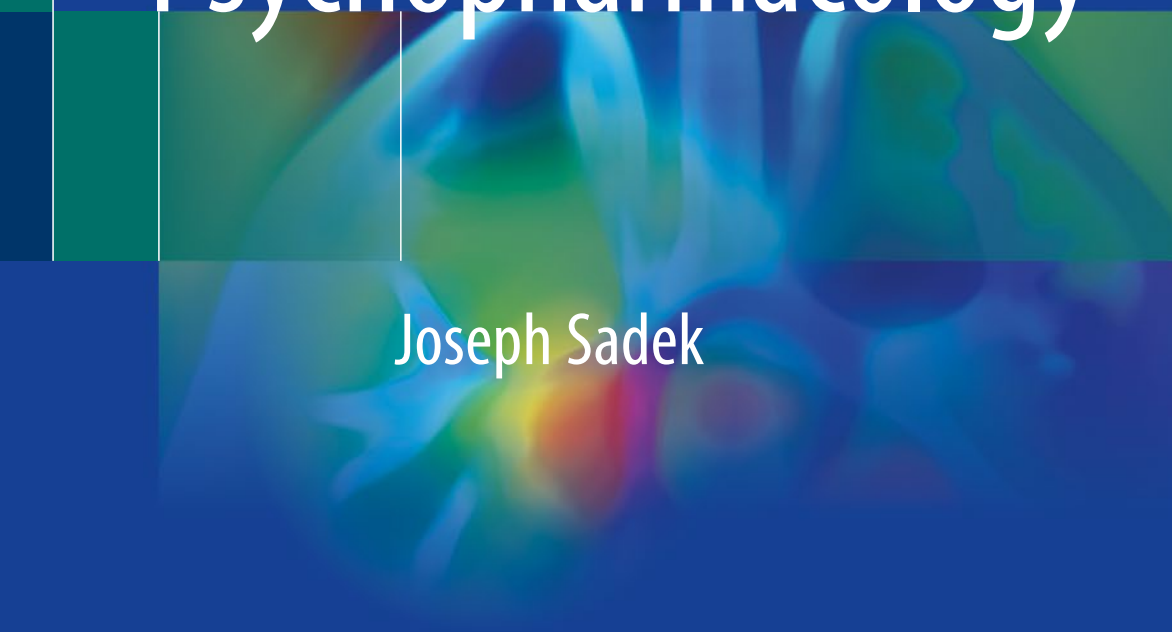
Clinician's Guide to Psychopharmacology



Joseph Sadek

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Foreword

This book by Dr. Joseph Sadek is a practical compendium of clinical knowledge about psychotropic medications. It is based on Dr. Sadek's years of clinical experience as well as his knowledge of the research base in psychopharmacology. He reviews each marked psychotropic drug in each drug class, with details about many features, including dosing and special indications or risks, as well as mechanisms and side effects. Texts of psychopharmacology can provide facts about drugs, but clinical experience typically is absent, and thus readers are not guided as to how to weigh those facts. By providing a wealth of factual detail as well as the context of his clinical experience, Dr. Sadek has produced a book that should be of utility to the practicing clinician as a helpful reference.

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Preface

This is the first edition of the clinician's guide to psychopharmacology. There are numerous available psychopharmacology books but I wanted to provide our clinicians with a simple, direct, evidence-based, and clinically relevant information. I also hope to produce a resource that is reader friendly and up to date.

The ECT chapter has very important information that came from Australia and New Zealand and endorsed by the American Psychiatric Association.

The antipsychotics chapter has simple questions and answers to guide clinicians in their learning journey. Other chapters are arranged to give direct and uncomplicated information.

This book provides readers with tools to understand psychotropic drugs, drawing on both the author's experience and the available evidence in the literature.

The information contained in this book are designed for educational purpose only, so clinicians are encouraged to look at other resources to complete their knowledge. The field of psychopharmacology is growing fast; therefore, not all the medications are captured in this book, but other editions will continue to be published.

Halifax, NS, Canada — Joseph Sadek

Legal Disclaimer

Warning

This document does not include all of the medications, safety, efficacy infromation available. It is provided as a professional courtesy to provide pertinent data that will assist you in forming your own conclusions and making your own decisions. Please consult each Product Monograph of each product for detailed prescribing infromation.

While the author of this book had made every effort to ensure the accuracy of the information contained in guide, please note that the information is provided "as is" and that the author makes no representation or warranty of any kind, either expressed or implied, as to the accuracy of the information or the fitness of the information for any particular use. To the fullest extent possible under applicable law, the author disclaims and will not be bound by any express, implied, or statutory representation or warranty (including, without limitation, representations or warranties of title or non-infringement). The guide is intended to give an understanding of a psychopharmacology and outline the adverse effects and indications of different medications. The guide is not intended as a substitute for the advice or professional judgment of a healthcare professional, nor is it intended to be the only approach to obtaining information on psychotropic drugs. The author continues to advise the readers to refer to product monograph of each medication and search the literature for new information.

Acknowledgments

I want to give my sincere thanks and gratitude to my wife Dr. Irene Sadek who has always been supportive and inspiring over the years. I also want to thank two children Joseph and Maryanne who were also very supportive and inspiring during the journey of producing this book.

I am extremely grateful to my mentor and supervisor during my residency elective at Harvard Medical School Professor Dr. Nassir Ghaemi who took time to write the forward of this book and make valuable contribution.

It would be impossible to produce this work and maintain the high standards of publishing without the thoughtful, insightful, and scholarly evaluation and expertise of the different reviewers. I would like to thank memebrs of the department of psychiatry, Dalhousie University and in particular Dr. Jason Morrison, Dr. Claire O'Donovan, Dr. Nicholas Delava, Dr. Michael Flynn, Dr. Scott Theriault, Dr. David Anderson (Dean of Medicine) and Dr. Darrell White (Senior Associate Dean) for all their support during the journey of production of this book.

Finally, special thanks to Ms. Maryanne Michelle Sadek, Dalhousie Medical School, for her efforts in compiling the appendices and conducting numerous literature reviews.

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About the Author

Joseph Sadek is an associate professor of psychiatry at Dalhousie University and the medical director of the Atlantic ADHD Center in Dartmouth, Nova Scotia. He is also the clinical and academic leader, Nova Scotia Hospital, Mayflower Unit, Dartmouth, NS, Canada. Dr. Sadek is a diplomat of the American Board of Psychiatry and Neurology (DABPN) and fellow of the Royal College of Physicians and Surgeons of Canada (FRCPC). In addition to his medical degree (1990), Dr. Sadek also holds a pharmacy degree (B.Sc. Pharm 1986) and an MBA from St. Mary's University. He also completed a one-year research training program at Harvard Medical School and obtained the certification of the Global Clinical Scholars Research Program (GCSRP) with commendation. He completed his psychiatry residency training at Dalhousie University, Nova Scotia, Canada, in 2004. Dr. Sadek served as the head of the Neurosciences professional competency unit for the Dalhousie Medical School. He started the first public adult ADHD clinic in Nova Scotia in 2007. Dr. Sadek served as the chair of the Suicide Prevention Task Force for the Province of Nova Scotia. He was also a member of the Dalhousie University Senate. He is heavily involved in both the undergraduate and postgraduate teaching and has published four books. His first book is called *Clinician's Guide to ADHD*, second edition, published in 2013. Other books are "Clinician's *Guide to Adult ADHD Comorbidities," "Clinician's Guide to ADHD Comorbidities in Children and Adolescents,"* and *"Clinician's guide to*

suicide risk assessment and management." Dr. Sadek has several peer-reviewed articles and received several awards for his work. Dr. Sadek received the Mental Health Program Quality Council Certificate of Excellence Award for commitment to quality review (2012) and Mental Health Program Quality Council Certificate of Excellence Award for development and implementation of suicide risk assessment form (2012). In 2017, he received the Saint Mary's University MBA 25th Anniversary Alumni Impact Award. In 2019, He was recognized by the Government of Nova Scotia House of Assembly in a special ceremony.

Chapter 1
General Pharmacology

1.1 Introduction

It is important to recognize that drugs may have biological effects on humans including adverse effects and therapeutic effects. It is described as **pharmacodynamics or PD**.

When humans administer a drug, there are several effects on the drug including **absorption, distribution, metabolism, and elimination or excretion**. It is defined as **pharmacokinetics or PK**. This process determines the levels of a drug and why blood levels can vary between different people.

1.2 What Are the Components of Pharmacokinetics?

Absorption
Distribution
Metabolism
Elimination or excretion

1.3 Pharmacokinetics

1.3.1 Absorption

1.3.1.1 Give Examples of Routes of Medication Administration (Fig. 1.1)?

1.3.1.2 Give Examples of How Drugs Cross Gut Wall?

Passive diffusion, active transport, pore filtration of low-molecular-weight drug, others such as pinocytosis.

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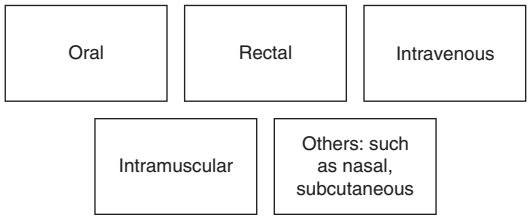

Fig. 1.1 Routes of medication administration

1.3.1.3 Describe the Process of Absorption?

Absorption of a drug occurs during its transport from the site of administration such as oral to the systemic circulation where the drug has to cross many cell membranes.

Before reaching the systemic circulation, part of the drug may be metabolized and that is called first-pass metabolism and is eventually lost. The remaining fraction which succeeds to reach the systemic circulation is called the bioavailability.

Calculation of bioavailability:

$$\text{Bioavailability}\left(F\right) = \text{AUC}_{\text{after administration by certain route}} \,/\, \text{AUC}_{\text{after IVI}}.$$

1.3.1.4 What Factors May Affect First-Pass Metabolism?

1. **The route of administration:** First-pass effect can be avoided by parenteral or sublingual administration and to a less extent by rectal administration. Intramuscular administration avoids first-pass metabolism but is influenced by solubility. Lipid-soluble, low-molecular-weight drugs are rapidly absorbed. The rate of absorption of intramuscular drugs is increased by exercise, and reduced by heart failure.
2. **The nature of the drug**:
   (a) Hepatic first-pass metabolism occurs for drugs whose liver metabolism is very active, e.g., propranolol, nitroglycerin, and morphine.
   (b) Intestinal mucosal first-pass metabolism occurs for tyramine and estrogens for example.
   (c) Pulmonary first-pass metabolism occurs for nicotine and opioids for example.
3. Hepatic first-pass metabolism is largely reduced by ↓ ***portal blood flow*** (e.g., portal hypertension; treatment with β-blockers, e.g., propranolol or H_2 receptor blockers, e.g., cimetidine; and ↓ hepatic enzyme activity, e.g., liver failure, enzyme inhibitors, e.g., chloramphenicol).

1.3.1.5 List Different Mechanisms by Which Drugs Cross the Gut Wall?

1. **Passive diffusion** is the most common mechanism but depends on *formulation* (enteric coating; particle size; diluents, e.g., lactose; binding agents, e.g., syrups; lubricants, e.g., talc; disintegrating agents, e.g., starch) and *solubility* (particle

size, ambient pH, drug pKa—when pH = pKa, 50% of the drug is ionized). To be absorbed by passive diffusion, a drug must be unionized since it is more lipid soluble; in an acid pH (stomach), basic drugs will be largely ionized and will not be absorbed. The unionized fraction of a drug is 10,000 times more lipid soluble than the ionized portion).

2. **Active transport:** The efflux transporter P-glycoprotein (P-gp) is responsible for cellular drug efflux, transporting substances from the intracellular to the extracellular compartments within the membranes of the gastrointestinal tract. P-gp can markedly affect the bioavailability of certain drugs, particularly those with low solubility.
3. **Pore filtration**: Passive movement of water-soluble substances of low molecular weight (<200 Da) is via aqueous channels (diameter less than 4 Å).
4. **Other mechanisms such as** pinocytosis.

1.3.1.6 What Are the Factors Affecting Absorption?

1. Dosage forms, synthesis technique, and excipients affect the disintegration of the dosage form into particles.
2. Drug: Molecular weight and solubility coefficient affect the dissolution of the particles into molecules.
3. The stability of the drug in gut contents (secretions; food; other drugs) affects the destruction of the molecules into fragments. Many drugs have the greatest absorption from an empty stomach but in some cases food increases absorption of the drugs such as diazepam.
4. The pH of gut (in relation to the pKa of the drug) affects the ionization of molecules into ions, e.g., TCAs.
5. The rate of gastric emptying, GIT transit time, surface area available for absorption, and presence of GI disease can modify the rate of crossing of the absorptive surface. Gastric emptying is delayed by drugs with anticholinergic properties, e.g., TCAs, MAOIs, and opiates. Intestinal mobility is increased by anxiety.

