is unlikely and discontinuation should be considered.
- Bupropion slows the weight gain that often occurs in the initial weeks after quitting smoking but with time, this effect becomes negligible.
- Bupropion and nicotine replacement therapy show similar quit rates: about 25%, or double that seen with placebo, are abstinent at 6 months.
- Equally effective in smokers with or without history of depression.

Fun Fact:

Much of the initial direct-to-consumer advertising that was done for Zyban was via print ads in smoke-free places such as airports.

Bottom Line:

Given high rate of comorbidity between smoking and depression, this is an attractive intervention for many patients. It is also a particularly good choice for patients who are not able to set a quit date prior to initiating treatment.

DISULFIRAM (Antabuse) Fact Sheet

FDA Indication:

alcohol dependence.

Dosing:

- Supplied as 250 mg, 500 mg unscored tablets as **Antabuse** (Teva) and generic.
- Start at 125 mg QPM (must be abstinent from alcohol >12 hours), increase to 250 mg QPM after several days. Maintenance is usually 250 mg–500 mg QPM but some patients can drink without a reaction at the 250 mg/day dose.
- Cost (for one month supply at 250 mg/day, priced Nov 2013):
  - Disulfiram (generic): $49.11, CVS Pharmacy
  - Antabuse: $159.19

Side Effects:

- Most common (most bothersome in bold): skin eruptions (eg, acne, allergic dermatitis), **drowsiness,** fatigue, impotence, **headache, metallic taste.**
- Serious but rare: severe (sometimes fatal) hepatitis or hepatic failure reported and may occur in patients with or without prior history of abnormal hepatic function. Rare psychotic episodes have been reported. Rarely may cause peripheral neuropathy or optic neuritis.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP450; t ½: not defined but elimination from body is slow and effects may persist for one or two weeks after last dose.
- While taking disulfiram, and for 1–2 weeks after stopping, avoid concomitant use of any medications containing alcohol (including topicals), metronidazole, or "disguised" forms of ethanol (cough syrup, some mouthwashes, oral solutions or liquid concentrates containing alcohol such as sertraline). Avoid vinegars, cider, extracts, and foods containing ethanol.

Clinical Pearls:

- Disulfiram inhibits the enzyme aldehyde dehydrogenase; when taken with alcohol, acetaldehyde levels are increased by 5- to 10-fold, causing unpleasant symptoms including flushing, nausea, vomiting, palpitations, chest pain, vertigo, hypotension and, in rare instances, cardiovascular collapse and death. This is the basis for its use as aversion therapy. Common advice to patients: "You'll wish you were dead but it (likely) won't kill you."
- Reaction may last 30–60 minutes to several hours or as long as alcohol remains in the blood. Most fatal reactions occur with disulfiram dosages >500 mg daily and >2 alcoholic drinks; however, deaths have also occurred with lower dosages after a single drink.
- Advise patients to carry an identification card or a medical alert bracelet that states they are taking the medication and listing the symptoms of the reaction and clinician contact information.
- Duration of therapy is until the patient is fully recovered and a basis for permanent self control has been established; maintenance therapy may be required for months or even years.

Fun Fact:

Its anti-protozoal activity may be effective in *Giardia* and *Trichomonas* infections.

Bottom Line:

Since craving is not reduced by disulfiram and any alcohol ingestion could result in a reaction, non-compliance can be common. Its use should be reserved for selected, highly motivated patients in conjunction with supportive and psychotherapeutic treatment

METHADONE (Dolophine, Methadose) Fact Sheet

FDA Indications:

opioid dependence; severe pain.

Dosing:

- Supplied as:
  - 5 mg, 10 mg, 40 mg scored tablets and 10 mg/ml oral concentrate as **Methadose** (Mallinckrodt) and generic.
  - 5 mg, 10 mg tablets as **Dolophine** (Roxane).
  - injectable formulation also available for use in pain.
- Schedule II controlled substance; distribution of 40 mg dispersible tablets restricted to authorized opioid addiction treatment facilities.
- Cost (for one month supply at 10 mg/ml dose, priced Nov 2013):
  - Methadone (generic): $7.48, Rite-Aid
  - Methadose: $9.75

Side Effects:

- Most common: constipation, dizziness, sedation, nausea, sweating.
- Serious but rare: may prolong the QTc interval and increase risk for torsade de pointes; caution in patients at risk for QTc prolongation; usually with doses >100 mg/day. Severe respiratory depression may occur; use extreme caution during initiation, titration, and conversion from other opiates to methadone. Respiratory depressant effects occur later and persist longer than analgesic effects, possibly contributing to cases of overdose.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through CYP2B6 and 3A4; t ½: 8–59 hours; inhibits CYP2D6.
- High potential for interactions. Avoid concomitant use with other potent sedatives or respiratory depressants. Use with caution in patients on medications metabolized by CYP2D6, which inhibit CYP3A4, prolong the QTc interval, or promote electrolyte depletion.

Clinical Pearls:

- May only be dispensed according to Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Substance Abuse Treatment (CSAT) guidelines. Regulations vary by area; consult regulatory agencies and/or methadone treatment facility.
- Methadone accumulates with repeated doses and dose may need reduction after 3–5 days to prevent CNS depressant effects.

Fun Fact:

A persistent but untrue urban legend claims the name "Dolophine" was coined in tribute to Adolf Hitler by its German creators. The name was in fact created after the war by the American branch of Eli Lilly and the pejorative term "adolphine" (never an actual name of the drug) didn't appear in the US until the early 1970s.

Bottom Line:

Opiate replacement therapy via methadone reduces or eliminates illicit use of opiates, criminality associated with opiate use, and allows patients to improve health and social functioning. It is a successful harm reduction model because it reduces the transmission of infectious diseases associated with opiate injection, such as hepatitis and HIV. Disadvantages include potential for accumulation with repeated doses (which may result in toxicity), interindividual variability in pharmacokinetic parameters, potential for drug interactions, challenges associated with dose titration, stigma associated with opiate replacement therapy, and limited availability of treatment programs (eg, don't exist in some geographic areas, wait lists in other areas).

NALTREXONE (ReVia, Vivitrol) Fact Sheet

FDA Indications:

alcohol dependence; opioid addiction (relapse prevention following detox).

