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Side Effects in a Nutshell

1. HAM side effects (antiHistamine—sedation, weight gain; antiAdrenergic— hypotension; antiMuscarinic (anticholinergic)—dry mouth, blurred vision, urinary retention, constipation, exacerbation of neurocognitive disorders (i.e., dementias). ■ Found in tricyclic antidepressants (TCAs) and low-potency antipsychotics. ■ Associated with increased risk of falls and delirium in elderly patients.
2. Serotonin syndrome: Confusion, flushing, diaphoresis, tremor, myoclonic jerks, hyperthermia, hypertonicity, rhabdomyolysis, renal failure, and death. ■ This uncommon psychiatric emergency occurs when there is too much serotonin, classically when selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) are combined. As this combination is rarely seen in practice anymore, serotonin syndrome is more commonly seen when a patient is prescribed multiple medications with serotonergic activity (e.g., SSRIs/SNRIs, lithium, trazodone, linezolid, Tramadol, triptans, dextromethorphan, St. John’s wort, ondansetron), or other illicit drugs with serotonergic activity (e.g., cocaine, MDMA, amphetamine). ■ Treatment: Stop medications, supportive care, possibly use cyproheptadine or even ECT.
3. Hypertensive crisis: Caused by a buildup of stored catecholamines (norepinephrine); triggered by the combination of MAOIs with tyramine-rich foods (e.g., red wine, cheese, chicken liver, cured meats) or with sympathomimetics. Treated with IV phentolamine or sublingual nifedipine.
4. Extrapyramidal side effects (EPS): Parkinsonism—mask-like face, cogwheel rigidity, bradykinesia, pill-rolling tremor; akathisia—restlessness, need to move, and agitation; dystonia—sustained, painful contraction of muscles of neck, tongue, eyes, diaphragm. ■ Occur more frequently with high-potency, typical (first generation) antipsychotics, but can also be seen with atypical (second generation) antipsychotics. ■ Reversible. ■ All EPS can be treated with benztropine (Cogentin), although for akathisia, beta-blockers such as propranolol are first-line. ■ Occur within hours to days of starting medications or increasing doses. ■ In rare cases, can be life threatening (e.g., dystonia of the diaphragm causing asphyxiation). ■ Drug-induced parkinsonism should be differentiated from primary neurodegenerative Parkinson disease.

5. Hyperprolactinemia: Occurs with high-potency, typical (first generation) antipsychotics and risperidone.
6. Tardive dyskinesia (TD): Choreoathetoid (involuntary, irregular, and repetitive) muscle movements, usually of the mouth and tongue (can affect extremities, as well). ■ Occurs after years of antipsychotic use (more likely with high-potency, first-generation antipsychotics). ■ Usually irreversible.
7. Neuroleptic malignant syndrome: Mental status changes, fever, tachycardia, hypertension, tremor, hyporeflexia, elevated creatine phosphokinase (CPK), "lead pipe" rigidity. ■ Can be caused by any antipsychotic after a short or long time (increased with high-potency, typical antipsychotics). PSYCHOPHARMACOLOGY

196 PSYCHOPHARMACOLOGY WARDS TIP Drugs that increase serotonin may be found in over-the-counter medicines (e.g., dextromethorphan, St. John's wort). They can cause serotonin syndrome when taken in high doses or in combination with other serotonergic agents. KEY FACT Keeping the "kinesias" (impairment of body function) straight: • Tardive dyskinesia is characterized by potentially permanent choreoathetoid movements and tongue protrusion. • Acute dystonia is characterized by (painful and reversible) twisting and abnormal postures. • Akathisia is characterized by the inability to sit still; feels like "ants in the pants." • Bradykinesia is characterized by decreased or slow body movement. Antidepressants ■ The major categories of antidepressants are: WARDS QUESTION Q: What are the key differences between serotonin syndrome and neuroleptic malignant syndrome (NMS)? A: Serotonin syndrome includes myoclonic jerks, hyperreflexia, hyperactive bowels, while NMS is marked by "lead pipe" rigidity, hyporeflexia, and ↑ CPK. ■ A medical emergency with up to a 20% mortality rate. ■ Treatment includes dantroline, bromocriptine, and ECT in emergencies. 8. Drug interactions: Cytochrome P450 is a group of enzymes in the liver that metabolizes many common drugs, including psychiatric medications. ■ Some medications induce the system, in other words the system metabolizes medications faster—drug levels decrease. ■ Some medications inhibit the system, in other words the system metabolizes medications more slowly—drug levels increase. ■ Common cytochrome P450 enzymes important in metabolizing psychiatric medications include CYP3A4, CYP2D6, CYP1A2, CYP2C9, and CYP2C19. ■ For example: A patient with schizophrenia who smokes a pack of cigarettes a day is prescribed olanzapine. The tobacco induces CYP450 enzyme to metabolize the olanzapine quickly, the drug level of olanzapine decreases, and the patient therefore requires a higher dose. CYP450 InDucers CYP450 Inhibitors Tobacco (1A2) Fluoxetine (2C19, 2C9, 2D6) Carbamazepine (1A2, 2C9, 3A4) Fluvoxamine (1A2, 2C19, 3A4) Barbiturates (2C9) Paroxetine (2D6) St. John's wort (2C19, 3A4) Sertraline (2D6) Duloxetine (2D6) 9. Metabolic syndrome: Antipsychotic medications (especially second-generation antipsychotics such as clozapine, olanzapine, quetiapine) can cause a metabolic syndrome which includes weight gain, hyperlipidemia, hyperglycemia, and hypertension that are associated with increased cardiovascular morbidity and mortality. Routine monitoring of patients on these medications should include weight checks or BMI, fasting lipid profile, A1C or fasting glucose, and vital signs; treatment with metformin may be considered. • SSRIs. • SNRIs. • Heterocyclic antidepressants, including TCAs and tetracyclic antidepressants. • MAOIs. • Miscellaneous antidepressants. ■ All antidepressants have similar response rates in treating major depression but differ in safety and side-effect profiles. ■ Approximately 60–70% of patients with major depression will respond to an antidepressant medication. ■ It usually takes 4–6 weeks on a given dose of an antidepressant for a patient to fully benefit from a trial of the medication, although many patients start responding sooner. ■ For

patients who are prone to side effects, it’s important to start at a low dose and titrate up slowly. ■ Some antidepressants have a withdrawal phenomenon, characterized by dizziness, headaches, nausea, insomnia, anxiety, electric-like shocks (“zaps”),

and malaise; depending on the dose and half-life, they may need to be tapered slowly before discontinuing. ■ Because of their safety and tolerability, SSRIs and related antidepressants have become the most common agents used to treat major depression. However, the choice of a particular medication used for a given patient should be made based on: • Patient’s particular symptoms • Previous treatment responses by the patient or a family member to a particular medication • Side-effect profile • Comorbid (medical and psychiatric) conditions • Risk of suicide via overdose on the medication • Cost (newer medications may be prohibitively expensive) SELECTIVE SEROTONIN REUPTAKE INHIBITORS ■ SSRIs inhibit presynaptic serotonin reuptake pumps, leading to increased availability of serotonin in synaptic clefts. Additionally, SSRIs cause downstream effects increasing brain plasticity—this mechanism has been hypothesized to explain the delay to onset of antidepressant effect. ■ Although structural differences are minimal, patients often respond differently (in regards to efficacy and side effects) to different SSRIs. ■ Based on their half-lives, most SSRIs can be dosed daily. Fluoxetine has a weekly dosing form available, as well. ■ There is no correlation between plasma levels and efficacy or side effects. ■ SSRIs are the most commonly prescribed antidepressants due to several distinct advantages: • Low incidence of side effects, most of which resolve with time. • No food restrictions. • Much safer in overdose. ■ Examples of SSRIs include: • Fluoxetine (Prozac):