1.3.2 Distribution

1.3.2.1 Why Drug Distribution Is Important?

Drug distributions refer to the movement of a drug to and from the blood and various tissues of the body and the relative proportion of the drug in the tissue. The amount of the drug delivered to each organ depends on the rate of blood flow to that organ. Well-perfused regions (e.g., liver, kidney) will have higher levels of the drug more rapidly than poorly perfused regions such as fat.

Some of the drug molecules are carried bound to plasma proteins. They are bound to albumin, globulins, and glycoproteins (and subsequently the large

drug-albumin complex cannot enter the organ). Others reach the organ in the free form. It is only the "free" fraction that can be active.

The free molecules may be in the non-ionized form (i.e., lipophilic, and accordingly are allowed to pass through the surrounding lipid membranes), or in the ionized form (i.e., hydrophilic, and their passage is limited due to the narrow size of the water-filled pores). Distribution may be roughly described by a parameter called Volume of Distribution or (V_d).

Volume of distribution is important because drugs with large V_d are not amenable to dialysis. V_d is important in estimating the loading dose of the drug and it is an estimate of the tissue uptake of the drug.

Lipophilic/lipid-soluble drugs easily cross the blood-brain barriers where ionized drugs (highly acidic/basic) cross slowly. Infection my increase the permeability of the blood-brain barrier.

Some drugs accumulate in certain tissues which can also act as reservoirs of extra drug. These tissues slowly release the drug into the bloodstream, preventing blood levels of the drug from decreasing rapidly and thereby prolonging the effect of the drug. Some drugs, such as those that accumulate in fatty tissues, leave the tissues so slowly that they circulate in the bloodstream for days after a person has stopped taking the drug.

1.3.2.2 How to Calculate Volume of Distribution?

V_d = amount of drug in the body / plasma or blood concentration.

1.3.2.3 List Some Conditions in Which Protein Binding Is Reduced?

Hepatic disease, renal disease, cardiac failure, malnutrition, carcinoma, surgery, burns, and last stage of pregnancy.

1.3.3 Metabolism (Drug Biotransformation)

The purpose of drug metabolism is to transform the lipid-soluble drugs into water-soluble metabolites that can be easily excreted. Metabolism could lead to more active drug, less active drug, or loss of activity of the drug. Differences in drug metabolism account for most of the variability seen in blood drug levels. Most metabolism occurs in the liver, with other sites including the gut, kidney, skin, brain, and lung. Metabolizing enzymes could be microsomal enzyme system such as the cytochrome system CYP450 oxidase or non-microsomal enzyme system such as dehydrogenase. Metabolism is divided into phase I, phase II, and phase III (transport). Phases 1 and II occur mainly in the liver.

1.3.3.1 What Are the Factors Affecting Drug Metabolism?

1. Physiological changes in metabolizing activity due to age and sex, or pathological factors which affect hepatic activity, e.g., liver cell failure.
2. Pharmacogenetic variations in metabolizing enzymes, e.g., slow and fast acetylators.
3. Enzyme induction which lowers the level of the drug or enzyme inhibition that increases the level of the drug.

1.3.3.2 Give Examples of the Effect of Genetics on Metabolism?

Hydroxylation and acetylation are under genetic control. Hydroxylation can significantly differ; for example poor metabolizers will have higher levels and hence more side effects. It is autosomal dominant in 8% of Caucasians. Acetylation occurs by the enzyme N-acetyltransferase. There are fast and slow acetylators which depend on the amount of enzyme, for example ratio of fast to slow = 40:60 in Europe and 85:15 in Japan.

1.3.3.3 What Are the Metabolic Processes Involved in the Hepatic Elimination of Drugs?

Phase I usually converts the parent drug to a more polar metabolite. It results in addition or exposure of functional group on parent compound. It includes oxidation, reduction, dealkylation, and hydrolysis of the drug molecule. Cytochrome P450s (CYPs) are very important in phase I. Cytochrome P450 is a superfamily of isozymes, divided into families, subfamilies, and specific forms based on amino acid sequence similarity. It contains more than 30 human isozymes such as CYP3A4, 2D6, and 2C9.

Phase II reactions involve addition of polar group by conjugation of the drug molecule (or metabolite) to an endogenous molecule such as acetylation, glucuronic acid, sulfate, amino acid, acetate, or glutathione.

This increases the water solubility of the drug to aid renal excretion.

In liver disease, impairment in drug metabolism may occur through decreased metabolizing enzyme capacity, decreased liver blood flow, and intra/extrahepatic shunting. Prediction of drug pharmacokinetics in the presence of hepatic impairment therefore relies on the knowledge of the total drug clearance from the body (CL) and the extent of hepatic extraction. Liver disorders that decrease drug metabolism include cirrhosis, alcoholic liver disease (chronic alcohol consumption may also increase drug metabolism via enzyme induction), viral hepatitis (may increase or decrease metabolism), and porphyria.

Cirrhosis, porphyria, and hepatoma do not appear to significantly alter hepatic glucuronidation and drugs solely eliminated via this mechanism are less likely to be affected (e.g., morphine, lorazepam) than drugs that are not glucuronidated.

Define Hepatic Clearance?

Hepatic drug clearance is a function of liver blood flow (since the greater the blood flow, the greater the amount of drug that is presented to the liver for metabolism) and the intrinsic enzyme metabolizing capacity of the liver for that drug.

Define the Hepatic Extraction Ratio?

The hepatic extraction ratio is the fraction of drug removed from the blood in one passage through the liver.

What Are the High-Clearance Drugs?

High-clearance drugs are liver blood flow dependent. The hepatic elimination of drugs with a high extraction ratio (e.g., drugs with a high first-pass metabolism) is limited by both blood flow and enzyme capacity. As a large proportion of the drug is removed in one pass of the liver, the degree of removal is dependent on the delivery of drug to the liver by hepatic blood flow.

Define Low-Clearance Drugs

Drugs with a low extraction ratio have a more limited capacity to be cleared. The presentation of more drugs (i.e., through increased blood flow) will not increase elimination further. Such drugs are less susceptible to alterations in liver function.

Dosing in Liver Disease

- For **severe** liver dysfunction (albumin<30 g/L, INR >1.2):
  (a) If the drug is a **high-clearance** drug (liver blood flow dependent) **reduce dose by 50%:**

- Antipsychotics
- Beta-blockers (most)
- Calcium channel blockers
- Lignocaine
- Nitrates
- Opioids (most)
- SSRIs

- Statins
- Tricyclic antidepressants

(b) If the drug is **low clearance** (flow independent—includes all other metabolized drugs) **reduce dose by 25%:**

- Amiodarone
- Anticonvulsants (most)
- Antimalarials
- Antiparkinsonians (except amantadine)
- Antithyroid
- Benzodiazepines
- NSAIDs
- Proton pump inhibitors
- Paracetamol
- Quinidine
- Retinoids
- Rifampicin
- Spironolactone
- Steroids
- Sulfonylureas
- Theophylline
- Warfarin

Low-therapeutic-index drugs require extra caution. Exact dosage adjustment is less critical for drugs with a wide therapeutic index.

1.3.4 Excretion or Elimination

1.3.4.1 What Are the Routes of Excretion?

Majority of drugs are excreted by kidney. Acidic urine is good for the excretion of basic drugs (TCAs, amphetamines). Acidic drugs are passively reabsorbed.

Routes of Excretion

1. The kidney is the most important route of elimination. Elimination occurs through (a) glomerular filtration for water-soluble molecules whose size is less than the glomerular pores and (b) active tubular secretion through either acid carrier, e.g., for penicillin, probenecid, and salicylic acid, or basic carrier, e.g., for amphetamine and quinine.
2. Other sites for excretion:
   (a) Lungs, e.g., volatile anesthetics
   (b) Saliva: e.g., iodides
   (c) Bile: e.g., rifampicin
   (d) *Milk*: this is important for lactating mothers

1.3.4.2 What Are the Factors Affecting Renal Excretion?

1. Glomerular filtration rate (GFR)
2. Plasma protein binding (PPB) and drug distribution: Drugs with large Vd are poorly excreted in urine
3. pH of urine
4. Plasma concentration of the drug
5. Drug properties such as molecular weight and pKa
6. Disease state and kidney function
7. Drug Interactions
8. Biological factors such as age and genetics

Renal Clearance = Rate of urinary excretion / plasma drug concentration

List Some of the Pharmacokinetic Changes in the Elderly (Table 1.1)?
List Some of the Pharmacokinetic Changes in Pregnancy (Table 1.2)?

Table 1.1 Pharmacokinetic changes in the elderly

Absorption	• Less acid in stomach—Increased gastric pH • Reduced rate of gastric emptying • Reduced intestinal blood flow
Distribution	• Decreased body weight • Decreased albumin • Decreased % of body water • Increased % of body fat
Metabolism	• Slowing of hepatic blood flow • Reduced hepatic transformation
Excretion	• Reduced GFR, but does not affect plasma creatinine due to reduced muscle mass • Half-life of lithium is increased by 50–100%

Table 1.2 Pharmacokinetic changes in pregnancy

Absorption	• No change
Distribution	• Increase in plasma volume and total body water • Decreased plasma albumin—TOTAL drug may fall but FREE drug remains the same
Metabolism	• Probably increased
Excretion	• Increased GFR by 70%

1.4 Drug Interactions

1.4.1 Cytochrome P450 Drug Interactions

1.4.1.1 Definitions

- **Substrates**: Drugs that are metabolized as substrates by the enzyme
- **Inhibitors:** Drugs that prevent the enzyme from metabolizing the substrates
- **Inducer**: Drugs that increase the enzyme's ability to metabolize the substrates (Table 1.3)

Table 1.3 Drug interactions table

1A2 substrate	1A2 inducer	1A2 inhibitor
Clozapine Cyclobenzaprine Duloxetine Fluvoxamine Haloperidol Imipramine Mexiletine Nabumetone Naproxen Olanzapine Riluzole Tacrine2 Theophylline Tizanidine Triamterene Zileuton Zolmitriptan	Carbamazepine Chargrilled meat Rifampin Tobacco	Amiodarone Cimetidine (W) Efavirenz Fluoroquinolones Fluvoxamine1 Ticlopidine
2B6 substrate	**2B6 inducer**	**2B6 inhibitor**
Artemisinin Bupropion1 Cyclophosphamide Efavirenz1 Ifosfamide Ketamine Meperidine Methadone Nevirapine Propofol Selegiline	Artemisinin Carbamazepine Efavirenz Nevirapine Phenobarbital Phenytoin Rifampin	Clopidogrel Thiotepa Ticlopidine2 Voriconazole

(continued)

Table 1.3 (continued)

2C9 substrate	2C9 inducer	2C9 inhibitor
NSAIDs: Diclofenac Ibuprofen Naproxen Piroxicam *Oral hypoglycemics:* Tolbutamide Glipizide Glyburide *Angiotensin II blockers:* Losartan Irbesartan *Others:* Celecoxib Fluvastatin Phenytoin Rosiglitazone Torsemide Valproic acid Warfarin Zafirlukast	Carbamazepine Nevirapine Phenobarbital Rifampin St. John's Wort	Amiodarone (M) Efavirenz Fluconazole (S) Isoniazid Metronidazole Paroxetine Sulfamethoxazole
2C19 substrate	**2C19 inducer**	**2C19 inhibitor**
PPIs: Esomeprazole Lansoprazole Omeprazole Pantoprazole *Antiepileptics:* Diazepam Phenytoin Phenobarbitone *Others:* Amitriptyline Carisoprodol Citalopram Clomipramine Clopidogrel Cyclophosphamide Imipramine Labetalol Proguanil Voriconazole	Efavirenz Rifampin Ritonavir St. John's Wort	Cimetidine Esomeprazole Felbamate Fluoxetine Fluvoxamine Isoniazid Ketoconazole Lansoprazole Omeprazole Oral contraceptives Pantoprazole Ticlopidine2 Voriconazole
2D6 substrate	**2D6 inducer**	**2D6 inhibitor**
Beta-blockers: Carvedilol S-metoprolol Propafenone Timolol *Antidepressants:* Amitriptyline Clomipramine	Dexamethasone Rifampin	Bupropion (S) Fluoxetine (S) Paroxetine (S) Quinidine (S) Duloxetine (M) Amiodarone (W) Cimetidine (W) Aripiprazole

Table 1.3 (continued)