Dosing:

- Supplied as:
  - 50 mg scored tablets as **ReVia** (Teva) and generic.
  - 380 mg injection as **Vivitrol** (Alkermes).
- Opioid dependence: start 25 mg for one day; if no withdrawal signs, increase to and maintain 50 mg/day (with food); doses >50 mg may increase risk of hepatoxicity.
- Alcohol dependence: start and maintain 50 mg QD.
- Injection: 380 mg IM (gluteal) Q4 weeks (for opioid or alcohol dependence). Do not initiate therapy until patient is opioid-free for at least 7–10 days (by urinalysis).
- Cost (for one month supply 50 mg/day, priced Nov 2013):
  - Naltrexone (generic): $38.14
  - ReVia: $105.77
  - Vivitrol (380 mg injection): $1,166.82

Side Effects:

- Most common (most bothersome in bold): **headache, nausea,** somnolence, vomiting.
- Serious but rare: black box warning regarding dose-related hepatocellular injury, the difference between apparent safe and hepatotoxic doses appears to be ≤ five-fold (narrow therapeutic window), discontinue if signs/symptoms of acute hepatitis develop.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through non-CYP450 pathway; t ½: 4 hours (5–10 days for IM).
- No significant interactions other than avoiding use with opiates (see below).

Clinical Pearls:

- Naltrexone acts as a competitive antagonist at opioid receptor sites.
- Patients may be more sensitive to opioids even after naltrexone is discontinued, after a missed dose, or near the end of the dosing interval. Lethal overdoses have occurred when patients resume using opioids at the end of a cycle of IM naltrexone or after discontinuing naltrexone.
- May precipitate acute withdrawal (pain, hypertension, sweating, agitation, and irritability) in opiate-using patients; ensure patient is opioid-free for at least 7–10 days prior to initiating.
- In naltrexone-treated patients requiring emergency pain management, consider alternatives to opiates (eg, regional analgesia, non-opioid analgesics, general anesthesia). If opioid therapy is required, patients should be under the direct care of a trained anesthesia provider.
- Efficacy of oral naltrexone in alcohol dependence (craving and relapse) is more convincing than in opiate dependence. In opiate dependence, craving is not decreased but euphoric effects are blocked. Monthly IM naltrexone may be more effective than oral at maintaining abstinence in opiate dependence, without concern for daily medication adherence.

Fun Fact:

Methylnaltrexone, a closely related drug, is marketed as Relistor for the treatment of opioid-induced constipation.

Bottom Line:

Naltrexone is more frequently used for alcohol dependence than for opiate dependence and is associated with more nausea, fatigue, and somnolence than acamprosate. Often used to minimize severity of drinking, while acamprosate is used to prevent relapse. Avoid naltrexone in hepatic impairment or in patients who take opiate-based pain medications. For opioid dependence, methadone and Suboxone more effective for most, although naltrexone may be appropriate for highly motivated opiate dependent patients, with injectable preferred over oral.

NICOTINE INHALED (Nicotrol Inhaler) Fact Sheet

FDA Indication:

smoking cessation.

Dosing:

- Supplied, by prescription, in a 4 mg delivered/cartridge as **Nicotrol Inhaler** (Pfizer).
- Use frequent continuous puffing for 20 minutes with each cartridge; 80 deep inhalations over 20 minutes releases 4 mg nicotine, of which 2 mg is absorbed. Use six to 16 cartridges per day. Taper after six to 12 weeks of use by gradual dose reduction over six to 12 additional weeks.
- Patients should be advised to completely stop smoking upon initiation of therapy.
- Cost (for one inhaler, 10 mg/cartridge, priced Nov 2013):
  - Nicotrol Inhaler: $233.39

Side Effects:

- Most common (most bothersome in bold): **headache, mouth/throat irritation**, dyspepsia, **cough,** unpleasant taste, rhinitis, tearing, sneezing.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through liver as well as kidneys and lungs; t ½: one to two hours.
- Minimal risk for drug interactions. Successful cessation of smoking may increase serum levels of medications metabolized by CYP1A2 (eg, clozapine, olanzapine, theophylline), which is induced by hydrocarbons in smoke; nicotine itself has no effect.

Clinical Pearls:

- Insert cartridge into inhaler and push hard until it pops into place. Replace mouthpiece and twist the top and bottom so that markings do not line up. Inhale deeply into the back of the throat or puff in short breaths. Nicotine in cartridge is used up after about 20 minutes of active puffing.
- Do not eat or drink 15 minutes before or during use. Puff lightly rather than inhale into lungs to minimize coughing.
- Local irritation in the mouth and throat may occur in as many as 40% of patients; coughing (32%) and rhinitis (23%) also common. These effects are generally mild, and occur less frequently with continued use. Use with caution in patients with bronchospastic disease due to potential airway irritation (other forms of nicotine replacement may be preferred).
- Higher ambient temperatures deliver more nicotine, lower temperatures deliver less.
- 1 cartridge delivers 80 puffs or about 2 mg of absorbed nicotine. Roughly 10 cartridges per day is equivalent to the nicotine of smoking 1 pack per day.

Fun Fact:

Nicotine inhaler is not really a true inhaler; puffing deposits the nicotine into the mouth and is then absorbed in the same manner as the nicotine gum or lozenge preparations.

Bottom Line:

Very high expense and unpleasant side effects make this form of nicotine replacement treatment (NRT) difficult to recommend as a first line option since no one NRT has been shown to be more effective than another.

NICOTINE NASAL SPRAY (Nicotrol NS) Fact Sheet

FDA Indication:

smoking cessation.

Dosing:

- Supplied, by prescription, in a bottle containing 10 mg/ml of nicotine. Each 10 ml bottle yields 200 sprays (0.5 mg/spray) as **Nicotrol NS** (Pfizer).
- Use one to two sprays/hour as needed; do not exceed more than 5 doses (10 sprays) per hour. Maximum of 40 doses/day (80 sprays). Each dose (2 sprays) contains 1 mg of nicotine.
- After initial 8 weeks of treatment, taper dose gradually over 4–6 weeks.
- Patients should be advised to completely stop smoking upon initiation of therapy.
- Cost (for one 10 mg/ml bottle, priced Nov 2013):
  - Nicotrol NS: 64.94, Target Pharmacy

Side Effects:

- Most common (most bothersome in bold): **headache,** dyspepsia, rhinitis, **nasal irritation**, sneezing, coughing.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through liver as well as kidneys and lungs; t ½: 1–2 hours.
- Minimal risk for drug interactions. Successful cessation of smoking may increase serum levels of medications metabolized by CYP1A2 (eg, clozapine, olanzapine, theophylline), which is induced by hydrocarbons in smoke; nicotine itself has no effect.