- Longest half-life, with active metabolites; therefore, no need to taper.
- Safe in pregnancy, approved for use in children and adolescents.
- Common side effects: Insomnia, anxiety, sexual dysfunction.
- Can elevate levels of antipsychotics, leading to increased side effects. • Sertraline (Zoloft):
- Higher risk for gastrointestinal (GI) disturbances.
- Very few drug interactions.
- Other common side effects: Insomnia, anxiety, sexual dysfunction. • Paroxetine (Paxil):
- A potent inhibitor of CYP26, which can lead to several drug–drug interactions.
- Common side effects: Anticholinergic effects (e.g., sedation, constipation, weight gain) and sexual dysfunction.
- Short half-life leading to uncomfortable withdrawal phenomena if not taken consistently. PSYCHOPHARMACOLOGY KEY FACT First-generation antipsychotics (typicals) are more associated with EPS and second-generation antipsychotics (atypicals) are more associated with metabolic side effects. KEY FACT The Food and Drug Administration (FDA) has a black box warning for all SSRIs potentially increasing “suicidal thinking and behavior.” This warning applies to children and young adults to age 25, but may be accurate for older adults as well. The absolute risk remains low and must be weighed against the risks of an untreated mood disorder. WARDS QUESTION Q: How are sexual side effects of SSRI treated? A: Either reducing the dose (if clinically appropriate), changing to a non-SSRI antidepressant, augmenting with bupropion, or, in men, by adding medications like sildenafil. WARDS TIP Patients should receive an adequate trial of antidepressant medication, usually at least 4–6 weeks at a full dose, before the medication is deemed non-efficacious.

198 PSYCHOPHARMACOLOGY • Fluvoxamine (Luvox): WARDS QUESTION Q: What are the SSRIs associated with most and least weight gain? A: Paroxetine is the most associated with weight gain. Fluoxetine and sertraline are the most weight-neutral.

- Fewest drug–drug interactions.
- Dose-dependent QTc prolongation. • Escitalopram (Lexapro): WARDS TIP Side Effects SSRIs can increase levels of warfarin, requiring increased monitoring when starting and stopping these medications. KEY FACT Serotonin syndrome is common when serotonergic drugs are used with MAOIs. SSRIs should not be used for at least 2 weeks before or after use of an MAOI, and at least 5–6 weeks with fluoxetine given its long half-life. ■ Other side effects include: ■ Venlafaxine (Effexor):
- Currently approved only for use in obsessive-compulsive disorder (OCD).
- Common side effects: Nausea and vomiting.
- Multiple drug interactions due to CYP inhibition. • Citalopram (Celexa):
- Levo-enantiomer of citalopram; similar efficacy, possibly fewer side effects.
- Dose-dependent QTc prolongation. ■ SSRIs have significantly fewer side effects than TCAs and MAOIs due to serotonin selectivity (not as much activity on histamine, adrenergic, or muscarinic receptors). ■ They are much safer in overdose. Most side effects occur because of the extensive number of serotonin receptors throughout the body, including the GI tract. ■ Many of the side effects of SSRIs resolve within a few days to weeks and include: • GI disturbance: Mostly nausea and diarrhea; giving with food can help. • Insomnia; also vivid dreams, often resolves over time. • Headache. • Weight changes (up or down). • Sexual dysfunction (30–40%): Decreased libido, anorgasmia, delayed ejaculation. These may occur weeks to months after taking an SSRI and typically do not resolve. • Restlessness: An akathisia-like state. • Serotonin syndrome: Caused by an excess of serotonin in the body. It can result from taking a single serotonergic agent, or by taking multiple serotonergic agents in combination. One example is triptans (for migraine headaches) used with SSRIs. Serotonin syndrome is characterized by fever, diaphoresis, tachycardia, hypertension, delirium, and neuromuscular excitability (especially hyperreflexia and “electric jolt” limb movements), potentially death. Treatment includes stopping all serotonergic agents, administering cyproheptadine, and ECT in emergencies. • Hyponatremia: Rare. • Decreased platelet aggregation leading to increased risk of bleeding and bruising. • Seizures: Rate of approximately 0.2%, slightly lower than TCAs. SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS) • Often used for depressive disorders, anxiety disorders like generalized anxiety disorder (GAD), and neuropathic pain.

• Low drug interaction potential. • Extended release (XR form) allows for once-daily dosing. • Due to its short half-life, discontinuation of this drug should be tapered to avoid an uncomfortable discontinuation syndrome. • Side-effect profile similar to SSRIs, with the exception of increased blood pressure (BP) in higher doses; do not use in patients with untreated or labile BP. • New form, desvenlafaxine (Pristiq), is the active metabolite of venlafaxine; it is expensive and without known benefit over venlafaxine. ■ Duloxetine (Cymbalta): • Often used for people with depression, neuropathic pain, and in fibromyalgia. • Side effects are similar to SSRIs (no hypertensive risk), but more constipation relating to its norepinephrine effects. • Hepatotoxicity may be more likely in patients with liver disease or heavy alcohol use, so liver function tests should be monitored when

indicated. MISCELLANEOUS ANTIDEPRESSANTS ■ Bupropion (Wellbutrin): • Norepinephrine-dopamine reuptake inhibitor. • Relative lack of sexual side effects as compared to the SSRIs. Can be added to other antidepressants to treat sexual dysfunction. • Some efficacy in treatment of adult attention deficit hyperactivity disorder (ADHD). • Effective for smoking cessation. • Weight neutral. • Side effects include increased anxiety, as well as increased risk of seizures and psychosis at high doses. • Contraindicated in patients with epilepsy or active eating disorders, and in those currently on an MAOI. Use with caution with agents that also lower the seizure threshold (like stimulants). Serotonin Receptor Antagonists and Agonists ■ Trazodone (Desyrel) and Nefazodone (Serzone): • Useful in the treatment of major depression, major depression with anxiety, and insomnia (secondary to its sedative effects). • They do not have the sexual side effects of SSRIs and do not affect rapid eye movement (REM) sleep. • Side effects include nausea, dizziness, orthostatic hypotension, cardiac arrhythmias, sedation, and priapism (especially with trazodone). • Because of orthostatic hypotension and sedation in higher doses, trazodone is not frequently used solely as an antidepressant. It is commonly used to treat insomnia often when initiating an SSRI (until insomnia improves as the depression resolves). • Nefazodone carries a black box warning for rare but serious liver failure (1 per 250,000–300,000 people) and is now off the market. PSYCHOPHARMACOLOGY WARDS QUESTION Q: Which antidepressant is least likely to cause sexual side effects? A: Wellbutrin (bupropion). KEY FACT Trazodone causes priapism: Remember the phrase “Trazo-bone.”