2D6 substrate	2D6 inducer	2D6 inhibitor
Desipramine		Diphenhydramine
Duloxetine		Chlorpheniramine
Fluoxetine		Clomipramine
Imipramine		Doxepin
Paroxetine		Haloperidol
Antipsychotics:		Methadone
Haloperidol		Ritonavir
Risperidone		Terbinafine
Thioridazine		
Others:		
Aripiprazole		
Atomoxetine		
Codeine		
Dextromethorphan		
Doxepin		
Flecainide		
Mexiletine		
Ondansetron		
Oxycodone		
Risperidone		
Tamoxifen		
3A4,5,7 substrate	**3A4,5,7 inducer**	**3A4,5,7 inhibitor**
Macrolide	Carbamazepine	*HIV antivirals:*
Antibiotics:	Efavirenz	Indinavir(S)
Clarithromycin	Nevirapine	Nelfinavir (S)
Erythromycin (not 3A5)	Phenobarbital	Ritonavir (S)
NOT azithromycin	Phenytoin	Clarithromycin (S)
Telithromycin	Pioglitazone	Itraconazole (S)
Antiarrhythmics:	Rifabutin	Ketoconazole (S)
Quinidine43-OH (not 3A5)	Rifampin	Nefazodone (S)
Benzodiazepines:	St. John's Wort	Erythromycin (M)
Alprazolam	Troglitazone	Grapefruit juice (M)
Diazepam43OH	Glucocorticoids	Verapamil (M)
Midazolam	Modafinil	Suboxone (M)
Triazolam	Troglitazone	Diltiazem (M)
Immune modulators:	Pioglitazone	Cimetidine (W)
Cyclosporine		Amiodarone
Tacrolimus (FK506)		NOT azithromycin
Sirolimus		Fluvoxamine
HIV antivirals:		Troleandomycin
Indinavir		Voriconazole
Ritonavir		Fluconazole
Saquinavir		Ciprofloxacin
Nevirapine		Gestodene
Prokinetics:		Nefazodone
Cisapride		Norfloxacin
Antihistamines:		Norfluoxetine
Astemizole		Mibefradil
Chlorpheniramine		

(continued)

Table 1.3 (continued)

2E1 substrate	2E1 inducer	2E1 inhibitor
Anesthetics: Enflurane Halothane Isoflurane Methoxyflurane Sevoflurane *Others:* Acetaminophen4N APQI Aniline Benzene Chlorzoxazone Ethanol N,N-dimethyl formamide Theophylline	Ethanol Isoniazid	Disulfiram

http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table

1.5 Prescribing Errors

1.5.1 What Are the Most Common Groups of Factors Associated with Errors?

- Related to knowledge and application of knowledge regarding drug therapy
- Knowledge and use of knowledge regarding patient factors that affect drug therapy
- Use of calculations, decimal points, or unit and rate expression factors
- Nomenclature factors (incorrect drug name, dosage form, or abbreviation)

1.5.2 Describe the Grouping of Errors According to Reason's Model of Accident Causation?

- **The active failure**: Mistakes due to inadequate knowledge of the drug or the patient. Skill-based slips and memory lapses
- **Error-provoking conditions**: Lack of training or experience, fatigue, stress, high workload for the prescriber, and inadequate communication between health-care professionals
- **Latent conditions** included reluctance to question senior colleagues

1.5.3 What Are the Common Factors Associated with Prescribing Errors?

- High-risk patients with factors affecting drug kinetics or dynamic process as in children, elderly, renal or hepatic impairment, pregnancy, or breastfeeding and drug interactions
- Pharmaceutical sampling and conflicts of interest in relationship with the pharmaceutical industry
- System issues

1.5.4 Common Prescribing Errors

- Decline in renal function (lithium, antimicrobials, ACE inhibitors), or hepatic function requiring alteration of drug therapy (anticonvulsant, benzo, antipsychotics, statins)
- Patient history of allergy to the same medication class
- Using the wrong drug name, dosage form, or abbreviation
- Incorrect dosage calculations, frequency, using adult dosage in pediatric population
- Not accounting for pharmacokinetic characteristics in pediatric population

1.5.5 Describe Some of the Pharmacokinetic Characteristics in Pediatric Population that Contribute to Errors?

1.5.5.1 Absorption Developmental Changes Include the Following

- Effects on gastric acidity, rates of gastric and intestinal emptying, surface area of the absorption site, gastrointestinal enzyme systems for drugs that are actively transported across the gastrointestinal mucosa, gastrointestinal permeability, and biliary function.
- Developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, can affect absorption patterns of drugs delivered via injections.

1.5.5.2 Metabolism

- Drug metabolism and elimination vary with age and depend on the substrate or drug, but most drugs, and most notably phenytoin DILANTIN, barbiturates, analgesics, and cardiac glycosides, have plasma half-lives 2–3 times longer in neonates than in adults.
- CYP450 enzyme system in the small bowel and liver is the most important known system for drug metabolism.
- CYP450 enzymes inactivate drugs.
- Phase I activity is reduced in neonates, increases progressively during the first 6 months of life, exceeds adult rates by the first few years for some drugs, slows during adolescence, and usually attains adult rates by late puberty.
- However, adult rates of metabolism may be achieved for some drugs (e.g., barbiturates, phenytoin 2–4 weeks postnatally).
- CYP450 activity can also be induced (reducing drug concentrations and effect) or inhibited (augmenting concentrations and toxic effect) by coadministered drugs.
- Phase II metabolism varies considerably by substrate. Maturation of enzymes responsible for bilirubin and acetaminophen conjugation is delayed.
- Enzymes responsible for morphine (MS CONTIN) conjugation are fully mature even in preterm infants.

1.5.5.3 Excretion in Kidney

- In kidney: controlled by glomerular filtration, tubular secretion, and tubular reabsorption.
- These processes mature at different rates in the pediatric population; age can affect systemic exposure for drugs where renal excretion is a dominant pathway of elimination.
- Maturation of other excretory pathways, including biliary and pulmonary routes of excretion, can be different as well.

1.5.5.4 Distribution

- Distribution of a drug may be affected by changes in body composition, such as the following:
- Changes in total body water and adipose tissue that are not necessarily proportional to changes in total body weight.
- Plasma protein binding and tissue binding changes arising from changes in body composition with growth and development may also influence distribution controlled by glomerular filtration, tubular secretion, and tubular reabsorption.
- These processes mature at different rates in the pediatric population; age can affect systemic exposure for drugs where renal excretion is a dominant pathway of elimination.

- Maturation of other excretory pathways, including biliary and pulmonary routes of excretion, can be different as well.

1.5.6 List Some of the Factors to Consider for Pediatric Prescribing?

1. The relative bioavailability of the pediatric formulation compared to the adult
2. Age of the pediatric population
3. Therapeutic index of the drug
4. Pharmacokinetic data from the adult population
5. Body size

1.5.7 List Some of the Challenges in Pediatric Prescribing?

- Complexity
- Common use of off-label medication
- Lack of standardization of recommended doses
- Lack of guidelines regarding conversion from adult to pediatric dosing regimens
- Need weight (pounds or kilograms)
- Physician must convert pounds to kilograms, determine dose based on weight, get frequency, correct preparation and concentration of the medication, and determine the individual dose

1.5.8 What Medications Are Prone to Prescribing Errors?

- Analgesics
- Asthma/allergy
- Antibiotics
- Antiepileptics

1.5.9 List Some of the Risk Factors Related to Adverse Drug Reactions?

- Age (children and elderly)
- Multiple medications
- Multiple comorbid conditions
- Inappropriate medication prescribing, use, or monitoring

- End-organ dysfunction
- Altered physiology
- Prior history of ADRs
- Extent (dose) and duration of exposure
- Genetic predisposition

1.5.10 Tips for Preventing Medication Errors

- Limit each prescription to one medication.
- Circle your name when using preprinted prescription pads.
- Approach medication names with caution.
- Eliminate drug abbreviations.
- Use metric measures for dosages.
- Add the patient's age (or weight) to the prescription.
- Avoid writing "as directed."
- Eliminate abbreviations in routes of administration.
- Specify the therapeutic duration.
- Prescribe specific quantities rather than dispensing for time periods.
- Remain cognizant of lethal doses of medications.

Chapter 2
Antidepressants

2.1 How Does ICD-10 Classify the Depressive Disorders?

F32	Depressive episode
F32.0	Mild depressive episode
*.00	without somatic syndrome
*.01	with somatic syndrome
F32.1	Moderate depressive episode
*.10	without somatic syndrome
*.11	with somatic syndrome
F32.2	Severe depressive episode without psychotic symptoms
F32.3	Severe depressive episode with psychotic symptoms
*.30	with mood-congruent psychotic symptoms
*.31	with mood-incongruent psychotic symptoms
F32.8	Other depressive episodes
F32.9	Depressive episode, unspecified
F33	Recurrent depressive disorder
F33.0	Recurrent depressive disorder, current episode mild
*.00	without somatic syndrome
*.01	with somatic syndrome
F33.1	Recurrent depressive disorder, current episode moderate
*.10	without somatic syndrome
*.11	with somatic syndrome
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
*.30	with mood-congruent psychotic symptoms
*.31	with mood-incongruent psychotic symptoms
F33.4	Recurrent depressive disorder, currently in remission
F33.8	Other recurrent depressive disorders
F33.9	Recurrent depressive disorder, unspecified

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2.2 List the Classes of Available of Antidepressants?

- The monoamine oxidase inhibitors **(MAOIs)** such as phenelzine, nialamide, isocarboxazid, tranylcypromine, moclobemide, selegiline.
- The tricyclic antidepressants **(TCAs)** such as amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, trimipramine, protriptyline, and doxepin.
- Selective serotonin reuptake inhibitors **(SSRIs)** such as fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine.
- Serotonin and norepinephrine reuptake inhibitors **(SNRI)** such as venlafaxine, desvenlafaxine, duloxetine, nefopam, and levomilnacipran.
- Norepinephrine-dopamine reuptake inhibitor **(NDRI)** such as bupropion.
- Selective norepinephrine reuptake inhibitors **(NRIs)** such as reboxetine, viloxazine, teniloxazine (also known as sulfoxazine or sufoxazine), and atomoxetine.
- Serotonin receptor antagonist with serotonin reuptake inhibition **(SARI)** such as trazodone, nefazodone, and vortioxetine.
- Serotonin 5-HT_{1A} autoreceptor partial agonist with serotonin reuptake inhibition **(SPARI)** such as vilazodone.
- Noradrenergic α_2-receptor antagonist with specific serotonergic receptor-2 and -3 antagonism **(NASSA)** such as mirtazapine and ®mianserin.
- Melatonergic agonists and selective serotonergic antagonists **(MASSAs)** such as agomelatine.
- Atypical antipsychotics that exhibit weak D_2 receptor antagonism with potently strong 5-$HT_{2A/2C}$ receptor blockade such as olanzapine, quetiapine, risperidone, lurasidone, aripiprazole, and brexpiprazole.
- NMDA-glutamatergic ionoceptor blockers that exhibit a direct action on the excitatory glutamatergic neurotransmission system such as ketamine, (apimostinel), and riluzole.

2.3 Monoamine Oxidase Inhibitors (MAOIs)

2.3.1 Introduction

The monoamine oxidase inhibitors were first used in the therapy of tuberculosis in the 1950s. They are a large group of hydrazide derivatives which were found to have antidepressant activity. They inhibit the enzyme monoamine oxidase that is responsible for inactivation of many amine neurotransmitters such as norepinephrine and serotonin, thus increasing their levels and activity in the brain. MAO inhibitors (with initial trade name and year of approval) currently in clinical use for depression include phenelzine (Nardil: 1961), tranylcypromine (Parnate: 1961), and isocarboxazid (Marplan: 1959).

MAO inhibitor use had declined over the years and they are currently not widely used.

2.3.2 *What Is the Mechanism of Action and Pharmacokinetics of MAOIs?*

Monoamine oxidase is an enzyme located on the outer mitochondrial membrane—it degrades monoamines, including noradrenaline, serotonin, dopamine, adrenaline, and tyramine.

There are two types:

MAO-A predominantly metabolizes noradrenaline, serotonin, epinephrine, and tyramine. There is higher risk for serotonin syndrome and hypertensive crisis.

MAO-B inhibition reduces breakdown of mainly dopamine and phenethylamine; therefore there are no dietary restrictions except in case of high doses when they lose the selectivity.

MAOIs operate in the nervous system, the liver, and the GI tract. When the usual metabolism of dietary tyramine by GI MAOs is inactivated by irreversible MAOIs, intact tyramine particularly in the gastrointestinal tract can enter the circulation and cause hypertensive crisis or hypertension.