Clinical Pearls:

- Prime pump prior to first use. Blow nose gently prior to use. Tilt head back slightly, breathe through mouth and spray once in each nostril. Do not sniff, swallow, or inhale through nose.
- Moderate to severe nasal irritation in 94% of patients in the first 2 days of use; severity decreases over time. Nasal congestion and transient changes in sense of smell and taste also reported. Avoid in patients with chronic nasal disorders (eg, allergy, rhinitis, nasal polyps, and sinusitis). Exacerbations of bronchospasm reported in patients with asthma.
- A heavy smoker may well use the maximum amount of 80 sprays/day, meaning they would need a new bottle every 2–3 days. This can be tremendously and prohibitively expensive.
- Potential for abuse and dependence appears to be greater than with other NRT.

Fun Fact:

In a published case report (*Am J Psychiatry* 2001), a 54 year-old man who could no longer afford his Nicotrol NS prescription found a commercial source for nicotine on the internet (sold as an insecticide). He purchased 25 g in a 1 g/ml solution for $30, diluted the nicotine solution with distilled water to 10 mg/ml and then placed the solution into empty spray bottles.

Bottom Line:

The idea of nasal administration of nicotine is appealing in that it more closely approximates the time course of plasma nicotine levels observed after cigarette smoking than other dosage forms; however, the high cost coupled with unpleasant side effects make this difficult to recommend as first line treatment especially since no one form of nicotine replacement therapy has been shown to be more effective than another.

NICOTINE POLACRILEX (Commit Lozenge, Nicorelief Gum, Nicorette Gum, Nicorette Lozenge, Thrive Gum) Fact Sheet

FDA Indication:

smoking cessation.

Dosing:

- Available, over the counter, as:
  - 2 mg, 4 mg gum as **Nicorette Gum** (GSK), **Thrive Gum** (Anda) and generics.
  - 2 mg, 4 mg lozenges as **Commit, Nicorette Lozenges** (GSK) and generics.
- Chew 1 piece of gum PRN urge to smoke, up to 24 pieces/day. Patients who smoke <25 cigarettes/day should start with 2 mg strength; patients smoking ≥25 cigarettes/day should start with the 4 mg strength. Use the following 12-week dosing schedule: weeks 1–6: chew 1 piece of gum every 1–2 hours; to increase chances of quitting, chew at least 9 pieces/day during the first 6 weeks; weeks 7–9: chew 1 piece of gum every 2–4 hours; weeks 10–12: chew 1 piece of gum every 4–8 hours.
- For lozenges: Patients who smoke their first cigarette within 30 minutes of waking should use 4 mg strength; otherwise 2 mg strength is recommended. Use the following 12-week dosing schedule: weeks 1–6: one lozenge every 1–2 hours; weeks 7–9: one lozenge every 2–4 hours; weeks 10–12: one lozenge every 4–8 hours. Use at least 9 lozenges/day during first 6 weeks to improve chances of quitting; do not use more than one lozenge at a time; maximum is 5 lozenges every 6 hours or 20 lozenges/day.
- Patients should be advised to completely stop smoking upon initiation of therapy.
- Cost (available in a variety of quantities. Priced Jan 2014):
  - Nicorette Lozenge, 2 mg (quantity 81): $38.98 (per lozenge price: $0.48)
  - Nicotine polocrilex generic lozenge, 2 mg (quantity 108): $30.98 (per lozenge price $0.29)
  - Nicorette gum, 2 mg (quantity 100): $38.98 (per piece price: $0.39).
  - Nicotine polocrilex generic gum, 2 mg (quantity 170): $30.98 (per piece price: $0.18)

Side Effects:

- Most common (most bothersome in bold): **headache, indigestion, nausea,** hiccups, tongue, mouth, and throat irritation or tingling, jaw ache (gum).

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through liver as well as kidneys and lungs; t ½: 1–2 hours.
- Minimal risk for drug interactions. Successful cessation of smoking may increase serum levels of medications metabolized by CYP1A2 (eg, clozapine, olanzapine, theophylline), which is induced by hydrocarbons in smoke; nicotine itself has no effect.

Clinical Pearls:

- Chew gum slowly until it tingles (about 15 chews), then park gum between cheek and gum until tingle is gone (about 1 minute); repeat until most of tingle is gone (~30 minutes).
- Lozenge should not be chewed or swallowed; allow to dissolve slowly (~20–30 minutes).
- Heavy smokers should use higher dose gum or lozenge and at least 9 pieces/day to maximize chances of success. Do not use more than one piece at a time.
- Each 4 mg lozenge or gum results in 2 mg of absorbed nicotine, equivalent to 2 cigarettes.

Fun Fact:

Nicotine gum is available in a variety of flavors: fruit, mint, cinnamon, orange, cherry, and “original.”

Bottom Line:

First line intervention for those patients who can stop smoking at initiation of therapy; nicotine in the form of gum or lozenge may act as a substitute oral activity, which may aid in behavior modification.

NICOTINE TRANSDERMAL (Habitrol, Nicoderm CQ) Fact Sheet

FDA Indication:

smoking cessation.

Dosing:

- Supplied, over the counter, as 7 mg, 14 mg, 21 mg/24 hour patch as **Nicoderm CQ** (Sanofi), **Habitrol** (Novartis) and generics.
- Apply new patch every 24 hours (same time each day, usually after awakening) to non-hairy, clean, dry skin on the upper body or upper outer arm; each patch should be applied to a different site. Adjustment may be required during initial treatment (move to higher dose if experiencing withdrawal symptoms; lower dose if side effects are experienced). Patients smoking >10 cigarettes/day: start with 21 mg/day for 6 weeks, then 14 mg/day for 2 weeks, then 7 mg/day for 2 weeks. Patients smoking ≤10 cigarettes/day: start with 14 mg/day for 6 weeks, then 7 mg/day for 2 weeks.
- Patients should be advised to completely stop smoking upon initiation of therapy.
- Cost (for one month supply at 14 mg/day, priced Jan 2014):
  - Nicotine transdermal (generic): $50
  - Nicoderm CQ: $77.96

Side Effects:

- Most common (most bothersome in bold): **application site reactions** (itching, burning, or redness), diarrhea, dyspepsia, abdominal pain.