200 PSYCHOPHARMACOLOGY α2-Adrenergic Receptor Antagonists ■ Mirtazapine (Remeron): KEY FACT HETEROCYCLIC ANTIDEPRESSANTS Mirtazapine (Remeron) is good for treating major depression in the elderly—It helps with both sleep and appetite. TRICYCLIC ANTIDEPRESSANTS

- Useful in treating chronic pain.
- Used as a sleep aid in low doses.
- More activating/least sedating.
- Least anticholinergic. • Mechanism of action is antagonism of the central presynaptic alpha-2adrenergic receptors, which causes an increased release of serotonin and norepinephrine. • Useful in the treatment of major depression, especially in patients who have significant weight loss and/or insomnia. • At lower doses, mirtazapine acts preferentially on histamine receptors causing sedation and increased appetite, but at higher doses acts preferentially on the norepinephrine receptors and can be more activating. • Side effects include sedation, weight gain, dizziness, tremor, dry mouth, constipation, and (rarely) agranulocytosis. • Fewer sexual side effects compared to SSRIs and few drug interactions. ■ TCAs inhibit the reuptake of norepinephrine and serotonin, increasing availability of monoamines in the synapse. ■ Because of the long half-lives, most are dosed once daily. ■ They are rarely used as first-line agents due to a higher incidence of side effects, titration of dosing, and lethality in overdose. ■ Tertiary amines (highly anticholinergic/antihistaminergic [more sedating]/ antiadrenergic [more orthostasis] with a greater lethality in overdose): • Amitriptyline (Elavil): Useful in chronic pain, migraines, and insomnia. • Imipramine (Tofranil):
- Has intramuscular form.
- Useful in enuresis and panic disorder. • Clomipramine (Anafranil): Most serotonin-specific, therefore has efficacy in the treatment of OCD. • Doxepin (Sinequan): ■ Secondary amines—Metabolites of tertiary amines (less anticholinergic/

antihistaminic/antiadrenergic): • Nortriptyline (Pamelor, Aventyl):

- Least likely to cause orthostatic hypotension.
- Useful therapeutic blood levels.
- Useful in treating chronic pain.
- Can be safely used in geriatric population. • Desipramine (Norpramin):

TETRACYCLIC ANTIDEPRESSANTS ■ Amoxapine (Asendin): • Metabolite of antipsychotic loxapine. • May cause EPS and has a similar side-effect profile to typical antipsychotics. Side Effects ■ TCAs are highly protein bound and lipid soluble, and therefore can interact with other medications that have high protein binding. ■ The side effects of TCAs are mostly due to their lack of specificity and interaction with other receptors. ■ Antihistaminic properties: Sedation and weight gain. ■ Antiadrenergic properties (cardiovascular side effects): Orthostatic hypotension, dizziness, reflex tachycardia, arrhythmias (block cardiac sodium channel), and electrocardiographic (ECG) changes (widening QRS, QT, and PR intervals). Avoid in patients with preexisting conduction abnormalities or recent MI, or with increased fall risk. ■ Antimuscarinic effects (also called anticholinergic): Dry mouth, constipation, urinary retention, blurred vision, tachycardia, and exacerbation of narrow angle glaucoma. Can lead to delirium in the elderly population. ■ Lethal in overdose—Must carefully assess the suicide risk when prescribing. Symptoms of overdose include agitation, tremors, ataxia, arrhythmias, delirium, hypoventilation from central nervous system (CNS) depression, myoclonus, hyperreflexia, seizures, and coma. ■ Seizures: Risk of seizure is directly related to the dose and serum level (i.e., higher risk of seizures at high doses and overdoses). ■ Serotonergic effects: Erectile/ejaculatory dysfunction in males, anorgasmia in females.
MONOAMINE OXIDASE INHIBITORS ■ MAOIs prevent the inactivation of biogenic amines such as norepinephrine, serotonin, dopamine, and tyramine (an intermediate in the conversion of tyrosine to norepinephrine). ■ By irreversibly inhibiting the enzymes MAO-A and B, MAOIs increase the number of neurotransmitters available in synapses. ■ MAO-A preferentially deactivates serotonin and norepinephrine, and MAO-B preferentially deactivates phenethylamine; both types also act on dopamine and tyramine. ■ MAOIs are not used as first-line agents because of the increased safety and tolerability of newer agents, notably SSRIs/SNRIs. However, MAOIs are rarely used for certain types of refractory depression and in refractory anxiety disorders: • Phenelzine (Nardil). • Tranylcypromine (Parnate). • Isocarboxazid (Marplan). PSYCHOPHARMACOLOGY WARDS TIP A 1-week supply of TCAs (as little as 1–2 g) can be lethal in overdose. WARDS QUESTION Q: What is the treatment for TCA overdose? A: IV sodium bicarbonate. WARDS TIP Major complications of TCAs—3Cs: Cardiotoxicity Convulsions Coma WARDS QUESTION Q: What are the most common side effects of TCAs? A: Anticholinergic effects: Dry mouth, urinary retention, constipation, and blurry vision. WARDS TIP MAOIs are considered more effective than TCAs in depression with atypical features, characterized by hypersomnia, increased appetite, heavy feeling in extremities, and increased sensitivity to interpersonal rejection.

202 PSYCHOPHARMACOLOGY Side Effects WARDS TIP ■ Orthostatic hypotension (most common). ■ Drowsiness. Selegiline (Emsam transdermal patch) is a MAOI used to treat depression that does not require following the dietary restrictions when used in low dosages. However, decongestants, opiates (such as meperidine, fentanyl, and tramadol), and serotonergic drugs must still be avoided. ■ Weight gain. ■ Sexual dysfunction. ■ Dry mouth. ■ Sleep dysfunction. ■ Liver toxicity, seizures, and edema (rare). ■ GAD: SSRIs, SNRIs (venlafaxine), TCAs. ■ Posttraumatic stress disorder: SSRIs. ■ Irritable bowel syndrome: SSRIs, TCAs. ■ Enuresis: TCAs (imipramine). ■ Chronic pain:

SNRIs, TCAs. ■ Fibromyalgia: SNRIs. ■ Migraine headaches: TCAs (amitriptyline). ■ Serotonin syndrome occurs when SSRIs and MAOIs are taken together or if other drugs cause increase in serotonin levels. • Initially characterized by lethargy, restlessness, confusion, flushing, hyperactive bowels, diaphoresis, tremor, and myoclonic jerks. • May progress to hyperthermia, hypertonicity, rhabdomyolysis, renal failure, convulsions, coma, and death. • Treatment includes immediately discontinuing serotonergic medications, ICU monitoring, and administration of cyproheptadine. ECT can be effective. • Wait at least 2 weeks before switching from SSRI to MAOI, and at least 5–6 weeks with fluoxetine. ■ Hypertensive crisis: Risk when MAOIs are taken with tyramine-rich foods or sympathomimetics. • Foods with tyramine (red wine, cheese, chicken liver, fava beans, cured meats) cause a buildup of stored catecholamines. • In addition to a markedly elevated BP, it is also characterized by headache, sweating, nausea, and vomiting, photophobia, autonomic instability, chest pain, arrhythmias, and death. ■ Patients with pyridoxine deficiency can have numbness or paresthesias, so they should supplement with B6. ■ “Start low and go slow” (low doses that are increased slowly). Antidepressant Use in Other Disorders ■ OCD: SSRIs (in high doses), TCAs (clomipramine). ■ Panic disorder: SSRIs, SNRIs, TCAs, MAOIs. ■ Eating disorders: SSRIs (in high doses), TCAs. ■ Persistent depressive disorder (dysthymia): SSRIs, SNRIs (e.g., venlafaxine, duloxetine). ■ Social anxiety disorder (social phobia): SSRIs, SNRIs, MAOIs. ■ Neuropathic pain: TCAs (amitriptyline and nortriptyline), SNRIs.