2.3.3 *Describe the Dosing and Monitoring Requirements of MAOIs* (Table 2.1)*?*

2.3.4 *What Are the Adverse Effects of MAOIs?*

Patients treated with MAOI antidepressants have side effects ranging from drowsiness, orthostatic hypotension, dizziness, headache, dry mouth, hyperpyrexia reaction, insomnia, urinary hesitancy, sexual dysfunction, constipation, dry mouth, blurred vision, muscle cramps, myoclonic twitches, lethargy, weight gain, and palpitations.

Table 2.1 Dosing and monitoring requirements of MAOIs

Drug	Class	Dose range	
Phenelzine (Nardil) 15 mg tablet	**Nonselective**	**45–90**	
Tranylcypromine (Parnate) 10 mg tab	**Nonselective**	**30–60**	
Isocarboxazid (Marplan) 10 mg tab	**Nonselective**	**30–60**	
Moclobemide	**Reversable MAOI**		**No diet restrictions** **No sexual SE**
Selegiline 5 mg capsule	**MAOI B inhibitor** **But at high dose becomes A and B**	**20–50**	**Oral used in** Parkinson's disease. Transdermal approved for depression

Cardiac toxicity and hypertensive crisis could happen when tyramine-containing foods are taken such as aged cheese, dry sausage, fava and broad beans, aged meat, yeast products or extract, smoked fish, soy sauce, smoked or pickled fish, and alcohol, particularly Chianti red wine, tap beer, and Sauerkraut.

Treatment of hypertensive crisis includes use of alpha-adrenergic antagonists, e.g., phentolamine, and avoiding beta-blockers.

2.3.5 What Is the Transition Period to Start Antidepressants for Patient Using MAOIs?

Current medication	Switched to	Wash out
Fluoxetine	MAOIs	5 weeks
MAOIs	Fluoxetine	2 weeks
TCA	MAOIs	5 days
MAOIs	TCA	2 weeks
SSRI, SNRI, NDRI	MAOIs	2 weeks

2.3.6 Give Some Examples Where the Medication Should Not Be Used or Used with Great Caution?

Pheochromocytoma, liver disease, congestive heart failure, unreliable patient, taking with other antidepressants that would cause serotonin syndrome or hypertensive crisis.

2.3.7 What Are Some of the Key Points in Educating Patients on MAOIs?

Rich tyramine-containing foods must therefore be avoided (above).

Caution is also required when combining MAOIs with certain other drugs. The metabolism of some is greatly slowed, and L-dopa and pethidine for example are best avoided.

Drugs with direct and indirect pressor actions such as adrenaline, ephedrine, and stimulants carry the risk of hypertensive crisis.

The combination of MAOIs and certain medications (TCAs, SSRIs, bupropion, meperidine, nefazodone, and stimulants) should be avoided.

2.4 The Tricyclic Antidepressants (TCAs)

2.4.1 Introduction and Classification

The tricyclic antidepressants share a tricyclic chemical structure somewhat resembling the phenothiazines.

Tricyclic antidepressants include:

Amitriptyline (Elavil: 1961) is the more sedating and is appropriate when the patient is anxious (agitated) or suffering from insomnia.

Clomipramine (Anafranil: 1989) is a more active serotonin reuptake inhibitor than the other TCAs and was found especially effective in OCD.

Desipramine (Norpramin: 1964), doxepin (Sinequan: 1969).

Imipramine (Tofranil: 1959) which is the less sedating and is appropriate when the patient shows psychomotor retardation.

Nortriptyline (Aventyl or Pamelor: 1964) (the N-demethylated metabolite of amitriptyline) has the most benign side effect profile of the TCAs and is often used in the elderly.

Protriptyline (Vivactil: 1967). Other agents with some unique characteristics are trimipramine (Surmontil: 1979) and amoxapine (Asendin: 1992).

2.4.2 Describe the Mechanism of Action and Pharmacokinetics of TCA?

The tricyclics are believed to act by inhibition of reuptake of serotonin and norepinephrine, thus increasing the levels of these neurotransmitters and DA to a smaller degree. They block muscarinic cholinergic receptors, H1 histamine receptors, and α-1 adrenergic receptors.

Tertiary amine TCAs (amitriptyline, imipramine, clomipramine, doxepin) have stronger 5-HT effects.

Secondary amine TCAs (nortriptyline, protriptyline, desipramine) have more potent NE reuptake blockade.

Tertiary amine TCAs have more adverse effects than secondary amine TCA.

The tricyclic antidepressants reach a peak plasma level in 2–8 h.

They are 90% or more protein bound.

They are highly lipophilic, and many have linear kinetics with half-life of 10–17 h.

Inactivation occurs largely via CYP450 enzymes, demethylation of tertiary TCAs to their secondary amine metabolites, hydroxylation, then glucuronidation, and excretion in the urine.

Plasma concentrations for therapeutic effect are usually stated to be between 50 and 300 ng mL.

Major toxicity and death are associated with concentrations above 1000 ng mL.

Patients with plasma TCA concentrations greater than 450 ng mL tend to develop cognitive or behavioral toxicity (agitation, confusion, memory impairment, pacing). See below.

2.4.2.1 Imipramine

Imipramine was the first tricyclic to be used as an antidepressant. A tertiary amine, it is metabolized in part to desipramine, its secondary amine derivative which also has antidepressant properties.

Several investigators have found that clinical response is directly related to the plasma concentration of imipramine and its metabolite desipramine. Some data indicates that there is a linear dose-response relationship with a well-defined lower plasma concentration limit for clinical response, but no upper limit beyond which unfavorable clinical effects occurred. It appears that a minimum combined imipramine and desipramine plasma level of 150 ng/mL is needed to achieve therapeutic response. An antidepressant response is rarely seen with lower plasma levels. Most patients respond to imipramine when the plasma imipramine and desipramine concentration exceeds 240 ng/mL. There is no upper limit beyond which clinical worsening occurs (i.e., no curvilinear relationship).

2.4.2.2 Amitriptyline

Amitriptyline is a tertiary tricyclic antidepressant that is metabolized to its secondary amine derivative, nortriptyline. Many studies show a linear relationship between plasma levels and clinical response.

2.4.2.3 Nortriptyline

A number of investigators have reported that there is a curvilinear plasma concentration/response relationship for nortriptyline with a therapeutic window at intermediate nortriptyline levels between 50 and 150 ng/mL. Plasma levels less than 50 ng/mL and greater than 150 ng/mL are associated with poor response.

2.4.2.4 Protriptyline

There have been relatively few studies that examine the relationship between clinical response with protriptyline and its plasma concentration. Some researchers found a significant inverse relationship between protriptyline level and clinical response. They suggested that patients with protriptyline levels greater than 250 ng/mL did not respond as well as those in the intermediate range of 130–250 ng/mL. The investigators suggested that there is a curvilinear plasma concentration/response relationship for protriptyline.

2.4.2.5 Doxepin

Researchers suggested that the best response was in the patients with plasma concentrations of doxepin plus desmethyldoxepin above 100 ng/mL.

While some studies have suggested this drug to have a therapeutic window and others a linear plasma level response curve, definitive studies have not been reported that confirm either relationship.

2.4.2.6 Clomipramine

Clomipramine is metabolized to desmethylclomipramine. Interindividual plasma concentrations of the parent compound and primary metabolite varied greatly. There was a significant curvilinear relationship between only desmethylclomipramine levels and clinical response, with little improvement at levels less than 250 ng/mL or greater than 700 ng/mL. No relationship was found between clinical improvement and plasma concentrations of either clomipramine or total domipramine and desmethylclomipramine.

2.4.2.7 Butriptyline

Butriptyline is a tertiary amine tricyclic antidepressant similar in structure to amitriptyline. There was no clear simple relationship between clinical response and plasma levels of this compound.

2.4.3 List the Dosing Requirements of TCA (Table 2.2)*?*

2.4.4 What Are the Adverse Effects of TCAs?

Drowsiness, constipation, dry mouth, blurred vision, urinary retention, tachycardia, lethargy, palpitations.

Table 2.2 Dosing requirements of TCA

Name	Therapeutic dose range
A**mitriptyline** (Elavil: 1961)	150–300
C**lomipramine** (Anafranil: 1989)	100–300 (risk of seizure above 250)
D**esipramine** (Norpramin)	150–300
Doxepin (Sinequan: 1969)	150–300
I**mipramine** (Tofranil: 1959)	150–300
N**ortriptyline** (Aventyl or Pamelor: 1964)	50–150
Protriptyline (Vivactil: 1967)	**15–60**
Trimipramine (Surmontil: 1979)	150–300
Amoxapine (Asendin: 1992). Tetracyclic	**150–400**

Severe reactions like confusional states and psychotic episodes may occur.

The adverse effects may be related to certain effects on receptors such as the following:

1. **Alpha-1 adrenergic** receptor blocking produces hypotension. In orthostatic hypotension there is a marked fall in blood pressure with change of position—most usually, on rising from lying or sitting to standing—there are dizziness and risk of falls.
2. **Histamine** receptor blockade is associated with drowsiness and increased appetite (weight gain).
3. **Acetylcholine** receptor (muscarinic) is associated with dry mouth, constipation, blurred vision, and difficulty initiating micturition.

2.4.4.1 Cardiac Toxicity

TCAs have the risk of cardiac conduction delays leading to heart block in patients with preexisting conditions, and overdose can cause life-threatening arrhythmias; extremely high plasma concentrations cause prolonged QRS duration and increased frequency of dysrhythmias. Therapeutic as well as only moderately elevated tricyclic antidepressant plasma levels can also cause cardiac toxicity in predisposed individuals as a result of the drug's quinidine-like action, leading to serious conduction disturbances at the AV node and the intraventricular level. But with proper plasma-level monitoring the quinidine-like action of tricyclic antidepressants may also enable the drugs to be used as effective antidysrhythmic agents as well as antidepressants in depressed cardiac patients and might be used as the single agent for both illnesses.

Any person above 40 should have EKG.

2.4.5 List Some Contraindications of TCAs?

- Narrow-angle glaucoma
- Patients taking MAOIs
- Prostatic hypertrophy (BPH)

2.5 Selective Serotonin Reuptake Inhibitors (SSRIs)

2.5.1 What Are the Indications of SSRIs?

- Treatment of major depression, recurrent depression, chronic persistent depression, maintenance treatment of depression. There is a debate about the efficacy of SSRIs in severe forms of depression.

- Treatment of OCD: FDA-approved products are fluvoxamine, fluoxetine, sertraline, and paroxetine. All the SSRIs have demonstrated efficacy in the treatment of OCD. Higher doses are required.
- GAD can be helped with most SSRIs, but escitalopram and paroxetine are FDA approved.
- Social anxiety disorder, particularly paroxetine.
- Panic disorder: Paroxetine, sertraline, and fluoxetine received an FDA-approved indication for the treatment of panic disorder. Dose should start at an extremely low dose and should be very gradually increased. Fluoxetine 5 mg can be initiated and very gradually titrated up.
- Bulimia: Fluoxetine showed some positive results.
- Post-traumatic stress disorder: SSRIs may be helpful in insomnia, hyperarousal, and agitation.
- Premenstrual dysphoric disorder (PMDD).
- Vasomotor symptoms: Paroxetine is FDA approved in decreasing hot flashes at 10 mg.
- Other unapproved or suggested use: Chronic pain, fibromyalgia, anger, or impulsive aggression associated with some personality disorders.

2.5.2 What Is the Mechanism of Action and Pharmacokinetics of SSRIs?

SSRIs selectively block the reuptake of 5-HT in presynaptic neurons through their inhibiting effects on the Na^+/K^+ adenosine triphosphatase (ATPase)-dependent serotonin transporter (SERT). SSRIs have relatively little affinity for histaminic (H1, H2), muscarinic, or α1-adrenergic receptors.

SSRI actions are helpful:

1. Prefrontal cortex (low mood)
2. Basal ganglia (OCD)
3. Limbic system (panic and anxiety)
4. Hypothalamus (eating disorders)

SSRI actions are unhelpful in midbrain structures (may cause insomnia) and spinal cord (may cause sexual dysfunction).

2.5.3 What Is the Dosing and Monitoring Requirements of SSRIs?

Therapeutic drug monitoring (TDM) is not required for SSRIs. The variability of SSRI plasma levels among individuals is so great that it is difficult to correlate efficacy or toxicity with plasma levels (Table 2.3).