Pharmacokinetics and Drug Interactions:

- Metabolized primarily through liver as well as kidneys and lungs; t ½: 3-6 hours.
- Minimal risk for drug interactions. Successful cessation of smoking may increase serum levels of medications metabolized by CYP1A2 (eg, clozapine, olanzapine, theophylline), which is induced by hydrocarbons in smoke; nicotine itself has no effect.

Clinical Pearls:

- Patch may be worn for 16 or 24 hours. If craving upon awakening, wear patch for 24 hours; if vivid dreams or sleep disruptions occur, wear patch for 16 hours, remove at bedtime.
- Do not cut patch; causes rapid evaporation, making the patch useless.
- Up to 50% of patients will experience a local skin reaction, which is usually mild and self-limiting but may worsen with continued treatment. Local treatment with hydrocortisone cream 1% or triamcinolone cream 0.5% and rotating patch sites may help. In fewer than 5% of patients, such reactions require discontinuation.

Fun Facts:

Studies have found that smoking seems to provide short-term relief from symptoms of ulcerative colitis; recent data have suggested the use of nicotine patches in some patients with flare-ups of ulcerative colitis (not maintenance treatment).

Bottom Line:

First line intervention in patients who are able to quit smoking at initiation of treatment and who are regular and constant smokers.

VARENICLINE (Chantix) Fact Sheet

FDA Indication:

smoking cessation.

Dosing:

- Supplied as 0.5 mg, 1 mg unscored tablets as **Chantix** (Pfizer).
- Start at 0.5 mg QD x 3 days, ↑ to 0.5 mg BID x 4 days then ↑ to 1 mg BID for 11 weeks. Titrate slowly and give with food and a full glass of water to decrease GI upset. Start one week before target quit date; may consider setting a quit date up to 35 days after starting varenicline (may improve likelihood of abstinence).
- Cost (for one month supply at 1 mg BID, priced Nov 2013):
  - Chantix: $228.44

Side Effects:

- Most common (most bothersome in bold): **nausea,** insomnia, headache, abnormal dreams, constipation, flatulence.
- Serious but rare: black box warning for serious neuropsychiatric events (including depression, suicidal thoughts, suicide, psychosis, hostility) reported, even in those without pre-existing psychiatric disease; not known whether these are related to the drug or to nicotine withdrawal, although not all patients had stopped smoking. Most resolved upon discontinuation.
- A study suggesting an increased risk of cardiovascular events including angina and MI has been challenged by a recent analysis of 22 studies involving more than 9000 patients that found no difference in such events between smokers using varenicline and controls.

Pharmacokinetics and Drug Interactions:

- Excreted mostly unchanged with minimal hepatic (non-CYP450) metabolism; t ½: 24 hours.
- Avoid concomitant use with alcohol: may increase risk of psychiatric adverse events. H2 blockers, quinolones and trimethoprim may increase varenicline levels. Successful cessation of smoking may alter pharmacokinetic properties of other medications (eg, clozapine, olanzapine, theophylline, warfarin, insulin).

Clinical Pearls:

- Dual mechanism of action: partial agonist at nicotinic receptors, mimicking nicotine effects on the brain and reducing withdrawal symptoms; blocks nicotine from binding to these receptors, thereby decreasing the reinforcing effect of smoking.
- If patient successfully quits smoking after 12 weeks, may continue for another 12 weeks. If not successful in first 12 weeks, then discontinue and reassess factors contributing to failure.
- Similar quit rates as bupropion at 6 months (25%) but higher quit rates compared to bupropion at one year if a second 12-week course of varenicline used.
- Can be combined with bupropion; use with nicotine replacement therapies likely to lead to increased side effects, particularly nausea, headache, vomiting and dizziness.
- Patients with pre-existing psychiatric illness were not studied in clinical trials; safety and efficacy not established in these populations. Use caution in such patients.

Fun Fact:

The show *Saturday Night Live* aired a parody of a Chantix commercial suggesting that side effects of *quitting* smoking could be dangerous (it's on YouTube).

Bottom Line:

Varenicline may offer potential for greater long-term success but before prescribing, consider the risks of possible serious neuropsychiatric events or worsening of underlying psychiatric illness for each patient, particularly psychiatric patients.

Appendices

Drug Interactions in Psychiatry

Drug interactions can be one of the most challenging aspects of psychopharmacology. Today's psychiatrists often use complex medication regimens, while patients frequently take drugs for multiple medical comorbidities. It's impossible to keep track of all of these, but it is important (1) to understand basic concepts of drug-drug interactions, (2) to know where to find information regarding such interactions, and (3) to know which interactions may be clinically relevant.

The majority of interactions in psychiatry will not result in a serious outcome. Many interactions, however, may result in decreased efficacy or increased adverse effects, and these can be easily avoided.

First, let's review some basic concepts. A drug interaction occurs when the pharmacologic action of one drug is altered by the coadministration of another drug. There are two major types of drug interactions: **pharmacodynamic** (what the drug does to the body) and **pharmacokinetic** (what the body does to the drug). Pharmacodynamic interactions impact the effects of the drug at the target site. Pharmacokinetic interactions, on the other hand, impact the amount of time the drug stays in the body and its distribution to active sites.

Pharmacodynamic interactions take place at the level of neurotransmitters and receptors. For example, clonazepam (Klonopin) makes people sleepy by stimulating GABA receptors. Quetiapine (Seroquel) also makes people sleepy, probably by blocking histamine receptors. Combine the two, and patients become *really* sleepy. Pharmacodynamic interactions may also cause two drugs to *oppose* one another. Many of the dementia medications, for example, increase acetylcholine levels, while many psychiatric medications have primary (eg, benztropine) or secondary (eg, clozapine) anticholinergic effects. Giving both together may negate the beneficial effects of the dementia medication.

Some notable—and potentially dangerous—pharmacodynamic interactions in psychiatry include serotonin syndrome (too many serotonergic agents used together); the MAOI-type hypertensive crisis (MAOIs taken with foods high in tyramine); and torsades de pointes (medications which increase QT interval, when taken together, may further increase potential for arrhythmia). We often try to avoid these problems by doing things like lowering doses or choosing alternative medications. In such cases, we're trying to avoid pharmacodynamic interactions.