■ Smoking cessation: Bupropion. ■ Premenstrual dysphoric disorder: SSRIs. ■ Insomnia: Mirtazapine, trazodone, TCAs (doxepin). Antipsychotics ■ Antipsychotics are used to treat psychotic disorders and bipolar disorders, as well as psychotic symptoms associated with other psychiatric and medical illnesses. • Typical or first-generation antipsychotics, sometimes referred to as neuroleptics, are classified according to potency and treat psychosis by primarily by blocking dopamine (D2) receptors. • Atypical or second-generation antipsychotics block both dopamine (D2) and serotonin (5HT-2A) receptors. ■ Most antipsychotics have a number of actions and receptor interactions in the brain that contribute to their varied efficacy and side-effect profiles. ■ Both typical and atypical antipsychotics have similar efficacies in treating the presence of positive psychotic symptoms, such as hallucinations and delusions. ■ Atypical antipsychotics were thought to be more effective at treating negative symptoms (such as flattened affect and social withdrawal), although this has not been consistently shown in the literature. ■ Atypical antipsychotics have largely replaced typical antipsychotics in use due to their side-effect profile. However, the risk of metabolic syndrome/ weight gain and other side effects, as well as the significant cost of the atypical antipsychotics means that currently both classes are used as first-line treatments. ■ The choice of which specific medication to prescribe should be made based on the patient’s individual clinical presentation, past response (favorable and unfavorable), side-effect profile, and preference. TYPICAL (FIRST-GENERATION) ANTIPSYCHOTICS All typical antipsychotics have similar efficacy, but vary in potency. Low-Potency, Typical Antipsychotics ■ Lower affinity for dopamine receptors and therefore a higher dose is required. Remember, potency refers to the action on dopamine receptors, not the level of efficacy. ■ Higher incidence of antiadrenergic, anticholinergic, and antihistaminic side effects compared to high-potency typical antipsychotics. ■ Lower incidence of EPS and (possibly) neuroleptic malignant syndrome. ■ More lethality in overdose due to QTc prolongation, and the potential for heart block and ventricular tachycardia. ■ Rare risk of agranulocytosis, and slightly higher seizure risk than high-potency antipsychotics. • Chlorpromazine (Thorazine):

- Commonly causes orthostatic hypotension.
- Can cause blue-gray skin discoloration as well as corneal and lens deposits. PSYCHOPHARMACOLOGY WARDS QUESTION Q: How is serotonin syndrome treated? A: First, discontinue the medication(s), next, provide supportive care and benzodiazepines. The serotonin antagonist cyproheptadine and ECT can also be used. WARDS TIP Warning about atypical antipsychotics: Although they are used to treat the behavioral symptoms of neurocognitive disorders (dementias) and delirium, studies show an increased risk of all-cause mortality and stroke when using these agents in the elderly, which, as a result, is listed as a FDA black box warning for these medications.

204 PSYCHOPHARMACOLOGY Midpotency, Typical Antipsychotics ■ Have midrange properties. • Loxapine (Loxitane): High-Potency, Typical Antipsychotics

- Can lead to photosensitivity.
- Also used to treat nausea and vomiting, as well as intractable hiccups.
- Comes in PO and IM formulations (effective in treating agitation in emergencies). • Thioridazine (Mellaril): Associated with retinitis pigmentosa.
- Higher risk of seizures.
- Metabolite is an antidepressant. • Thiothixene (Navane): Can cause ocular pigment changes. • Molindone (Moban). • Perphenazine (Trilafon). ■ Greater affinity for dopamine receptors; therefore, a relatively low dose is needed to achieve effect. ■ Less sedation, orthostatic hypotension, and anticholinergic effects. ■ Greater risk for extrapyramidal symptoms and (likely) TD. • Haloperidol (Haldol): Can be given PO/IM/IV. Decanoate (long acting) form available. • Fluphenazine (Prolixin): Can be given PO/IM. Decanoate form available. • Trifluoperazine (Stelazine): Approved for nonpsychotic anxiety. • Pimozide (Orap): Associated with QTc prolongation and ventricular tachycardia. Ms. B is a 28-year-old, overweight female who presents to your outpatient clinic following discharge from an inpatient psychiatry unit. Police found her in a local shopping mall, talking to herself and telling a passerby that the devil had “stolen her soul.” She appeared disheveled and scared. During the hospitalization, she was diagnosed with schizophrenia, and olanzapine was prescribed and titrated to 30 mg at bedtime for delusional thinking and disorganized behavior. She has since been living with her parents, and her hygiene and self-care have improved. Although Ms. B reports occasional auditory hallucinations telling her that her parents do not like her, she recognizes that the voices are not real and is not distressed by them. She has become involved in a vocational skills program and hopes to work at a local supermarket. However, during her last appointment with her primary care doctor, she was told she had an elevated fasting glucose of 115 and triglycerides of 180, and that she had gained 12 pounds in the past 3 months with a waist circumference of 36 inches. Her blood pressure was normal, but she reported a family history of diabetes and high blood pressure. What is the next step? Given her diagnosis of schizophrenia, and that Ms. B has had an adequate partial response to pharmacological treatment, she should continue to be treated with an antipsychotic. However, her recent laboratory results are suggestive of metabolic syndrome, and thus she is at an increased risk for cardiovascular disease. While this patient has responded well to olanzapine,

this medication along with other atypical antipsychotics have been associated with increased weight gain and impaired glucose metabolism. It is unclear if her laboratory test results were abnormal prior to starting olanzapine, are elevated secondary to treatment, or a combination of both. In treating Ms. B, first steps include recommending lifestyle modifications and close monitoring of her weight, blood sugar levels, lipids, and waist circumference, while collaborating closely with her primary care physician. If a change in her antipsychotic medication is warranted after weighing the risks and benefits of altering her treatment, other atypical antipsychotics such as ziprasidone or aripiprazole (both less associated with weight gain), or typical antipsychotics might be considered; these medications would then be cross-tapered. When choosing medications, consideration must be given to a history of response, tolerability, side-effect profile, patient preference, and cost. Side Effects ■ The positive symptoms of schizophrenia are treated by action of the medications in the mesolimbic dopamine pathway. The mesolimbic pathway includes the nucleus accumbens, the fornix, the amygdala, and the hippocampus. ■ The negative symptoms of schizophrenia are thought to occur due to (decreased) dopaminergic action in the mesocortical pathway. ■ Extrapyramidal symptoms occur through blockade of the dopamine pathways in the nigrostriatum. ■ Increased prolactin is caused by dopamine blockade in the tuberoinfundibular area. ■ Antidopaminergic effects: • EPS:

- Parkinsonism—Bradykinesia, mask-like face, cogwheel rigidity, pill-rolling tremor. Treat with benztropine (Cogentin) or lower dose if appropriate.
- Akathisia—Subjective anxiety and restlessness, objective fidgetiness. Patients may report a sensation of inability to sit still. Best treated with dose reduction (if appropriate), b-blockers, or benzodiazepines.
- Dystonia—Sustained painful contraction of muscles of neck (torticollis), tongue, eyes (oculogyric crisis). It can be life threatening if it involves the airway or diaphragm. Treat with benztropine (Cogentin) or diphenhydramine (Benadryl), or lower the dose if appropriate. • Hyperprolactinemia—Leads to decreased libido, galactorrhea, gynecomastia, impotence, amenorrhea. ■ Anti-HAM effects: Caused by actions on Histaminic, Adrenergic, and Muscarinic receptors: • Antihistaminic—Results in sedation, weight gain. • Anti-a1 adrenergic—Results in orthostatic hypotension, cardiac abnormalities, and sexual dysfunction. • Antimuscarinic—Anticholinergic effects, resulting in dry mouth, tachycardia, urinary retention, blurry vision, constipation, and precipitation of narrow-angle glaucoma. ■ Tardive dyskinesia: • Choreoathetoid (writhing, irregular) movements of mouth and tongue (or other body parts) that may occur in patients who have used antipsychotics for more than 6 months. PSYCHOPHARMACOLOGY KEY FACT Haloperidol (Haldol) is often given as an intramuscular injection to treat acute agitation or psychosis. The commonly used phrase: “5 and 2,” in psychiatric emergencies refers to 5 mg of IM haloperidol and 2 mg of IM lorazepam in order to quickly sedate an agitated patient. WARDS TIP Haloperidol and fluphenazine are also available in long-acting, intramuscular forms (decanoate) that are useful if patients are poorly compliant with their oral medication. Risperidone (Consta), aripiprazole (Maintena), and paliperidone (Invega Sustenna) also have long-acting injectibles, but they are more expensive. KEY FACT There is a roughly 5% chance of developing tardive dyskinesia for each year treated with a typical antipsychotic. WARDS QUESTION Q: How are dystonia and akathisia treated? A: The first-line treatment for dystonia is benztropine (Cogentin). Diphenhydramine (Benadryl) can also be used. The first-line treatment for akathisia is decreasing the dose

of the causative agent (if appropriate), or adding propranolol or a benzodiazepine.

206 PSYCHOPHARMACOLOGY KEY FACT Clozapine, the first atypical antipsychotic, is less likely to cause tardive dyskinesia. ■ Elevated liver enzymes, jaundice. • Older age is a risk factor. • Women and patients with affective disorders may be at an increased risk. • Although up to 50% of cases will remit (without further antipsychotic use), most cases are permanent. • Treatment involves discontinuation of current antipsychotic if clinically possible and changing to a medication with less potential to cause TD. ■ Less common side effects include neuroleptic malignant syndrome (NMS): • Though uncommon, occurs more often in young males early in treatment with high-potency typical antipsychotics. • It is a medical emergency and has up to a 20% mortality rate if left untreated. • It is characterized by FALTERED:

- Fever (most common presenting symptom).
- Autonomic instability (tachycardia, labile hypertension, diaphoresis).
- Leukocytosis.
- Tremor.
- Elevated CPK.
- Rigidity (lead pipe rigidity is considered almost universal).
- Excessive sweating (diaphoresis).
- Delirium (mental status changes). • Treatment involves discontinuation of current medications and administration of supportive medical care (hydration, cooling, etc.). • Sodium dantrolene, bromocriptine, and amantadine may be used but have their own side effects and unclear efficacy. ECT can also be effective. • This is not an allergic reaction. • Patient is not prevented from restarting the same antipsychotic at a later time, but will have an increased risk for another episode of neuroleptic malignant syndrome. ■ Ophthalmologic problems (irreversible retinal pigmentation with high doses of thioridazine, deposits in lens and cornea with chlorpromazine). ■ Dermatologic problems, including rashes and photosensitivity (blue-gray skin discoloration with chlorpromazine). ■ Seizures: All antipsychotics lower the seizure threshold, although low-potency antipsychotics are more likely. ATYPICAL (SECOND-GENERATION) ANTIPSYCHOTICS ■ Atypical antipsychotics block both dopamine and serotonin receptors and are associated with different side effects than typical antipsychotics. ■ In particular, they are less likely to cause EPS, TD, or neuroleptic malignant syndrome. ■ They may be more effective than typical antipsychotics in treating negative symptoms of schizophrenia. ■ Atypical antipsychotics are also used to treat acute mania, bipolar disorder, and as adjunctive medications in unipolar depression. ■ They are also used in treating borderline personality disorder, PTSD, and certain psychiatric disorders in childhood (e.g., tic disorders).

• Clozapine (Clozaril):

- Less likely to cause TD.
- Only antipsychotic shown to be more efficacious than the others; used in treatment refractory schizophrenia.
- Only antipsychotic shown to decrease the risk of suicide.

- More anticholinergic side effects than other atypical or high-potency typical antipsychotics. Associated with tachycardia, constipation, and hypersalivation.
- Risk of severe side effects • 1% incidence of agranulocytosis; clozapine must be stopped if the absolute neutrophil count (ANC) drops below 1500 per microliter. All patients must undergo regular ANC monitoring weekly for the first 6 months of treatment, followed by biweekly for 6 months, and then monthly monitoring. • 4% incidence of seizures. • Small risk of myocarditis. • Risperidone (Risperdal):
- Can cause increased prolactin.
- Associated with orthostatic hypotension and reflex tachycardia.
- Long-acting injectable (LAI) form named Consta. • Quetiapine (Seroquel): Much less likely to cause EPS; common side effects include sedation, orthostatic hypotension, and weight gain. • Olanzapine (Zyprexa): Common side effects include significant weight gain, sedation, and dyslipidemia. Comes in PO/IM/LAI formulations. • Ziprasidone (Geodon): Less likely to cause significant weight gain, associated with QTc prolongation, and must be taken with food (50% reduction in absorption without a 300-calorie meal). Comes in PO and IM formulations. • Aripiprazole (Abilify):
- Unique mechanism of partial D2 agonism.
- Can be more activating (akathisia) and less sedating.
- Less potential for weight gain.
- Comes in PO, IM, and LAI formulations. ■ Newer (more expensive) antipsychotics: • Paliperidone (Invega):
- Metabolite of risperidone.
- Long-acting injectable forms: Sustenna—monthly; Trinza—every 3 months. • Asenapine (Saphris) orally dissolving (sublingual) tablet. • Iloperidone (Fanapt). • Lurasidone (Latuda): Must be taken with food; used in bipolar depression. Side Effects ■ Metabolic syndrome. • This must be monitored with baseline weight, waist circumference (measured at iliac crest), BP, HbA1c, and fasting lipids. PSYCHOPHARMACOLOGY WARDS TIP Onset of antipsychotic side effects NMS: Any time (but usually early in treatment) Acute dystonia: Hours to days Parkinsonism/Akathisia: Days to weeks Tardive dyskinesia: Months to years The Abnormal Involuntary Movement Scale (AIMS) can be used to quantify and monitor for tardive dyskinesia. WARDS TIP Thirty percent of patients with treatment-resistant psychosis will respond to clozapine.