Table 2.3 Dosing and monitoring requirements of SSRIs

Medication	Dose range	% protein bound	Half-life	Active metabolite	Comments
Citalopram (Celexa)	10–60	91	35	No	
Escitalopram (Lexapro, Cipralex)	10–30	56	30	No	
Fluoxetine (Prozac)	20–80	94	34 h; norfluoxetine >1 week	Yes norfluoxetine	Max benefit in depression is 20–40 mg and less at 60 mg
Paroxetine	10–60	99	20	No	Available in 10-mg, 20-mg, 30-mg, and 40-mg scored tablets
Paroxetine CR (Paxil CR)	12.5–62.5	99	15–20	No	
Sertraline (Zoloft)	50–200	95	26	Yes	Linear dose-response curve
Fluvoxamine (Luvox)	Initiated at 50–100 mg/day Range 100–200 Maximum 300	77	15	No	Not FDA approved in depression Shortest half-life

2.5.4 Describe Some of the Adverse Effects of SSRIs?

CNS: Headache, sleep disturbance (increased or decreased sleep), sedation, tremors, dizziness, decreased seizure threshold, and paresthesia. SSRIs may disrupt sleep continuity and may exacerbate bruxism and restless leg syndrome. Some patients reported cognitive side effects.

Sexual dysfunction: Men: delayed or absent orgasm/ejaculation and erectile dysfunction. Both men and women could experience reduction in libido and arousal and anorgasmia. Some researchers suggested that Paroxetine and Sertraline are linked to more sexual dysfunction but more than 50% of patients on SSRIs experience sexual dysfunction. In rare cases, sexual dysfunction may continue after discontinuation of SSRIs (post-SSRI sexual dysfunction).

Gastrointestinal: Nausea, diarrhea, constipation, decreased appetite, dry mouth. Weight gain or weight loss.

Other: Bruising, agitation, sweating, bleeding, a decrease in bone mineral density, hyponatremia, increased liver enzymes, increase in QT interval with some SSRIs such as citalopram doses greater than 40 mg/day.

SSRIs are safer than older antidepressants in overdose with rare fatalities.

2.5.5 Warning

- Development of serotonin syndrome: Sweating, diarrhea, abdominal pain, tachycardia, elevated blood pressure, myoclonus, hyperreflexia, pyrexia, and agitation. Rarely fatal.
- Increased risk for suicide attempts or thoughts during the first month after starting SSRIs.
- Risk of induction of mania.
- Discontinuation syndrome (particularly the shorter acting agents paroxetine, sertraline, and fluvoxamine) with abrupt cessation including flu-like symptoms, sensory disturbance, insomnia, imbalance, dizziness, headache, and nausea. Could last for 1 to 2 weeks. To decrease risk, taper dose by 25% per week.

2.5.6 What Are Some of the Possible Strategies that May Be Useful in Reducing SSRI-Induced GI Adverse Effects?

- Take with food.
- Slow titration with starting with half the dose.
- Combine with mirtazapine (remeron).
- Use 5-HT3 antagonists, such as ondansetron (Zofran), but they are awfully expensive.

2.5.7 What Are Some of the Possible Strategies that May Be Useful in the Management of Sedation Associated with SSRIs?

- Take the SSRI medication at bedtime.
- Add a stimulant such as methylphenidate 20 mg am.
- Add modafinil or armodafinil (longer acting) 100–200 mg am.
- Add a low dosage of bromocriptine 2.5 mg qd or bid.

2.5.8 What Are Some of the Possible Strategies that May Be Useful in the Management of Sexual Dysfunction with SSRIs?

- If the patient is taking a short-acting SSRI such as paroxetine or fluvoxamine, hold the dose for 24 h prior to sexual activity.

- Add wellbutrin 300 mg daily.
- Add buspirone 20–60 mg daily.
- Add phosphodiesterase inhibitor such as sildenafil (Viagra) 25–100 mg/day or tadalafil or vardenafil.
- Add cyproheptadine at dosages of 4–12 mg/day but it may reverse the antidepressant or antiobsessive effects of the SSRIs and patients will suffer from sedation.
- Add the α-adrenergic agonist yohimbine.
- Add the herb Ginkgo biloba at higher dosage (e.g., 240 mg/day) for weeks or saffron.
- Add flibanserin, a 5-HT1A agonist and 5-HT2 antagonist.
- Add dopaminergic agents such as amantadine or amphetamine products.
- Switch to a lower risk agent such as agomelatine, bupropion, mirtazapine, vilazodone, and vortioxetine [1].

2.5.9 What Are Some of the Possible Strategies that May Be Useful in the Management of SSRI-Induced Hyperhidrosis or Perspiration?

- Add glycopyrrolate 1 mg up to QID.
- Add oxybutynin 5 mg daily.
- Add clonidine 0.1 mg po 1–3 times daily [2].

2.5.10 What Are the Recommendations of the SSRI Use in Pregnancy and Lactation?

Population registries suggested that there is a small increase in the incidence of anencephaly, craniosynostosis, omphalocele, preterm delivery, preeclampsia, and miscarriage.

Some researchers suggest that paroxetine was associated with 1.7-fold risk increase of cardiac malformation.

Paroxetine and fluoxetine have the strongest association with negative outcomes (significant malformations, persistent pulmonary hypertension of the newborn (PPHN), and postnatal adaptation syndrome (PNAS)).

The associations between sertraline and citalopram with negative outcomes remain mixed and generally unsubstantiated.

The safety of escitalopram and fluvoxamine remains unclear because of the few available studies.

Recently, it was suggested that sertraline and citalopram should be first-line drug treatments for anxiety and depression in pregnant women in the SSRI class. Sertraline can be continued in breastfeeding as the concentration found in breast milk is exceptionally low and has not been linked to infant complications [3, 4].

2.5.11 Comment on the SSRI Dosing for Children and Adolescents (Table 2.4)?

2.6 Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)

2.6.1 Give Examples of SNRIs?

Venlafaxine (Effexor)
Desvenlafaxine (Prestiq)
Duloxetine (Cymbalta)
Milnacipran (Savella)
Levomilnacipran (Fetzima)

Table 2.4 SSRI dosing for children and adolescents

Name	FDA approval	Initial dose	Titration	Maximum dose
Fluoxetine (Prozac)	≥8 years old with depression ≥7 years old with OCD	<12 years, 5 mg/day ≥12 years, 10 mg/day	5 mg daily	40 mg/day
Sertraline (Zoloft)	≥6 years old with OCD	<12 years, 12.5 mg/day ≥12 years, 25 mg/day	25 mg for <12 50 mg ≥12	200 mg/day
Fluvoxamine (Luvox)	≥8 years old with OCD	25 mg/day	25 mg (divide BID for doses >50 mg/day)	<12 years, 200 mg/day ≥12 years, 300 mg/day
Citalopram (Celexa)		<12 years, 10 mg/day ≥12 years, 20 mg/day	<12 years, 5 mg; ≥12 years, 10 mg	40 mg daily
Escitalopram (Cipralex)	≥12 years old with depression	<12 years, 5 mg/day ≥12 years, 10 mg/day	5 mg for <12 10 mg for ≥12	20 mg daily

2.6.2 How Do SNRIs Differ from Tricyclic Antidepressants?

- SNRIs do not possess a tricyclic-like structure.
- They do not have a clinically relevant affinity for any monoaminergic, histaminergic, or cholinergic receptors or for the sodium channel. As a result, they are safer (i.e., have a lower risk of arrhythmia and seizures) and better tolerated (i.e., have a slightly lower risk of sedation, somnolence, and weight gain).

2.6.3 What Are the Indications of SNRIs?

Venlafaxine is approved for MDD as well as generalized anxiety disorder, social anxiety disorder, and panic disorder.

Desvenlafaxine is an active metabolite of venlafaxine and approved by the Food and Drug Administration (FDA) for the treatment of MDD in adults in 2009.

Duloxetine is approved for MDD, GAD, diabetic peripheral neuropathic pain, fibromyalgia, and musculoskeletal pain. In some countries, it is approved for stress urinary incontinence.

Levomilnacipran is approved for MDD and fibromyalgia.

SNRIs may be more effective in the treatment of MDD than SSRIs.

2.6.4 Describe the Mechanism of Action of SNRIs?

All SNRIs inhibit the reuptake of 5-HT and NE with a difference in their potencies for the respective transporters, resulting in clinical implications. SNRIs have an ascending rather than a flat dose-response curve.

Venlafaxine, a phenylethylamine, is a relatively weak 5-HT and weaker NE uptake inhibitor with a 30-fold difference in binding of the two transporters. Therefore, it has a clear dose progression, with low doses predominantly binding to the 5-HT transporter and acting like SSRI and with more binding of the NE transporter as the dose ascends.

No significant anticholinergic, antihistaminic, or antiadrenergic blocking effects.

No significant P450 isoenzyme inhibition.

Requires slow taper to avoid discontinuation syndrome.

Desvenlafaxine is an active metabolite of venlafaxine. It causes selective reuptake inhibition at the serotonin (5-HT) and norepinephrine (NE) transporters, resulting in an increased extracellular concentration of 5-HT and NE with a much weaker affinity for dopamine transporters (DATs). Desvenlafaxine also affects hypothalamus. Desvenlafaxine has higher affinity for serotonin transporter as compared to NE transporter.

Duloxetine is a more potent 5-HT and NE reuptake inhibitor with a more balanced profile of binding at about 10:1 for 5-HT and NE transporter binding. It has a range of actions impacting synaptic 5-HT, NA, and DA.

It has no significant anticholinergic, antihistaminic, or antiadrenergic blocking effects.

Levomilnacipran ER is a relatively more active enantiomer of racemic milnacipran. It has twofold higher potency for norepinephrine compared to serotonin reuptake inhibition and preferentially inhibits norepinephrine reuptake compared to duloxetine, venlafaxine, and desvenlafaxine.

2.6.5 Describe the Pharmacokinetics of SNRIs?

The above SNRIs are well absorbed orally and they are metabolized by the liver and eliminated by the kidneys.

Venlafaxine is metabolized to the active metabolite O-desmethylvenlafaxine (ODV; desvenlafaxine) by CYP2D6.

Its half-life is about 5 h, with that of the ODV metabolite being 12 h. Both parent compound and metabolite have low protein binding and neither inhibits CYP enzymes. Therefore, they both are potential options to avoid drug-drug interactions, although venlafaxine may be subject to drug-drug interactions with CYP2D6 inhibitors. Half-life is increased in patients with hepatic and renal impairment.

Desvenlafaxine is the primary metabolite of venlafaxine and has a favorable drug-drug interaction profile. Its bioavailability is 80% after an oral administration. Its peak plasma concentration (Tmax) occurs in seven and half hours after oral administration. Food does not appear to have a clinically significant difference on bioavailability. It is metabolized by conjugation and to a minor extent by oxidation through CYP3A4. 45% is excreted unchanged by the kidneys. It is not affected by CYP2D6 enzyme inducer or inhibitors.

Duloxetine is 90% protein bound. It is metabolized by 2D6 and 1A2 and eliminated by the kidneys 70% and feces 20%. It also inhibits 2D6. *T½* = 12 h.

Levomilnacipran ER is well absorbed after oral administration with a bioavailability of 92%. T max occurs 6–8 h after oral administration and has a protein binding of 15%. Food does not affect the oral bioavailability of levomilnacipran. It has minor involvement with other pathways in the CYP450 system than 3A4. It is mainly excreted unchanged in the urine. It has an elimination half-life of around 12 h with a prolongation in patients with renal impairment.

2.6.6 What Are the Dosing Requirements of SNRIs?

Venlafaxine can be started at 37.5 mg and increased by 37.5 mg every 3 days or 75 mg per week until 150 mg. For anxiety a dose of 75–150 mg might be helpful. Most patients respond between 75 and 225 mg. Maximum dose is 375 mg.

Desvenlafaxine: available in 50 and 100 mg tablets. The recommended dose for desvenlafaxine is 50 mg/day. In a patient with hepatic impairment, the dose above

100 mg/day is not recommended. In patients with moderate and severe renal impairment, the maximum dose was 50 mg/day and 50 mg every other day, respectively.

Duloxetine is initiated at 30 mg and increased in 3 days to 60 mg. An increase to 90 mg could happen after 4 weeks on 60 mg. The maximum disease is 120 mg.

Levomilnacipran: It is an extended-release (ER) formulation, allowing once-daily dosing. The recommended dose range for levomilnacipran is 40–120 mg/day. The starting dose is 20 mg/day and then it can be increased to 40 mg/day after 2 days. The dose can be further titrated in increments of 40 mg every two or more days.

In patients with renal impairment maximum dose is 40 mg per day.

Discontinuation of SNRI should be very gradual by 25% dose reduction weekly.

2.6.7 What Are the Adverse Effects of SNRIs?

Venlafaxine: At low doses, the adverse effect profile is similar to an SSRI with nausea, diarrhea, fatigue or somnolence, and sexual side effects, while venlafaxine at higher doses can produce mild increases in blood pressure, diaphoresis, tachycardia, tremors, and anxiety.