Other examples are widespread, and reflect behaviors that are quite common. For instance, when a patient who has been on long-term clonazepam for generalized anxiety presents with depressive symptoms, we generally try to avoid sedating antidepressants in order to prevent daytime sleepiness. As another example, levodopa is a good treatment for Parkinson's disease, but it can cause psychosis by revving up dopamine. Rather than decreasing the dose of levodopa, clinicians often turn to a drug like quetiapine to antagonize levodopa's pro-psychotic effect, while retaining its beneficial effects on movement.

Many psychiatrists consider these adjustments as simply the "art of prescribing," adjusting doses and adding medications to permit or compensate for psychodynamic interactions. It's important, though, that we make such changes on the basis of our understanding of the underlying biology, and in ways that do not cause undue harm (biological, psychological, financial) to our patients.

Pharmacokinetic interactions are harder to predict, since they are non-intuitive, and are strictly unrelated to the pharmacologic action of drugs. Pharmacokinetic interactions depend on where and when two or more drugs come in contact during drug processing. Drugs can interact with one another at four different junctures:

- absorption (the process of getting the drug into the bloodstream),
- distribution (ferrying drugs to different tissues once they've been absorbed),
- metabolism (dismantling drugs into simpler components), or
- excretion (sending drugs into the sewage system).

We'll discuss each one in turn, focusing on some common examples in psychopharmacology.

Absorption. Drug-food, rather than drug-drug, interactions are most relevant during absorption. For example, ziprasidone (Geodon) and lurasidone (Latuda) absorption is decreased by 50%–60% when taken without food, which is why we instruct our patients to take these drugs after a full meal (at least, we should be doing this!). Food also speeds absorption of both sertraline (Zoloft) and quetiapine, but only by 25% or so, usually not enough to be clinically relevant. Meanwhile, food famously *slows* absorption of erectile dysfunction drugs such as sildenafil (Viagra) and vardenafil (Levitra)—but not tadalafil (Cialis).

Distribution. Valproic acid (Depakote) is highly protein bound, and only the unbound portion (the "free fraction") of the drug has a therapeutic effect. Aspirin is also highly protein bound, so if your patient combines the two drugs, the aspirin will kick some of the valproic acid off its protein—mainly albumin—which would cause the free fraction of the drug to increase. Standard valproic acid levels in the lab usually do not distinguish between free and bound fractions, so a serum level might be normal, even though the actual functioning valproic acid can be very high. And this could potentially cause side effects. One way to check for this interaction is to order a free valproate level; the normal therapeutic range is about 5 mcg/ml to 10 mcg/ml, much less than the total valproic acid therapeutic range of about 40 mcg/ml to 100 mcg/ml.

Excretion. Lithium, unlike almost all other drugs in psychiatry, is not metabolized. Instead, it is excreted unchanged in the urine. Because of this, various drugs that affect kidney function can severely affect lithium excretion. Caffeine, for example, speeds up kidney function and can reduce lithium levels. On the other hand, ibuprofen (along with other NSAIDs) and ACE inhibitors decrease lithium excretion, increase lithium levels, and could potentially cause toxic effects.

Liver metabolism. Most drug-drug interactions take place in the liver, where drugs are processed in order to render them water soluble, so that the body can excrete them via the urine or feces. There are two phases of liver metabolism. Phase I involves the famous cytochrome P-450 enzymes, or CYP450. These enzymes attack drugs in a variety of ways, such as "hydroxylation" (adding a hydroxyl group), "dealkylation" (taking away an alkyl group), and several others. Unfortunately for those of us trying to remember drug interactions, there are many subfamilies of CYP450 enzymes: CYP 1A2, 2C19, 2D6, 3A4, and several others. Phase II metabolism continues the process of biotransformation, relying mainly on glucuronidation—which is rarely a factor in drug interactions in psychiatric practice.

Practical Implications of Drug-Drug Interactions

To understand drug-drug interactions, you'll need to refamiliarize yourself with some basic terms. Drugs are **substrates** of specific enzymes (the medication relies on that/those enzymatic pathway(s) for metabolism). An **inhibitor** is a drug that binds more tightly to an enzyme than the usual substrate and prevents the enzyme from doing its job; as a result, the substrate for that enzyme gets stuck in a game of musical chairs as it scurries around looking for a free enzyme system to break it down. Since this drug is not getting metabolized as quickly as it otherwise would (the inhibitor is preventing it from doing so), its serum levels become higher than expected. On the other hand, **inducers** stimulate the production of extra enzymes. With more enzymes around, the substrate for that enzyme is broken down more rapidly, leading to lower levels.

Now that you know the basics, how can you most efficiently apply them to your practice? Here are some suggestions.

- Identify the 10 drugs that you most commonly prescribe, and memorize the major drug interactions for each one.
- Antidepressants, antipsychotics, antibiotics, antiretrovirals, and older anticonvulsants have a high likelihood of significant drug interactions—so be particularly vigilant if your patient is taking any of these.
- Recognize the drugs with a narrow therapeutic window, ie, when the toxic dose is not much higher than the therapeutic dose. Commonly used narrow therapeutic window drugs include lithium, carbamazepine (Tegretol), warfarin (Coumadin), digoxin, phenytoin (Dilantin), and phenobarbital.
- Recognize drugs that cause serious side effects and outcomes if blood levels are significantly decreased or increased (eg, oral contraceptives, lamotrigine (Lamictal), clozapine, TCAs, warfarin).
- Drugs with long half-lives, such as diazepam (Valium), aripiprazole (Abilify), can be particularly troublesome when involved in drug interactions, because metabolic inhibitors—or hepatic dysfunction—can make them ultra long lasting. Be cautious with any new or rarely prescribed drugs: neither you nor anybody else has had much experience with them, and unreported drug interactions can appear.
- The risk of drug interactions can increase exponentially as the number of drugs increases. Setting a threshold to check for interactions is helpful (eg, any patient on three or more drugs).