208 PSYCHOPHARMACOLOGY WARDS TIP Patients on clozapine must have weekly blood draws for the first 6 months to check WBC and absolute neutrophil counts because of the risk of agranulocytosis. With time, the frequency of blood draws decreases. ■ QTc prolongation. Mood Stabilizers WARDS TIP Quetiapine, olanzapine, aripiprazole, risperidone, asenapine, and ziprasidone have FDA approval for treatment of mania. WARDS TIP Antipsychotics may be used as adjuncts to mood stabilizers early in the course of a manic episode. Atypical antipsychotics are often prescribed as monotherapy in the acute or maintenance treatment of bipolar disorder. LITHIUM ■ Onset of action takes 5–7 days. WARDS QUESTION Q: What is the only mood stabilizer shown to decrease suicidality? A: Lithium. Side Effects • Weight gain: Metformin can be used to reduce or prevent. • Hyperlipidemia. • Hyperglycemia—Rarely, diabetic ketoacidosis has been reported. ■ Some anti-HAM effects (antihistaminic, antiadrenergic, and antimuscarinic). ■ Elevated liver function tests (LFTs)—Monitor yearly for elevation in LFTs and ammonia. ■ Mood stabilizers are used to treat acute mania and to help prevent relapses of manic episodes (maintenance treatment)

in bipolar disorder and schizoaffective disorder. Less commonly, they may be used for: • Augmentation of antidepressants in patients with major depression refractory to monotherapy. • Potentiation of antipsychotics in patients with schizophrenia or schizoaffective disorder. • Treatment of aggression and impulsivity (e.g., neurocognitive disorders, intellectual disability, personality disorders, other medical conditions). • Enhancement of abstinence in treatment of alcoholism. ■ Mood stabilizers include lithium and anticonvulsants, most commonly valproic acid, lamotrigine, and carbamazepine. ■ Lithium is the drug of choice in acute mania and as prophylaxis for both manic and depressive episodes in bipolar and schizoaffective disorders. ■ It is also used in cyclothymic disorder and unipolar depression. ■ Lithium is metabolized by the kidney, so dosing adjustments may be necessary in patients with renal dysfunction. ■ Prior to initiating, patients should have an ECG, basic chemistries, thyroid function tests, a complete blood count (CBC), and a pregnancy test. ■ Blood levels correlate with clinical efficacy and should be checked 4–5 days after initiation of treatment and after every dose change. ■ The major drawback of lithium is its high incidence of side effects and very narrow therapeutic index: • Therapeutic range: 0.6–1.2. (Individual patients can have significant side effects even within this range.) • Toxic: >1.5. • Potentially lethal: >2.0. ■ Toxic levels of lithium cause altered mental status, coarse tremors, convulsions, delirium, coma, and death. ■ Clinicians need to regularly monitor blood levels of lithium, thyroid function (thyroid-stimulating hormone), and kidney function.

■ Fine tremor. ■ Cognitive slowing or dulling. ■ Nephrogenic diabetes insipidus (polydipsia, polyuria). ■ GI disturbance. ■ Weight gain. ■ Sedation. ■ Thyroid enlargement, hypothyroidism. ■ ECG changes. ■ Benign leukocytosis. ■ Lithium is associated with an increased risk of Ebstein’s anomaly, a cardiac defect in babies born to mothers taking lithium, although the absolute risk is very low. Weighed against the risk of untreated bipolar disorder, many women take lithium during pregnancy. Anticonvulsants CARBAMAZEPINE (TEGRETOL) ■ Especially useful in treating mania with mixed features and rapid-cycling bipolar disorder; less effective for the depressed phase. ■ Acts by blocking sodium channels and inhibiting action potentials. ■ Onset of action is 5–7 days. ■ Must check pregnancy test prior to initiating therapy as it increases the risk of neural tube defects. ■ Carries risk of rash, SIADH, hyponatremia, benign leukopenia, and aplastic anemia (rare). ■ CBC, LFTs must be obtained before initiating treatment and regularly monitored during treatment. ■ Carbamazepine induces its own metabolism. Patients may therefore need a dose increase in the first few weeks to months. • Serum carbamazepine levels should be measured initially and after every few weeks for the first several months. Therapeutic level is 8–12 mcg/mL. Side Effects ■ The most common side effects are GI and CNS (e.g., drowsiness, ataxia, sedation, confusion). ■ Potential dangerous skin rash (Stevens–Johnson syndrome). ■ Leukopenia, hyponatremia, aplastic anemia, thrombocytopenia, and agranulocytosis. ■ Elevation of liver enzymes, causing hepatitis. ■ Teratogenic effects when used during pregnancy (neural tube defects). ■ Significant drug interactions with many medications metabolized by the cytochrome P450 pathway, including inducing its own metabolism through autoinduction (requiring increasing dosages). ■ Toxicity: Confusion, stupor, motor restlessness, ataxia, tremor, nystagmus, twitching, and vomiting. PSYCHOPHARMACOLOGY KEY FACT When prescribing lithium, it is important to monitor lithium levels, creatinine, and thyroid function tests. To remember labs for lithium: P THY BEER Pregnancy Thyroid Benign leukocytosis Electrolytes EKG Renal WARDS TIP Blood levels are useful for lithium, valproic acid, carbamazepine, and clozapine. Remember the 8–12 rule for therapeutic windows of lithium (0.8–1.2), carbamazepine (8–12), and valproic acid (80–120). WARDS TIP The following factors increase Li+ levels: • NSAIDs (e.g., ibuprofen) • Aspirin (+/–) • Thiazide diuretics •

Dehydration • Salt deprivation • Sweating (salt loss) • Impaired renal function

210 PSYCHOPHARMACOLOGY VALPROIC ACID (DEPAKOTE AND DEPAKENE) KEY FACT Carbamazepine is like “PacMan”: It causes the CYP450 enzyme to chew up medications, resulting in low medication levels and requiring higher dosages than usual. ■ Monitoring of LFTs and CBC is necessary. WARDS TIP Lithium’s side effect of leukocytosis can be advantageous when combined with other medications that decrease WBC count (e.g., clozapine). Lamotrigine (Lamictal) WARDS QUESTION Q: What is a potential consequence of using benzodiazepines (BDZ) with alcohol? A: BDZs can be lethal when mixed with alcohol. Respiratory depression may cause death. Oxcarbazepine (Trileptal) ■ Less risk of rash and hepatic toxicity. ■ Monitor sodium levels for hyponatremia. Gabapentin (Neurontin) WARDS TIP ■ Little efficacy in bipolar disorder. Pregabalin (Lyrica) In chronic alcoholics or those with liver disease, use benzodiazepines that are not metabolized by the liver. There are a LOT of them: Lorazepam Oxazepam Temazepam ■ Little efficacy in bipolar disorder. ■ Beneficial side effect is weight loss. ■ Useful in treating acute mania, mania with mixed features, and rapid cycling. ■ Multiple mechanisms of action: Blocks sodium channels and increases GABA concentrations in the brain. ■ Comes in PO (Depakote), liquid (Depakene), and IV formulations. ■ Drug levels should be checked after 4–5 days. Therapeutic range is 80–120 µg/mL. ■ Contraindicated in pregnancy, so care should be given in women of childbearing age (neural tube defects). ■ Side effects include GI distress, sedation, cognitive slowing, weight gain, LFT elevations, hyperammonemia, thrombocytopenia, pancreatitis. ■ Efficacy for bipolar depression, though little efficacy for acute mania or prevention of mania. ■ Believed to work on sodium channels that modulate glutamate and aspartate. ■ Most common side effects are dizziness, sedation, headaches, and ataxia. ■ Most serious side effect is Stevens–Johnson syndrome (life-threatening rash involving skin and mucous membranes) in 0.1%. This is most likely in the first 2–8 weeks, but is minimized by starting with low doses and increasing slowly. ■ Valproate will increase lamotrigine levels, and lamotrigine will decrease valproate levels. ■ As effective in mood disorders as carbamazepine, but better tolerated. ■ Often used adjunctively to help with anxiety, sleep, neuropathic pain. ■ Used in GAD (second-line) and fibromyalgia. Tiagabine (Gabitril): Questionable benefit in treating anxiety Topiramate (Topamax) ■ May be helpful with impulse control disorders. ■ Can cause hypochloremic, metabolic acidosis as well as kidney stones. ■ The most limiting side effect is cognitive slowing and sleepiness resulting in its nickname, “Dope-a-max.”