A disadvantage of venlafaxine relative to the SSRIs is the potential for dose-dependent blood pressure elevation, most likely due to the NE reuptake inhibition caused by higher doses at or above 225 mg per day.

Venlafaxine also has several potential advantages over the SSRIs, including an ascending dose-antidepressant response curve, with possibly greater overall efficacy at higher doses.

Desvenlafaxine: nausea, headache, dizziness, insomnia, dry mouth, fatigue, sweating, tremors, blurred vision, sedation, increased anxiety, mydriasis, dyspepsia, anorexia, weight loss, affective lability, muscle spasms, and taste perversion. Serious AEs were reported in 0.9% of patients. An analysis of AEs reported completed suicide in one, suicidal attempt in three, and suicidal ideations in five patients taking desvenlafaxine. Small increases in pulse and blood pressures were observed and were clinically insignificant. Dose-dependent lipid abnormalities were clinically significant in 1% of patients.

Duloxetine: nausea, dry mouth, dizziness, constipation, insomnia, sexual dysfunction, headache, sweating, sedation, asthenia, and liver toxicity. Hypertension is uncommon.

Levomilnacipran: headache, nausea, constipation, dry mouth, increased heart rate, palpitation, and sweating. In one clinical trial, serious AEs were reported in two patients (1.1%) in the levomilnacipran ER 40 mg group (chest pain and deep vein thrombosis in one patient, and aggression in one patient) and one patient (0.6%) in the 80 mg group. During medication taper, a new AE emerged: nasopharyngitis which was more frequently reported in 40 mg group (zero patients in the placebo group; three patients in the 40 mg group; one each in the 80 mg and 120 mg groups).

Other AEs included increases in liver transaminases, and mild increase in blood pressure and pulse, urinary hesitation, and erectile dysfunction.

All medications in the class can cause serotonin syndrome when combined with MAOIs.

Abrupt discontinuation or dose reduction was associated with dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. The discontinuation rates are higher among patients taking it for a longer duration, needing a gradual taper.

2.6.8 What Are the Recommendations of SNRI Use in Pregnancy and Lactation?

Despite limited studies, venlafaxine- and duloxetine-associated literature does not suggest an increased risk of congenital malformations.

In pregnant rats and rabbits, desvenlafaxine and levomilnacipran cause a decrease in fetal weight with no evidence of teratogenicity. However, there are no adequate studies in pregnant women [3].

2.7 Novel and New-Generation Antidepressants

2.7.1 Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs)

2.7.1.1 Bupropion (BPR)

What Are the Psychiatric Indications for Bupropion (BPR)?

It is a phenylethylamine used for the treatment of depression and as a support to smoking cessation. Some researchers suggested some small helpful effects in ADHD with decreasing severity of ADHD symptoms. It is approved when combined with naltrexone for the treatment of obesity [5].

What Is the Mechanism of Action of Bupropion (BPR)?

It produces its antidepressant effect through norepinephrine and dopamine reuptake inhibition. It is also a noncompetitive inhibitor of the nicotinic $\alpha_4\beta_2$ acetylcholine receptors and explains its usefulness during smoking cessation therapy. It also acts by allosteric blockade of the 5-hydroxytryptamine $(5\text{-HT})_{3A}$ receptors.

Describe the Pharmacokinetics, Dosing, and Therapeutic Drug Monitoring of Bupropion (BPR)?

Bupropion has exceptionally low oral bioavailability due to extensive first-pass effect.

It is 80–85% protein bound.

The biotransformation of BPR is mediated mainly by CYP2B6, producing three active metabolites: hydroxyBPR; erythrohydroBPR, and threohydroBPR.

The main BPR metabolites are CYP2D6 inhibitors; hydroxyBPR possesses the highest inhibitory activity, followed by the other metabolites and finally by the parent drug; therefore it increases the level of atomoxetine and desipramine up to fivefold.

Carbamazepine can decrease exposure to BPR.

SSRIs paroxetine, fluvoxamine, sertraline, and norfluoxetine (the main fluoxetine metabolite) are all capable of inhibiting CYP2B6 and increasing BPR level.

BPR can increase valproate levels in humans.

Tobacco smoking does not affect the plasma levels of BPR.

Dose range: 100–450 mg.

Bupropion is administered in its sustained formula at a dose of 100 mg/day; increase by 100 mg/week up to 200 mg twice daily up to 450 mg/day. Dose should not increase beyond 450 mg due to tenfold increase in risk of seizures. It is contraindicated in eating disorders for the same reason.

TDM (level 2 recommended).

For BPR therapy, the reference therapeutic level range through (C_{min}) refers mainly to hydroxyBPR; it is 850–1500 ng/mL, with a risk of toxicity of 2000 ng/mL.

Suggested plasma level is 75–350 nmol/L [6].

What Are the Adverse Effects, Warning, and Contraindications of Bupropion (BPR)?

Most common: nausea, headache, insomnia, agitation, dry mouth, constipation, irritability, weight loss, and anxiety.

Vivid dreams, hallucinations, unusual thoughts or behavior, changes in attention, memory and perception, confusion, tremors, severe blistering, peeling, skin rash or itching, fever, swollen glands, joint pain, increased blood pressure, weight loss, increased suicidal thoughts, and general ill feeling have also been described.

Seizures are the most serious adverse effects of bupropion.

In bupropion-related intoxications, major toxicity symptoms include seizures, agitation, confusion, sinus tachycardia, hypertension, nauseas and vomiting, and hallucinations. Metabolic acidosis, delusions, tremors, lethargy, sinus tachycardia QRS interval widening, QTc prolongation, and cardiac arrest, paresthesia, and coma are also mentioned.

Although oral administration of bupropion is thought to have low abuse potential, there is growing evidence of misuse of bupropion. After nasal insufflation of the

content of several tablets of bupropion, abusers reported euphoria, increased energy, and arousal [6].

What Are the Recommendations of Bupropion Use in Pregnancy?

Some researchers suggest that the first-trimester bupropion exposure might increase the risk of congenital heart defects but the absolute risk of a congenital heart defect remains low at 2.1/1000 births in exposed infants when compared to the estimated prevalence of 0.82/1000 births in the general population.

2.7.2 Serotonin Antagonists and Reuptake Inhibitors (SARIs)

Trazodone.

2.7.3 Describe some of the Indications and off-Label Uses for Trazodone?

Trazodone was approved for treatment of major depression in 1981 by the FDA.

It has useful therapeutic effect on the anxiety component in depressed patients.

Researchers suggest using the sustained-release formulations in depressive disorder. Immediate-release formulations have good potential as hypnotics and are used in MDD.

They are not useful in OCD or panic disorder but could be beneficial in PTSD.

Other off-label uses include bulimia, substance- or alcohol-use disorders, fibromyalgia and chronic pain, central nervous system degenerative diseases such as dementia and other organic disorders, diabetic neuropathy, and sexual dysfunction. It has been used in the treatment of hypoactive sexual desire disorder (HSDD).

2.7.4 What Is the Mechanism of Action and Pharmacokinetics of Trazodone?

Trazodone (Desyrel) is a triazolopyridine derivative antidepressant that belongs to the class of serotonin receptor antagonists and reuptake inhibitors (SARIs). It blocks postsynaptic 5-HT2 receptors and weekly inhibit reuptake of serotonin and norepinephrine, resulting in selective activation of 5-HT1 receptors. It has some antagonism in alpha 1 adrenergic receptor. Both nefazodone and trazodone affect REM sleep and improve sleep continuity.

It is metabolized by CYP3A4 and is 93% protein bound.

2.7.5 What Are the Dosing Requirements of Trazodone?

Dose range is 50–400 mg in outpatient setting but could reach 600 mg in inpatient setting at bedtime. Small doses such as 25–50 mg had been used to improve sleep quality.

150 mg at bedtime should be used for depression and it could be increased by 50 mg every 3–4 days if needed.

12.5 mg is given 2–3 times daily or as needed for sexual arousal problems.

2.7.6 What Are the Adverse Effects of Trazodone?

Daytime sleepiness and excessive sedation, headache, dizziness, orthostatic hypotension, and tachycardia. Priapism with increased libido had been reported. Nausea, vomiting, constipation, and decreased appetite are not common.

Trazodone presents minimal anticholinergic features, so it is generally considered to have less cardiotoxic potential than other antidepressant drugs, but cardiotoxicity should be considered in overdose.

2.7.7 What Are the Risk Factors for Developing Priapism with Trazodone?

Patients with sickle cell anemia or sickle cell trait, leukemia, autonomic nervous system dysfunctions, and hypercoagulable states.

Patients taking SSRIs (dose related).

Patients using cocaine or who have overdosed on cocaine or trazodone [7].

2.7.8 What Are the Recommendations of Trazodone Use in Pregnancy and Lactation?

Some researchers suggest that the first-trimester trazodone exposure does not increase the risk of congenital malformations.

2.7.8.1 Nefazodone

It is a phenylpiperazine antidepressant, a triazolone analog of the SARI trazodone and of the antipsychotic aripiprazole. It was originally introduced and developed for clinical use in the USA in 1994 as an alternative for trazodone, because of its reduced sedative effect at full dosage. In addition to its antidepressant effects,

nefazodone was found to be helpful in the treatment of migraine headaches and chronic pain especially for patients suffering from spinal column disorders.

Usual dose is 100 mg twice daily to a maximum of 300 mg twice daily.

Nefazodone has now been voluntarily discontinued in many countries (but not in the USA) due to its severe and potentially fatal liver toxicity. It has a serious FDA warning.

A controlled study found that nefazodone exposure in the first trimester did not increase the rates of major malformation above the baseline.

2.7.9 Melatonergic Agonists and Selective Serotonergic Antagonists (MASSAs)

2.7.9.1 Agomelatine (Valdoxan)

Describe the Use of Agomelatine?

Agomelatine has been used in the treatment of depression. It also improves overall sleep quality without daytime sedation. Some researchers suggest that it can be used in anxiety. The effect size is small compared to other antidepressants.

Agomelatine has been described as a useful augmentation to other antidepressants, in OCD and in severe depression.

What Is the Mechanism of Action and Pharmacokinetics of Agomelatine?

It is a naphthalene analog of melatonin. Agomelatine is a melatonergic MT_1 and MT_2 receptor agonist and serotonergic 5-HT_{2B} and 5-HT_{2C} receptor antagonist.

Agomelatine induces resynchronization of circadian rhythms and enhances the level of dopamine and norepinephrine in the frontal cortex.

AGT bioavailability is low, about 5%, due to massive first-pass metabolism. Biotransformation is affected mainly by CYP1A2, with a small contribution by CYP2C9/19. It has two inactive metabolites. Food intake does not alter the absorption or bioavailability of agomelatine. The elimination of agomelatine is rapid, with a plasma half-life between 1 and 2 h. About 80% of the drug is eliminated through urinary excretion of the metabolites, whereas a small amount of the metabolites undergoes fecal excretion.

Drug Interactions

Fluvoxamine, a potent CYP1A2 inhibitor, markedly inhibits the metabolism of agomelatine, resulting in a 60-fold increase of AGT exposure.

Combination of AGT with estrogens (moderate CYP1A2 inhibitors) results in severalfold increased exposures to AGT.

Smoking induces CYP1A2 and has been shown to decrease the bioavailability of AGT.

Agomelatine has a risk of liver injury and monitoring of liver function throughout treatment is recommended (Freiesleben and Furczyk 2015).

What Is the Dosing and Monitoring Requirements of Agomelatine?

Dose: 25 mg po HS and Can Be Increased to 50 mg po HS

Monitoring: TDM of AGT at "level 4" (potentially useful), that is, it should be restricted to special cases due to apparent lack of correlation between plasma levels and activity. Therapeutic AGT level range is reported after 1–2 h (C_{max}), due to its rapid elimination. The range is 7–300 ng/mL, with a risk of toxicity of 600 ng/mL.

List Some of the Adverse Effects of Agomelatine?

Nausea and dizziness (most reported), somnolence, insomnia, migraine headaches, anxiety, constipation, diarrhea, fatigue, back pain, and sweating.

Up to 1% of patients might have increase in serum hepatic transaminases, as high as three times the upper limit of the normal range. The effect is reversed by stopping the drug. The manufacturer recommends baseline liver function tests with follow-up testing at six, 12, and 24 weeks. Agomelatine does not enhance serotonin and has exceptionally low risk of serotonin syndrome. There are no discontinuation syndrome and no abnormal bleeding due to serotonergic effects on platelets nor the upper gastrointestinal tract.

What Are the Recommendations of Agomelatine Use in Pregnancy and Lactation?

Some researchers suggest that the first-trimester agomelatine exposure does not increase the risk of congenital malformations. The data available is not sufficient to reach a definite conclusion [8–11].