Another important concern with drug interactions is timing. *Inhibition* happens quickly. It can occur with the first dose of a medication and it can subside quickly. How long it takes to subside depends on the inhibitor's half-life. Generally, the inhibition will stop after five half-lives. On the other hand, for *induction* to occur, the body has to synthesize more CYP450 enzymes, and this can take up to four weeks. This accounts for the delayed "auto-induction" of carbamazepine. Likewise, for induction to subside, these extra enzymes need to

be broken down, a process that could also take several weeks. As a general rule of thumb, any drug prescribed with its inhibitor should be started at half the usual dose and titrated more slowly. Conversely, a drug prescribed with its inducer may need to be dosed higher after the few weeks it takes for induction to occur.

Useful References for Drug Interactions

It's ideal to have a useful resource to use to look up interaction information. The task of keeping track of interactions has become less daunting with the advent of free software from companies like Epocrates (www.epocrates.com) and Medscape (www.medscape.com), which allow you to check for potential interactions among all possible combinations of drugs.

But there are various problems with the computerized databases you'll find at these sites or, if you have one, in your electronic-prescribing system. For one, they tend to be overly inclusive, often listing every conceivable interaction, no matter how unlikely. For example, citalopram (Celexa), an SSRI considered by most of us to be a pretty safe choice in combination with just about any drug, looks pretty dangerous in the Epocrates database. Moreover, these databases are often populated with drug-class information rather than medication specific information making important nuances unavailable to the user. That's where your clinical judgment and experience comes in!

- **Free**
  - Medscape (www.medscape.com/druginfo/druginterchecker)
  - www.epocrates.com (you'll need to register first)
  - www.drugs.com/drug_interactions.html
  - medicine.iupui.edu/clinpharm/ddis/
- **Not free**
  - Lexi-Interact (http://bit.ly/fugKmk), $75 one year subscription

We also provide a table here for your reference.

Adapted from Goren J & Carlat D*, The Carlat Psychiatry Report* 2011;9(2):1–5

CYP450 Drug Interactions for Some Commonly Prescribed Medications

CYP450 Family	Inducers	Inhibitors	Substrates ("Victim" Drugs)	Symptoms When Induced	Symptoms When Inhibited
1A2	Carbamazepine Cigarette smoke Omeprazole Rifampin Ritonavir St. John's wort	Ciprofloxacin Fluvoxamine Norfloxacin	Asenapine	Loss of efficacy (psychosis)	Insomnia / EPS
			Caffeine	Withdrawal headaches	Jitteriness
			Clomipramine	Loss of efficacy (depression / OCD)	Seizures / arrhythmias / anticholinergic effects
			Clozapine	Loss of efficacy (psychosis)	Seizures / sedation / anticholingergic effects
			Duloxetine	Loss of efficacy (depression)	Increased blood pressure
			Fluvoxamine	Loss of efficacy (depression / OCD)	GI / sedation
			Melatonin	Loss of efficacy (insomnia)	Sedation
			Mirtazapine	Loss of efficacy (depression)	Sedation
			Olanzapine	Loss of efficacy (psychosis)	Sedation
			Ramelteon	Loss of efficacy (insomnia)	Sedation
2B6	Carbamazepine Phenobarbital Phenytoin Rifampin	Clopidogrel Fluoxetine Fluvoxamine Ketoconazole Memantine Ticlopidine	Bupropion	Loss of efficacy (depression)	Seizures / jitteriness / insomnia
			Methadone	Opiate withdrawal	CNS and respiration depression
			Selegiline	Loss of efficacy (depression)	Insomnia / diarrhea
2C9	Barbiturates Carbamazepine Rifampin St. John's wort	Disulfiram Fluconazole Fluoxetine Fluvoxamine Isoniazid Metronidazole Modafinil	Diazepam	Loss of efficacy / insomnia / anxiety / seizures	Sedation / BZD intoxication
			NSAIDs	Loss of pain control	GI effects
			Methadone	Opiate withdrawal	CNS and respiratory depression
			Oral hypoglycemics	Loss of glycemic control	Hypoglycemia
			Tricyclics	Loss of efficacy (depression / anxiety)	Seizures / arrhythmia / anticholinergic
			Warfarin	Loss of anticoagulant efficacy	Increased bleeding
2C19	Barbiturates Carbamazepine Rifampin	Fluconazole Fluoxetine Fluvoxamine Modafinil Oxcarbazepine	Atomoxetine	Loss of efficacy (ADHD)	GI / constipation
			Barbiturates	Loss of efficacy / insomnia / anxiety / seizures	Sedation / barb intoxication
			Citalopram	Loss of efficacy (depression / anxiety)	GI effects
			Diazepam	Loss of efficacy / insomnia / anxiety / seizures	Sedation / BZD intoxication
			Escitalopram	Loss of efficacy (depression / anxiety)	GI effects
			Methadone	Opiate withdrawal	CNS and respiratory depression
			Sertraline	Loss of efficacy (depression / anxiety)	GI effects
			Tricyclics	Loss of efficacy (depression / anxiety)	Seizures / arrhythmia / anticholinergic

2D6	Not inducible	(bupropion) Fluoxetine Methadone Paroxetine (venlafaxine) (vilazodone)	Aripiprazole	NA	Akathisia / sedation
			Atomoxetine	NA	GI / constipation
			Codeine / Hydrocodone	NA	Less / no analgesia (not converted to morphine)
			Doxepin	NA	Sedation / anticholinergic
			Duloxetine	NA	Increased BP
			Escitalopram	NA	GI effects
			Fluoxetine	NA	GI effects
			Fluvoxamine	NA	GI effects / sedation
			Iloperidone	NA	Tachycardia / hypotension / stiffness
			Methamphetamine	NA	Insomnia / decreased appetite
			Mirtazapine	NA	Somnolence
			Mixed amphetamine salts	NA	Insomnia / decreased appetite
			Paroxetine	NA	GI effects / anticholinergic / sedation
			Perphenazine	NA	EPS / Sedation
			Risperidone	NA	EPS / orthostasis
			Trazodone	NA	Sedation
			Tricyclics	NA	Seizures / arrhythmia / anticholinergic
			Venlafaxine	NA	GI effects