Anxiolytics/Hypnotics ■ Include benzodiazepines (BDZs), barbiturates, and buspirone. ■ Common indications for anxiolytics/hypnotics include: • Anxiety disorders. • Muscle spasm. • Seizures. • Sleep disorders. • Alcohol withdrawal. • Anesthesia induction. BENZODIAZEPINES ■ BDZs are the most widely prescribed psychotropic medications. ■ BDZs work by potentiating the effects of gamma-aminobutyric acid (GABA). ■ They reduce anxiety and can be used to treat akathisia. ■ Many patients become physically dependent on these medications and require increasing amounts for the same clinical effect (i.e., tolerance). ■ Potential for abuse. ■ Choice of BDZ is based on time to onset of action, duration of action, and method of metabolism. ■ Relatively safer in overdose than barbiturates. ■ Long acting (half-life: >20 hours) • Diazepam (Valium):

- Rapid onset.
- Used during detoxification from alcohol or sedative-hypnotic-anxiolytics, and for seizures.
- Effective for muscle spasm.

- Less commonly prescribed to treat anxiety because of euphoria. • Clonazepam (Klonopin):
- Treatment of anxiety, including panic attacks.
- Avoid with renal dysfunction; longer half-life allows for once or twice daily dosing. ■ Intermediate acting (half-life: 6–20 hours) • Alprazolam (Xanax):
- Treatment of anxiety, including panic attacks.
- Short onset of action leads to euphoria, high abuse potential. • Lorazepam (Ativan):
- Treatment of panic attacks, alcohol and sedative-hypnotic-anxiolytic detoxification, agitation.
- Not metabolized by liver.
- Used with haloperidol in IM formulations to quickly sedate agitated patients. • Oxazepam (Serax):
- Alcohol and sedative-hypnotic-anxiolytic detoxification.
- Not metabolized by liver. PSYCHOPHARMACOLOGY

212 PSYCHOPHARMACOLOGY • Temazepam (Restoril): WARDS QUESTION Q: How is benzodiazepine (BDZ) overdose treated? A: Flumazenil; however, be careful not to induce withdrawal too quickly—this can be life threatening. ■ Short acting (half-life: <6 hours) • Midazolam (Versed): Side Effects ■ Drowsiness. ■ Impairment of intellectual function. ■ Anterograde amnesia. NON-BDZ HYPNOTICS ■ Diphenhydramine (Benadryl): ■ Ramelteon (Rozerem): NON-BDZ ANXIOLYTICS ■ Buspirone (BuSpar):

- Because of dependence, rarely used for treatment of insomnia.
- Not metabolized by liver.
- Very short half-life.
- Primarily used in medical and surgical settings. ■ Reduced motor coordination (careful in elderly). ■ Withdrawal can be life threatening and cause seizures. ■ Toxicity: Respiratory depression in overdose, especially when combined with alcohol. ■ Zolpidem (Ambien)/Zaleplon (Sonata)/Eszopiclone (Lunesta): • Work by selective receptor binding to the omega-1 receptor on the GABA-A receptor, which is responsible for sedation. • Should be used for short-term treatment of insomnia. • Compared to BDZs, less tolerance/dependence occurs with prolonged use (but still can occur). • Zaleplon has a shorter half-life than zolpidem, which has a shorter half-life than eszopiclone. • Reports of anterograde amnesia, hallucinations, parasomnias (e.g., sleepwalking, sleepeating), increased fall risk, and GI side effects may limit their tolerability. • An antihistamine with moderate anticholinergic effects. • Side effects include sedation, dry mouth, constipation, urinary retention, and blurry vision. • Selective melatonin MT1 and MT2 agonist. • No tolerance or dependence, making it an effective and safe sleep aid. • Partial agonist at 5HT-1A receptor, thereby decreasing serotonergic activity. • Slower onset of action than BDZs (takes several weeks for effect). • Not considered as effective as other options, and so it is often used in combination with another agent (e.g., an SSRI) for the treatment of generalized anxiety disorder. • Does not potentiate the CNS depression of alcohol (useful in alcoholics), and has a low potential for abuse/addiction. • Dosed three times per day.

■ Hydroxyzine (Atarax): • An antihistamine. • Side effects include sedation, dry mouth, constipation, urinary retention, and blurry vision. • Useful for patients who want quick-acting, short-term medication, but who cannot take BDZs for various reasons. ■ Barbiturates (e.g.,

butalbitol, phenobarbital, amobarbitol, pentobarbital): Rarely used because of the lethality of overdose, significant withdrawal, potential for abuse, and side-effect profile. ■ Propranolol: • Beta-blocker. • Useful in treating the autonomic effects of panic attacks or social phobia (i.e., performance anxiety), such as palpitations, sweating, and tachycardia. • Also used to treat akathisia (side effect of antipsychotics). Psychostimulants Used in ADHD and in treatment refractory depression. ■ Dextroamphetamine and amphetamines (Dexedrine, Adderall): • Dextroamphetamine is the d-isomer of amphetamine. • Schedule II due to high potential for abuse/diversion. • Monitor BP, and watch for weight loss, insomnia, exacerbation of tics, decreased seizure threshold. ■ Methylphenidate (Ritalin, Concerta): • CNS stimulant, similar to amphetamine. • Schedule II. • Watch for leukopenia or anemia. • Monitor BP and CBC with differential, and watch for weight loss, insomnia, exacerbation of tics, decreased seizure threshold. ■ Atomoxetine (Strattera): • Inhibits presynaptic norepinephrine reuptake, resulting in increased synaptic norepinephrine and dopamine. • Less appetite suppression and insomnia. • Not classified as a controlled substance. • Less abuse potential than dextroamphetamine/methylphenidate but less effective. • Rare liver toxicity, and possible increase in suicidal ideation in children/ adolescents. ■ Modafinil (Provigil): Used in narcolepsy, not ADHD. Cognitive Enhancers Used in major neurocognitive disorders (dementias). ACETYLCHOLINESTERASE INHIBITORS ■ Donepezil (Aricept): • Once-daily dosing. • Some GI side effects. • Used in mild-to-moderate neurocognitive disorders (dementias). PSYCHOPHARMACOLOGY

214 PSYCHOPHARMACOLOGY ■ Galantamine (Razadyne): KEY FACT Alzheimer medications, such as donepezil and rivastigmine, work by reversible inhibition of acetylcholine esterase. ■ Rivastigmine (Exelon): ■ Memantine (Namenda): PSYCHOSIS AGITATION/CONFUSION/DELIRIUM DEPRESSION ANXIETY SEDATION/POOR CONCENTRATION SELECTED MEDICATIONS ■ Albuterol: Anxiety, confusion. ■ Isoniazid: Psychosis. • Twice-daily dosing. • GI side effects. • Used in mild-to-moderate neurocognitive disorders (dementias). • Twice-daily dosing. • Has daily patch form, with fewer side effects. • Used in mild-to-moderate neurocognitive disorders (dementias). NMDA (GLUTAMATE) RECEPTOR ANTAGONIST • Used in moderate-to-severe neurocognitive disorders (dementia). • Fewer side effects than cholinesterase inhibitors. • Should be used in conjunction with acetylcholinesterase inhibitor. Reference List of Medications That May Cause Psychiatric Symptoms Sympathomimetics, analgesics, antibiotics (e.g., isoniazid, antimalarials), anticholinergics, anticonvulsants, antihistamines, corticosteroids, antiparkinsonian agents. Antipsychotics, anticholinergics, antihistamines, antidepressants, antiarrhythmics, antineoplastics, corticosteroids, NSAIDs, antiasthmatics, antibiotics, antihypertensives, antiparkinsonian agents, thyroid hormones. Antihypertensives, antiparkinsonian agents, corticosteroids, calcium channel blockers, NSAIDs, antibiotics, peptic ulcer drugs. Sympathomimetics, antiasthmatics, antiparkinsonian agents, hypoglycemic agents, NSAIDs, thyroid hormones. Antianxiety agents/hypnotics, anticholinergics, mood stabilizers, antibiotics, antihistamines, antipsychotics (e.g., clozapine, quetiapine, olanzapine). ■ Procainamide, quinidine: Confusion, delirium.