2.7.10 Norepinephrine Reuptake Inhibitors (NRIs)

2.7.10.1 Reboxetine (Edronax)

What Is the Mechanism of Action and Therapeutic Use of Reboxetine?

Reboxetine is a specific noradrenergic reuptake inhibitor and was the first NRI commercially available for major depression. In one study, RBX at low doses was effective an augmentation agent in treating depression in patients who did not respond to SSRIs.

It is available in Europe but was rejected in the USA due to lack of efficacy.

Describe the Pharmacokinetics of Reboxetine?

Half-life = 12 h.

RBX is primarily metabolized in the liver by CYP3A4, with the formation of *O*-desethylRBX. Low reboxetine serum levels have been reported with the concurrent administration of CYP3A4 inducers such as phenobarbital and carbamazepine.

RBX reduces several effects of methylenedioxymethamphetamine (MDMA).

Coadministration of RBX with MRT produced a significant reduction of the cortisol, ACTH, and prolactin secretion stimulation.

Describe the Dosing and Monitoring Requirements of Reboxetine?

It is available in 4 mg tablets and recommended dose is 4 mg twice daily.

In renal or hepatic insufficiency, the dose should be reduced to 2 mg BID.

TDM (level 3 useful): The reference therapeutic range through (C_{min}) is 60–350 ng/mL, with a risk of toxicity of 300 ng/mL.

What Are the Recommendations of Reboxetine Use in Pregnancy and Lactation?

No clinical trial data on exposure to reboxetine during pregnancy are available. It is not approved in the USA for marketing but it is available in other countries. Limited information indicates that maternal doses of up to 10 mg daily produce low levels in milk and appear to not result in any adverse effects in breastfed infants. Until more data are available, reboxetine should be used with careful monitoring during breastfeeding.

2.7.10.2 Viloxazine VLX

It is a bicyclic methylmorpholine derivative and is under investigation for possible use in ADHD.

Drug Interactions

VLX is a potent inducer of CYP1A2. It could influence the plasma levels of other drugs metabolized by CYP1A2, such as antidepressants (some tricyclics, fluvoxamine, agomelatine, and duloxetine), antipsychotics (clozapine, olanzapine, and

haloperidol), xanthines, and some cardiovascular drugs (mexiletine, propranolol, and verapamil).

VLX is known to cause increases in the serum levels of some antiepileptics, such as carbamazepine (by up to 250%) and phenytoin (by about 37%), but not oxcarbazepine. Carbamazepine significantly decreases VLX levels.

TDM (Level 3 Useful)

The reference therapeutic VLX level range through (C_{min}) is 20–500 ng/mL. Cases of intoxication with up to 4 g of the drug have been reported, with only mild CNS symptoms or, in some instances, seizures or extrapyramidal symptoms.

Teniloxazine

It is an NRI, selective over serotonin and dopamine reuptake, and a 5-HT_{2A} antagonist.

Due to the extremely limited diffusion of this drug, most of its pharmacological characteristics are unclear, and its DDIs have never been studied.

2.8 Atomoxetine HCI: ATX Strattera® (ATX)

2.8.1 What Is the Mechanism of Action and Therapeutic Uses of Atomoxetine?

2.8.1.1 Nonstimulant Medication Used in Treatment of ADHD

Atomoxetine, a highly selective norepinephrine reuptake inhibitor, is approved for the treatment of ADHD in children over the age of 6 years, adolescents, and adults. Unlike the stimulants, ATX is not a controlled substance; therefore, clinicians can provide samples and prescribe refills. It acts by blocking the norepinephrine reuptake pump on the presynaptic membrane and increasing the availability of intrasynaptic norepinephrine.

Atomoxetine is especially useful for ADHD patients who do not respond or develop unacceptable side effects to stimulant use or in ADHD patients with comorbid tics, anxiety, and SUD. Atomoxetine has also been shown to be an effective treatment for ADHD patients with comorbid anxiety and depression.

2.8.1.2 Describe the Pharmacokinetics of Atomoxetine?

The drug is mainly metabolized in the liver by CYP2D6 to 4′-hydroxyATM which is equipotent to the parent drug; the metabolite is then glucuronidated to 4′-hydroxyATM-*O*-glucuronide, which is inactive. Atomoxetine undergoes extensive biotransformation, which is affected by poor metabolism by cytochrome P450 (CYP) 2D6 in a small percentage of the population; these patients have greater exposure to, and slower elimination of, atomoxetine than extensive metabolizers. Patients with hepatic insufficiency show an increase in atomoxetine exposure (product monograph).

2.8.1.3 What Are Some of the Drug Interactions of Atomoxetine?

Simultaneous administration of bupropion or paroxetine and ATM causes a fivefold increase in exposure to the ATX. ATM itself does not have strong CYP-inhibiting or CYP-inducing properties.

2.8.1.4 Describe the Dosing and Monitoring Requirements of Atomoxetine?

Atomoxetine is usually prescribed once daily, although twice-daily dosing can also be used. Atomoxetine should be initiated at doses of about 0.5 mg/kg body weight for about 2 weeks, and then titrated upward based on clinical response to 1.2 and 1.4 mg/kg, or a maximum total dose of approximately 100 mg/day.

Dose range: 10–100 mg daily.

The initial dose for ADHD therapy is 40 mg/day divided into one or two administrations, to be titrated to 60 mg, then 80 mg after a few days of therapy, and up to 100 mg/day after 2–4 weeks if symptom control is not optimal. ATM also shares with antidepressants the risk of increasing suicidal ideation.

Higher doses have been used. It comes in seven doses (10, 18, 25, 40, 60, 80, and 100 mg). The capsules should never be opened as it may cause irritation of the gastric lining. It may take several weeks before the benefits from atomoxetine become apparent; therefore, it is important to inform patients about this to ensure continued compliance despite apparent little impact on symptoms during the initial stages of treatment.

Measurements of blood levels are not required but can be useful (TDM (level 3 useful)).

The reference therapeutic ATX concentration range is reported after 60–90 min from administration (C_{max}) due to its short half-life, and is 200–1000 ng/mL, with a risk of toxicity of 2000 ng/mL.

2.8.2 List Some of the Main Adverse Effects of Atomoxetine?

Common adverse effects with atomoxetine use include gastrointestinal upset, headaches, fatigue, and mild increase in heart rate and blood pressure. Rare, but important, adverse effects that should be discussed with patients include liver toxicity and increased suicidal thoughts. ATX should be discontinued in patients who have jaundice and patients should contact their doctors if they develop pruritus, jaundice, dark urine, right upper quadrant tenderness, or unexplained flu-like symptoms. Currently, laboratory monitoring outside of routine medical care usually is not necessary. An analysis of clinical trials by the manufacturer showed increased suicidal thoughts in 4 (0.4%) out of 1000 patients, but there were no attempted or completed suicides (product monograph). Nevertheless, the FDA warns clinicians to counsel patients about this potential risk.

2.8.3 What Are the Recommendations of Atomoxetine Use in Pregnancy and Lactation?

Atomoxetine has not been well studied for use during pregnancy. Two small human studies have not suggested a greater chance for birth defects. When looking at doses typically used by humans, animal studies did not suggest a risk for birth defects. However, with levels higher than those used with human treatment, there is some question of a chance for birth defects. It is not known if this information would apply to women who are considered poor metabolizers. There are no published reports on the use of atomoxetine while breastfeeding.

2.9 Noradrenergic and Selective Serotonergic Antidepressants (NaSSAs)

2.9.1 Mianserin (MSR)

2.9.1.1 What Is the Mechanism of Action and Pharmacokinetics of Mianserin?

Mianserin is a tetracyclic second-generation antidepressant. In addition to its antidepressant effects, mianserin also has anxiolytic, sedative-hypnotic, antiemetic, and appetite-enhancing effects.

Mianserin is considered a2-adrenergic agonist and 5-HT2 antagonist but it has a very wide receptor activity spectrum, being an antagonist/inverse agonist at histamine H_1; serotonin 5-HT_{1D}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7; adrenergic α_1 and α_2 receptors; and a NRI as well (antagonist of the norepinephrine transporter).

It has high affinity toward H_1 receptors which contributes to its strong sedative effects.

It has low muscarinic affinity so it has low anticholinergic SE.

It has two enantiomers (s and R) that have significantly different pharmacological activities: *S*-(+) -MSR is about 2 to 300 times more potent than *R*- (−).

Metabolism: three main pathways: 8-hydroxylation, *N*-demethylation, and *N*-oxidation.

N-desmethyl MSR and 8-hydroxy MSR retain antidepressant properties but are less sedating than mianserin, while mianserin *N*-oxide seems to be much less active.

8-Hydroxylation is mediated mainly by cytochrome P 450 (CYP) isoform 2D.

N-demethylation of both enantiomers is catalyzed mainly by CYP2B6.

N-oxidation is catalyzed mainly by CYP1A2 (and 3A4).

Drug Interactions.

There is some lack of data from studies on humans regarding MSR interactions.

2.9.1.2 Describe the Dosing and Monitoring Requirements of Mianserin?

Dose range: 60–120 mg.

60 mg daily can be used when it is used in partial responders or as augmentation**.**

Therapeutic Drug Monitoring (TDM)

TDM can be used to ensure that drug concentrations fall within the reference ranges at (C_{min}), i.e., 15–70 ng/mL, with risk of toxicity of 140 ng/mL.

2.9.1.3 List Some of the Main Adverse Effects of Mianserin?

Sedation, dizziness, weight gain; cognitive impairment, headache, tachycardia, and dry mouth. Lowering white count and fatal agranulocytosis had been reported. CBC should be ordered monthly for the first 3 months. The lowering of white count typically happens between 4 and 6 weeks after starting the treatment.

2.9.1.4 What Are the Recommendations of Mianserin Use in Pregnancy and Lactation?

Mianserin is not approved for marketing in the USA by the U.S. Food and Drug Administration but it is available in other countries. Limited data are available regarding its use in pregnancy and lactation. If used, it should be used carefully and with monitoring in lactating mothers. Current information indicates that maternal

doses up to 60 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months (Lactmed).

2.9.2 Mirtazapine (MRT)

2.9.2.1 Describe Some of the Conditions that Mirtazapine Was Used For?

- Generalized anxiety disorder (GAD) and depression. It could have good efficacy in the treatment of patients who do not respond to other classes. It has faster onset of the therapeutic activity and offers better control of anxiety.
- Post-traumatic stress disorder.
- May be useful in movement disorders or akathisia caused by antipsychotics.
- It can be effective in pain reduction and enhancement of depressed mood in patients with pain and co-occurring depression. Mirtazapine was helpful in some patients with refractory chronic tension—headache. It also may decrease sleep disturbances in neuropathic pain and fibromyalgia.

2.9.2.2 What Is the Mechanism of Action and Pharmacokinetics of Mirtazapine?

It involves the increased release of serotonin and norepinephrine due to the antagonism on autoreceptors and presynaptic α_2 adrenergic autoreceptors. It also blocks 5-HT2a, 5-HT2c, and 5-HT 3. MRT also causes 5-HT_2 and 5-HT_3 blockade and H_1 antagonism.

Metabolism

MRT is almost totally biotransformed in the liver by action of CYP2D6, 3A4, and 1A2.

The two main metabolic pathways involve demethylation forming *N*-desmethylMRT (that has activity similar to that of the parent drug, but with lower potency) or oxidation forming 8-hydroxyMRT. Some researchers suggest that CYP2D6 is responsible for 8-hydroxylation while CYP3A4 is responsible for *N*-demethylation.

The drug is sold as a racemate. The *R* (−) -enantiomer shows the longest elimination half-life from plasma.

2.9.2.3 Describe the Dosing and Monitoring Requirements of Mirtazapine?

Starting dose: 7.5–15 mg at bedtime, which could be increased every 1–2 weeks by 15 mg increment, not to exceed a total dose of 60 mg/day.

Therapeutic drug monitoring (TDM) (level 2 recommended).

It can be used for dose titration as well as for special indications and problems, and it can increase the likelihood of response in nonresponders. The reference therapeutic MRT level range at (C_{min}) is 30–80 ng/mL, with a risk of toxicity of 160 ng/mL.

2.9.2.4 What Are the Adverse Effects of Mirtazapine?

Sedation in over 50% of patients. Increases appetite and weight; less frequent are headache, edema, and hepatic enzyme-level increase, which can evolve into jaundice and thus require treatment interruption. Not associated with cardiovascular effects nor significant sexual side effects.

Mirtazapine is possibly linked to increase of suicide risk in adolescents.

2.9.2.5 Compare Adverse Effects of Mirtazapine to Some of the Other Classes of Antidepressants?

TCA: Mirtazapine was significantly less likely to cause hypertension or tachycardia (risk ratio [RR] 0.51) and tremor (RR 0.43) than tricyclic antidepressants (TCAs).