CYP450 Family	Inducers	Inhibitors	Substrates ("Victim" Drugs)	Symptoms When Induced	Symptoms When Inhibited
3A4	Barbiturates Carbamazepine Oxcarbazepine Phenytoin Rifampin St. John's wort	Clarithromycin Fluconazole Fluvoxamine Grapefruit juice Ketoconazole Protease inhibitors	Alprazolam	Loss of efficacy / insomnia / anxiety / seizures	Sedation / BZD intoxication
			Aripiprazole	Loss of efficacy (psychosis)	Akathisia / sedation
			Buprenorphine	Opiate withdrawal	CNS and respiratory depression
			Buspirone	Loss of efficacy (anxiety)	GI effects / jitteriness
			Calcium channel blockers	Loss of efficacy (hypertension)	Hypotension
			Carbamazepine	Loss of efficacy / seizures	Sedation / arrhythmia
			Citalopram	Loss of efficacy (depression / anxiety)	GI effects
			Clonazepam	Loss of efficacy / insomnia / anxiety / seizures	Sedation / BZD intoxication
			Diazepam	Loss of efficacy / insomnia / anxiety / seizures	Sedation / BZD intoxication
			Escitalopram	Loss of efficacy (depression / anxiety)	GI effects
			Guanfacine	Loss of efficacy (ADHD)	Sedation / dry mouth / dizziness
			Levomilnacipran	Loss of efficacy (depression)	GI effects
			Lurasidone	Loss of efficacy (psychosis)	Sedation / akathisia
			Methadone	Opiate withdrawal	CNS and respiratory depression
			Mirtazapine	Loss of efficacy (depression / insomnia)	Somnolence
			Oral contraceptives	Loss of efficacy (pregnancy)	GI effects
			Quetiapine	Loss of efficacy (psychosis)	Sedation / orthostasis
			Statins (not pravastatin)	Loss of efficacy (hyperlipidemia)	Rhabdomyolysis
			Sildenafil / tadalafil / vardenafil	Loss of efficacy (sexual dysfunction)	Headache / flushing / prolonged erection
			Tiagabine	Loss of efficacy (seizures)	Dizziness / somnolence / difficulty concentrating
			Trazodone	Loss of efficacy (insomnia)	Sedation / orthostasis
			Triazolam	Loss of efficacy / insomnia / anxiety / seizures	Sedation / BZD intoxication
			Tricyclics	Loss of efficacy (depression / anxiety)	Seizures / arrhythmia / anticholinergic
			Vilazodone	Loss of efficacy (depression / anxiety)	GI effects
			"Z drugs" (zaleplon, zolpidem, eszopiclone)	Loss of efficacy (insomnia)	Sedation / confusion

( ) indicates less potent inhibitory effect, therefore generally less of a risk except at higher doses

Psychiatric Medications in Pregnancy and Lactation

Pregnancy presents a unique problem to the psychiatrist. Contrary to what many may think or assume, pregnancy does not protect a woman from an acute episode, a recurrence, or an exacerbation of psychiatric illness. Withholding medications during pregnancy can *sometimes* be an appropriate option, but this is generally not recommended. And since all psychotropic medications cross the placenta to at least *some* degree, their potential effects on the fetus, on labor and delivery, and on the neonate must be considered and balanced with the risk of *not* treating the mother with medication. A similar risk-benefit assessment must be considered in the case of a mother who wishes to breastfeed her child, as psychotropic medications are excreted into breast milk to varying degrees.

As a pharmacist specializing in psychopharmacology, I am commonly consulted by psychiatrists to provide updated information on the safety of medications in pregnancy and breastfeeding. It is a difficult task, because the quantity and quality of data vary greatly. I developed the accompanying table by pulling together a variety of sources, including isolated case reports, case series, birth registries, retrospective surveys, prospective comparative cohort studies, case control studies, and meta-analyses. Making judgments about which medication to use—or not use—in a pregnant or lactating woman is a delicate balancing act, involving an assessment of the severity of the underlying illness versus the uncertainties inherent in prescribing medications when the available data are limited.

In reading the following table, keep the following in mind: In the general US population, the baseline rate of major malformations is between one and four percent, depending on the population studied and the definitions of "malformations" used. If treatment is necessary, monotherapy with the lowest effective dose and for the shortest duration is prudent. Safety data are generally more robust with older agents, and for that reason older agents—with a few key exceptions—are more preferable than newer drugs with less established safety profiles.

Almost all drugs enter breast milk. The exposure to the infant is described as a percentage of the maternal dose—that is, how much of the weight-adjusted maternal dose is actually excreted into the breast milk. When less than 10% of a mother's dose of medication is excreted into the breast milk, it is generally considered compatible with breastfeeding (with some exceptions) since these low serum levels are unlikely to lead to adverse effects in the infant.

While the table provided here summarizes the current knowledge about psychotropic medication in pregnancy and lactation, it is important to note that information in this area is constantly evolving. If you regularly treat women of childbearing age, we suggest that you keep up with new data, consult with experts in this area, and utilize available resources such as the Organization of Teratology Information Specialists at www.otispregnancy.org or 866-626-6847, Motherisk at www.motherisk.org (see "Drugs in Pregnancy" and "Breastfeeding and Drugs" links), or the LactMed database of the National Library of Medicine at http://1.usa.gov/15eWNH. Another good resource is the MGH Center for Women's Mental Health at www.womensmentalhealth.org. These resources, along with our table, provide information based upon the available evidence (or lack thereof), but the ultimate clinical decision comes down to careful and individualized consideration between the physician and the patient and her family.

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Psychiatric Medications in Pregnancy and Lactation