■ Tetracycline: Depression. ■ Nifedipine, verapamil: Depression. ■ Cimetidine: Depression, confusion, psychosis. ■ Steroids: Aggressiveness/agitation, mania, depression, anxiety, psychosis. Other Treatments ELECTROCONVULSIVE THERAPY (ECT) Patients are often premedicated with atropine, and then given general anesthesia and muscle relaxants (e.g., succinylcholine). A generalized tonic-clonic seizure is then induced using unilateral or bilateral electrodes placed on the head. While the mechanism of action of ECT is not fully known, there are likely anticonvulsant

effects, as well as brain perfusion and connectivity changes involved. ECT is the most effective treatment for major depressive disorder, especially with psychotic features, as well as for acute mania and catatonia. It is often used in patients who cannot tolerate medications or who have failed other treatments. ECT is discontinued after symptomatic improvement, typically a course of 8–12 sessions given three times weekly. Monthly maintenance ECT is often used to prevent relapse of symptoms, and the addition of nortriptyline or venlafaxine may prolong remission even further. The most common side effects are muscle soreness, headaches, amnesia, and confusion. Bilateral electrode placement is more efficacious, but increases memory impairment and confusion. Evidence shows that the memory loss is almost always temporary and returns to baseline at 6 months. DEEP BRAIN STIMULATION (DBS) DBS is a surgical treatment involving the implantation of a medical device that sends electrical impulses to specific parts of the brain. DBS in select brain regions has provided benefits for Parkinson disease and disabling dystonia, as well as for chronic pain and tremors. Its underlying principles and mechanisms are still not clear. DBS directly changes brain activity in a controlled manner and its effects are reversible (unlike those of lesioning techniques). DBS has been used to treat various affective disorders, including major depression. While DBS has proven helpful for some patients, there is potential for serious complications and side effects. REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) rTMS is a noninvasive method to excite neurons in the brain. Weak electric currents are induced in the tissue by rapidly changing magnetic fields, a process called electromagnetic induction. In this way, brain activity can be triggered with minimal discomfort. rTMS can produce longer-lasting changes than nonrepetitive stimulation. Numerous small-scale studies have demonstrated efficacy in the treatment of major depression; however, studies show less efficacy than for ECT, and the price of treatment is high. Side effects include seizures (rare), as well as headache and scalp pain. LIGHT THERAPY Light therapy, or phototherapy, consists of exposure to daylight or to specific wavelengths of light using lasers, light-emitting diodes, fluorescent lamps, dichroic lamps or very bright, full-spectrum light, for a prescribed amount of time and, in PSYCHOPHARMACOLOGY

216 PSYCHOPHARMACOLOGY KETAMINE INFUSION Typical Antipsychotics (D2 antagonism) Watch for NMS (fever, lead pipe rigidity). some cases, at a specific time of day. The recommendation is for using a 10,000 lux bright white light for 30 minutes per day in the early morning. Light therapy is used to treat major depression with a seasonal pattern (seasonal affective disorder), with some support for its use with nonseasonal psychiatric disorders. Ketamine is an NMDA receptor antagonist that is most commonly used as an anesthetic agent. Ketamine can be given as an IV infusion for the treatment of unipolar major depression. It’s effect is rapid (with response within 40–120 minutes), but the effect dissipates by day 10–14. Ketamine carries a risk of dissociation/psychosis, bladder toxicity, and neurotoxicity. Currently, use of IV ketamine for depression is still mostly limited to research settings, but increasingly through specialized ketamine clinics. Esketamine, the intranasal formulation of ketamine, was recently FDA approved for treatment-resistant depression. Most Common Psychiatric Medications for Wards Drug name (Brand) Dosing Side Effects Monitoring Other chlorpromazine (Thorazine) 200–800 mg Hypotension, sedation, orthostasis EKG, BMI, QTc Least potent PO, IM fluphenazine (Prolixin) 6–20 mg EPS, sedation PO, IM, LAI haloperidol (Haldol) 2–20 mg EPS, sedation PO, IM, LAI perphenazine (Triaflon) 8–32 mg EPS, sedation PO, IM EPS tx: Akathisia (propranolol 10 mg TID), Parkinsonism/Dystonia - (benztropine 1–2 mg daily) Atypical Antipsychotics (D2 and 5HT2a antagonism) Drug name (Brand) Dosing Side Effects Monitoring Other clozapine (Clozaril) 300–900 mg Anticholinergic, orthostatis, agranulocytosis, drooling Weekly ANC Most efficacious Lower suicide risk aripiprazole (Abilify) 5–30

mg Akathisia For all: A1C, fasting glucose, lipid profile, BMI, LFTs, renal function PO and LAI lurasidone (Latuda) 40–120 mg Akathisia Give with food olanzapine (Zyprexa) 10–30 mg Metabolic syndrome, orthostasis, sedating PO, IM, LAI paliperidone (Invega) 3–12 mg Hyperprolactinemia, EPS, sedation, metabolic syndrome PO and LAI quetiapine (Seroquel) 50–800 mg Metabolic syndrome, orthostasis, sedating PO, check QTc risperidone (Risperdal) 2–6 mg Hyperprolactinemia, EPS, sedation, metabolic syndrome PO and LAI

Mood Stabilizers Drug name Brand) Dosing Side Effects Monitoring Other Lithium 900–1800 mg GI upset, tremor, nephrogenic DI, renal failure Thyroid, renal, serum drug level (0.8–1.2) lamotrigine (Lamictal) 100–200 mg GI upset, SJS rash Monitor for rash Dose slowly valproic acid (Depakote) 500–2000 mg GI upset, weight gain, liver toxicity Liver, ammonia, serum drug level (80–120) carbamazepine (Tegretol) 800–1600 mg Hyponatremia, agranulocytosis Liver, renal, serum drug level (8–10) Antidepressants Drug name (Brand) Dosing Side Effects/Monitor Other fluoxetine (Prozac) 20–80 mg SSRI’s: GI upset, sexual dysfunction, bleeding, discontinuation syndrome sertraline (Zoloft) 50–200 mg Safe in pregnancy escitalopram (Lexapro) 10–20 mg Few med interactions venlafaxine (Effexor) 75–225 mg Tremor, HTN, akathisia Short half-life duloxetine (Cymbalta) 40–120 mg Monitor LFTs Treats pain, fibromyalgia mirtazapine (Remeron) 15–45 mg Sedation, weight gain Activating at higher doses buproprion (Wellbutrin) 150–450 mg Activating, insomnia Increased seizure risk Watch for 5HT syndrome (Fever, hyperreflexia, myoclonus, GI disturbance) PSYCHOPHARMACOLOGY Ebstein’s anomaly Lower suicide risk Contraindicated in pregnancy: neural tube defect Contraindicated in pregnancy: neural tube defect PacMan inducer Long half-life