Medication	Pregnancy	Breastfeeding	Recommendations
Anxiolytics / Hypnotics			
Benzodiazepines (various agents)	Possible increased incidence of cleft lip or palate; floppy infant syndrome; neonatal withdrawal syndrome	Excretion varies with different benzodiazepines, but it is always less than 10%. Excessive sedation in infant, lethargy with consequent feeding difficulty and weight loss reported	Try to avoid use in first trimester. Lorazepam (Ativan) may be best-in-class to use due to lack of active metabolites and relatively shorter half-life
Buspirone (Buspar)	Fewer data; difficult to determine risks	Low to undetectable infant levels reported	Due to lack of data, other agents with larger safety database should be considered first
Diphenhydramine (Benadryl)	Fairly consistent data show lack of associated malformations	Larger doses or more prolonged use may cause adverse effects in the infant	Considered to be the safest hypnotic in pregnancy and breastfeeding
Trazodone (Desyrel, Oleptro)	Fewer data show no increased risk of malformations	<1% excretion; not expected to cause adverse effects in breastfed infants	Probably safe
Non-benzodiazepines: Eszopiclone (Lunesta) Zaleplon (Sonata) Zolpidem (Ambien)	Fewer data show no increased risk of malformations	Relatively low levels in breast milk. Most data are with zolpidem. Zolpidem is relatively hydrophilic and excreted rapidly; therefore, may be favored	Reserve for second-line use due to paucity of data. If unavoidable, use zolpidem, at lowest dose possible
Mood Stabilizers			
Valproate (Depakote)	Most teratogenic of all mood stabilizers, with a 6.2 to 20.3% rate of congenital malformations, with neural tube defects most prominent. Teratogenic effects are dose related with greatest risk at doses >1000 mg per day	Relatively low excretion (0.68%); considered compatible with breastfeeding	Best to avoid in pregnancy unless absolutely required
Lithium (Eskalith, Lithobid)	Rate of major malformations reported to be 4 to 12%. Increased risk of cardiovascular malformation, Ebstein's anomaly; risk is lower than previously thought (0.05 to 0.1%). Increased maternal risk of diabetes, polyhydramnios, thyroid dysfunction during pregnancy	30 to 50% excretion; not recommended due to high risk of toxicity	Avoid, particularly in first trimester. Check serum levels and thyroid function frequently during pregnancy. Changes in metabolism and total body water necessitate frequent dose adjustment, particularly in third trimester
Carbamazepine (Tegretol)	Rate of major malformation reported to be 2.2 to 7.9%. Neural tube defects (0.5 to 1%), craniofacial defects, cardiovascular malformations and hypospadias reported	Relatively high levels in breast milk but with few adverse effects reported. Sedation, poor sucking, withdrawal reactions and 3 cases of hepatic dysfunction have been reported	Avoid if possible
Lamotrigine (Lamictal)	Rate of major malformations reported to be 1 to 5.6%. Increased risk of oral clefts (0.4%)	Based on limited data, thought to be safe; however, infant exposure can be high and can vary widely (reports of 18%–60% of maternal concentrations); monitor infant. Relatively high infant exposure (22.7%); avoid or exercise caution	Considered to be the safest of the anticonvulsants though good safety data is sparse
Oxcarbazepine (Trileptal)	Unlike carbamazepine, there is no epoxide metabolite formed so oxcarbazepine may be less teratogenic; a Danish study showed no increased risk of major malformation. However, data with oxacarbazepine are limited	Limited information suggests oxcarbazepine would not be expected to cause adverse effects in breastfed infants, especially if the infant is older than 2 months. Monitor infant for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants and when using combinations of anticonvulsants	Use caution until more data available
Antipsychotics			

Conventionals	No increased risk of malformations seen with high potency agents. Small increased risk with low potency agents such as chlorpromazine (Thorazine). Transient extrapyramidal side effects; sedation; withdrawal symptoms in neonate	Relatively low excretion reported although little data available. Sedation and Parkinsonism effects possible in breastfed infants	Haloperidol (Haldol), fluphenazine (Prolixin) favored during pregnancy because of long history of safe use
Atypicals	Fewer data available, most showing no increased risk of malformations. Maternal hyperglycemia, impaired glucose tolerance and weight gain may lead to maternal complications. Large for gestational age infants reported	Excretion low, usually <3%, with exception of clozapine (Clozaril) which is seen in relatively high concentrations in breast milk	Second line after conventional due to paucity of data
Antidepressants			
Tricyclics	Relatively large database; recent meta-analysis of 300,000 live births revealed no increased risk of malformations. Neonatal anticholinergic effects. Transient neonatal withdrawal symptoms reported	<1 to 5% excretion; appear relatively safe during breastfeeding, with possible exception of doxepin	Well characterized and considered reasonable options. Desipramine (Norpramin), nortriptyline (Pamelor) preferred due to lower anticholinergic and orthostatic hypotension risks
SSRIs	Controversial data regarding cardiovascular malformation with first trimester paroxetine (Paxil) exposure. Larger and more recent studies show no overall increased risk for malformations with SSRIs. Conflicting reports with some showing decreased gestational age, low birth weight, poor neonatal adaptation, low APGAR scores. Conflicting reports regarding SSRI use in later pregnancy and persistent pulmonary hypertension (PPHN). Neonatal toxicity reported as transient jitteriness, tremulousness and tachypnea reported. No problems detected in behavioral or cognitive development—greatest data with fluoxetine (Prozac)	Relatively low excretion, varies by agent: • Fluoxetine: 3 to 9% • Paroxetine: <4% • Sertraline (Zoloft): <2% • Citalopram (Celexa): 5 to 10% • Fluvoxamine (Luvox): <2%	Sertraline results in lowest fetal drug exposure and lowest (undetectable) levels in breastfed infants; may be considered favored SSRI. Paroxetine use most controversial. Fluoxetine less favored for breastfeeding due to long half-life and active metabolite; disturbed sleep, colic, irritability, poor feeding reported
Duloxetine (Cymbalta)	Little data	No published data though exposure is low	Other agents with more data favored
Mirtazapine (Remeron)	Sparse data but one small study suggests no increased rate of major malformation	Low excretion; compatible with breastfeeding	May be useful also for pregnancy associated emesis, insomnia
Venlafaxine/ desvenlafaxine (Pristiq)	Earlier data regarding major malformations reassuring, but one more recent study suggested a possible association with birth defects; additional studies needed. Increased maternal blood pressure may be a concern during pregnancy, particularly at higher doses	2 to 9.2% excretion; no adverse outcomes reported	Other agents with more data favored
Bupropion (Wellbutrin)	No increased risk of malformation shown thus far	<1% excretion with no adverse outcomes reported	Well characterized and considered reasonable option. May also help with smoking cessation during pregnancy
Stimulants			
Amphetamines and methylphenidate	No apparent congenital malformations; may constrict blood flow to placenta, which reduces oxygen flow to developing fetus. May cause premature delivery, small for gestational age and low-birth-weight babies; however, data inconclusive. Neonatal withdrawal possible	0.2% excreted into breast milk; adverse effects usually not observed	Caution in pregnancy due to possibility of vasoconstriction and ability to disrupt blood flow to the fetus

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Note: Trade names are capitalized, bolded page numbers are for fact sheets, and non-bolded page numbers are for quick-scan tables.

Note: CME quizzes must be taken online at www.thecarlatreport.com or http://thecarlatcmeinstitute.com/self-assessment (for ABPN SA course subscribers).