SSRI: Mirtazapine was significantly more likely to cause weight gain or increased appetite, increased salivation, somnolence, and fatigue, but less likely to cause flatulence, sweating, sexual dysfunction, tremor, nausea or vomiting, sleep disturbance, and diarrhea.

SNRI: Mirtazapine was significantly more likely to cause fatigue (RR 2.02), but less likely to cause sleep disturbance (RR 0.03), sweating (RR 0.03), and constipation (RR 0.25).

Trazodone: Mirtazapine was significantly more likely to cause weight gain or increased appetite (RR 4.00) (Watanabe N 2010).

2.9.2.6 What Are Some of the Drug Interactions of Mirtazapine?

Considered a weak competitive inhibitor of CYP1A2, CYP2D6, and CYP3A4.

Has a specific form of pharmacodynamic interaction with MAOIs that leads to increase of serotonin levels and development of serotonin syndrome.

Alcohol, anxiolytics, or hypnotics can potentiate the sedative effects of MRT.

Some case reports of interaction with clozapine and risperidone.

2.9.2.7 What Are the Recommendations of Mirtazapine Use in Pregnancy and Lactation?

Some researchers suggest that the first-trimester mirtazapine exposure was not associated with an increased risk of major malformation. Mirtazapine seems to be safe in pregnancy, especially regarding incidence of congenital malformations. There are not enough data available to come to a conclusion on the safety of mirtazapine during lactation [12, 13].

2.10 Novel Antidepressants

2.10.1 What is the mechanism of action of Vortioxetine (Trintelix)?

Vortioxetine was approved for the treatment of MDD in 2013 by the FDA. It contains the beta polymorph of vortioxetine hydrobromide and is administered as an immediate-release tablet.

Vortioxetine exerts its therapeutic effects through multimodal activity with a modulation of 5-HT receptors and an inhibition of 5-HT transporters. The antidepressant effect of the vortioxetine is mediated through its antagonist effect on the 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors; partial agonist activity on the 5-HT1B receptor; agonist effect on the 5-HT1A receptor; and inhibition of the 5-HT transporter. Besides the modulatory effect on the 5-HT receptors and transporter, it also enhances the extracellular concentration of various neurotransmitters such as dopamine, histamine, noradrenaline, and acetylcholine.

Vortioxetine modulates the essential neurotransmitters which are involved in cognitive regulation such as glutamate, acetylcholine, histamine, dopamine, and noradrenaline.

2.10.2 Describe the Dosing Requirements of Vortioxetine (Trintelix)?

Vortioxetine is available as 5, 10, and 20 mg tablets.

Starting dose can be 5 mg or 10 mg once daily. The dose can increase from 10 to 20 mg based on the tolerability and clinical response.

2.10.3 Describe the Pharmacokinetics of Vortioxetine (Trintelix)?

In vivo, vortioxetine shows a linear and dose-proportional relationship, i.e., c-max, and AUC increases linearly with dose (2.5–60 mg). It has moderate oral bioavailability that is independent of food intake.

Vortioxetine has an extensive volume of distribution as the plasma protein binding is 80–90%.

Possibly higher dose may lead to better outcome.

It takes 3–16 h to attain maximum plasma concentration after dosing, and with multiple doses, the terminal half-life is approximately 60–70 h.

Metabolism: extensively in the liver through oxidation and subsequent glucuronic acid conjugation to a pharmacologically inactive carboxylic acid metabolite. The CYP450 primarily responsible is CYP2D6.

The increased risk of bleeding is explained by inhibition of serotonin uptake by platelets, an increase in gastric acid secretion, and modulation of the CYP450 metabolism.

2.10.4 List Some of the Main Adverse Effects of Vortioxetine (Trintelix)?

Nausea (reported as 10%), headache, diarrhea, dry mouth, and increased risk of bleeding. Sexual dysfunction including abnormal orgasm, ejaculation disorder, decreased libido, and erectile dysfunction was reported but at a low rate.

In a study of vortioxetine 15 mg, two serious AEs (stress fracture and suicidal ideation) were reported.

Sudden discontinuation of vortioxetine after 2 weeks of treatment showed no clinically significant withdrawal effect versus placebo.

2.10.5 What Are the Recommendations of the Medication Use in Pregnancy?

In a pregnant patient, vortioxetine 5 mg was discontinued after 1 month. Delivery of the healthy baby (3800 mg in weight) was reported. It can cause decreased fetal weight and delayed ossification in animal studies. The data available are insufficient.

2.11 Serotonin Partial Agonist Reuptake Inhibitor (SPARI)

2.11.1 Vilbryd

2.11.1.1 What Is the Mechanism of Action and Pharmacokinetics of Vilazodone (Vilbryd)?

Vilazodone is an indolealkylamine antidepressant which has a dual mechanism of action. It acts as an SSRI and a partial 5-HT_{1A} receptor agonist. It was approved for the treatment of MDD in adults by FDA in 2011. It is, thus, a serotonin partial agonist reuptake inhibitor (SPARI). It is not approved in pediatric population but

approved in adults. It shows faster effect than SSRIs. Some studies indicated that after 1 week, some patients noticed some improvements.

It seems that the rapid effect can be explained by the dual mechanism of action. The SSRI effect leads to increase in serotonin level but the concentration of serotonin in the synaptic cleft does not rise immediately, in part due to the negative feedback mechanism from the presynaptic 5-HT_{1A} autoreceptors. Because vilazodone is a 5-HT_{1A} partial agonist as well as an SSRI, it may disrupt the negative feedback loop by occupying 5-HT_{1A} receptors and displacing serotonin or by accelerating attenuation of the 5-HT_{1A} negative feedback signal.

2.11.1.2 Describe the Pharmacokinetics of Vilazodone (Vilbryd)?

Vilazodone has a dose-proportional pharmacokinetic activity (5–80 mg).

Peak concentration is reached in 4–5 h after administration.

Elimination half-life = 25 h.

Protein binding: 96–99% protein bound.

Vilazodone is extensively metabolized through both cytochrome P450 (CYP) pathways (major: CYP3A4, minor: CYP2C19 and CYP2D6), with little to unchanged drug recovered in the urine (1%) and feces (2%).

Researchers suggest decreasing the dose of vilazodone by 50% when combined with strong CYP3A4 inhibitors; conversely, increasing the vilazodone dosage up to a maximum of 80 mg/day should be considered when it is given in combination with strong CYP3A4 inducers such as carbamazepine.

2.11.1.3 Describe the Dosing Requirements of Vilazodone (Vilbryd)?

Dose range: 20–40 mg daily but can go to 80 mg daily.

Start with 10 mg for 1 week, then 20 mg daily for 1 week, and then 40 mg daily. It is possible to increase the vilazodone dose up to 80 mg. That dose should be considered when it is given in combination with strong CYP3A4 inducers such as carbamazepine.

It should be taken with food.

2.11.1.4 List Some of the Main Adverse Effects of Vilazodone (Vilbryd)?

Nausea, vomiting, diarrhea, insomnia, somnolence, dizziness, and dry mouth.

Vilazodone has an advantage over SSRIs and other antidepressants of lower sexual adverse effects and being close to weight neutral.

Abrupt discontinuation of vilazodone may lead to dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures.

Vilazodone toxicity or poisoning may produce serious and life-threatening clinical effects, including serotonin syndrome, QRS prolongation, ataxia, seizures, and coma. Young children, who may become critically ill after ingestions of very small amounts of the drug, are at especially high risk.

2.11.1.5 What Are the Recommendations of Vilazodone Use in Pregnancy and Lactation?

There is a lack of adequate and well-controlled studies of vilazodone in pregnant women, needing a careful analysis of potential benefits and risks of treatment [14–16].

2.12 Ketamine and Esketamine

2.12.1 Describe the Role of Ketamine and Esketamine (ESK) in Depression?

Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist that leads to increased synaptic plasticity and may elicit a rapid antidepressant response in individuals with depression.

In Canada, several formulations of ketamine are approved for general anesthesia. Ketamine has showed potential as a novel, rapid-acting therapeutic option for patients with treatment-resistant depression (TRD) and PTSD. Rapid remissions (within a couple of hours) have been claimed for intravenous administration of ketamine in acute depression [17].

2.12.2 Esketamine (Spravato)

Nasal spray for adult treatment-resistant depression.

Indications: SPRAVATO is a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. It is not approved as an anesthetic agent.

2.12.2.1 Dosage and Administration

Assess blood pressure before and 40 min after the treatment.

Advise patients to avoid food for at least 2 h before administration and to avoid drinking liquids at least 30 min prior to administration.

2.12.2.2 Induction Phase

Induction phase	Weeks 1 to 4	Day 1 starting dose: 56 mg (2 devices) Subsequent doses 56 or 84 mg (2 or 3 devices)
Maintenance phase	Weeks 5 to 8	Give 56 mg to 84 mg Give once every 2 weeks or once weekly of 56 to 84 mg
	Weeks 9 and after	Give once every 2 weeks or once weekly of 56 to 84 mg

2.12.2.3 Administration

Spravato is for nasal use only. The nasal spray device delivers a total of 28 mg of esketamine.

To prevent loss of medication, do not prime the device before use. Use two devices (for a 56 mg dose) or three devices (for an 84 mg dose), with a 5-min rest between use of each device.

If a patient misses treatment sessions and there is worsening of depression symptoms, per clinical judgement, consider returning to the patient's previous dosing schedule (give the medication once weekly instead of every two weeks or twice weekly instead of once a week).

Administer SPRAVATO intranasally and assess blood pressure prior to and after administration. It is supplied as a nasal spray device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine.

2.12.2.4 Contraindications

Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. Intracerebral hemorrhage and hypersensitivity to esketamine, ketamine, or any of the excipients.

2.12.2.5 Warnings and Precaution

- Sedation is very common and can be prolonged so patients must be observed for 2 h post-administration.
- Esketamine (Spravato) has a potential to induce dissociative symptoms including distortion of time, space, and illusions; derealization; and depersonalization (61–75% of treated patients developed dissociative symptoms).
- Esketamine (Spravato) can be abused and misused. It is a controlled substance.
- Hypertension is a risk. Approximately 8–17% of Spravato-treated patients and 1–3% of placebo-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 h after administration at least once during the first 4 weeks of treatment. BP monitoring before and after treatment is extremely important.

– Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine.
– Increased suicidal thoughts or behavior applied to all antidepressants.

Increases in blood pressure: Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. Spravato may impair attention, judgment, thinking, reaction speed, and motor skills. It may impair the ability to drive and operate machinery until the next day after a restful sleep.

2.12.2.6 Adverse Effects

The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk. Breastfeeding is not recommended and may cause fetal harm.

2.12.2.7 Drug Interactions

1. Central nervous system depressants: Concomitant use of CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation. Closely monitor for sedation with concomitant use of Spravato with CNS depressants.
2. Psychostimulants: Concomitant use of psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of Spravato with psychostimulants.
3. Monoamine oxidase inhibitors (MAOIs): Concomitant use of monoamine oxidase inhibitors (MAOIs) may increase blood pressure.

2.12.2.8 Therapeutic Drug Monitoring

No reliable therapeutic plasma concentration range has been established yet for ESK in depression.

2.12.2.9 Metabolism

Esketamine is primarily metabolized to noresketamine metabolite via cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19. Noresketamine is metabolized via CYP-dependent pathways and certain subsequent metabolites undergo glucuronidation (product monograph).

2.12.3 Describe the Association Between Antidepressants and Hyponatremia and SIADH?

All antidepressants are associated with hyponatremia. Strongest association with mirtazapine and lowest association with trazodone and bupropion [18].

2.12.4 Describe Some of the Research Information of Drug-Induced Liver Injury with Antidepressants?

Antidepressants are important causes of drug-induced liver injury accounting for 2–5% of clinically apparent cases.

The MAO inhibitors can cause serum aminotransferase elevations and rarely lead to clinically apparent liver injury, generally with a hepatitis-like clinical presentation 1–3 months after starting therapy.

The various tricyclic antidepressants are capable of causing transient serum aminotransferase elevations to varying degrees and, in rare instances, clinically apparent acute liver injury. Various pattern of hepatic injury have been associated with different tricyclic antidepressants (liverTox).

2.12.5 Describe the Cardiac Adverse Effects of Antidepressants?

The TCAs are highly cardiotoxic in overdose, and may worsen outcome in established cardiovascular disease. Numerous studies suggested the use of sertraline in patients with a history of cardiac disease. Fluoxetine, citalopram, and mirtazapine have been prescribed after MI, and paroxetine and citalopram have been prescribed after coronary artery disease.

Duloxetine and venlafaxine are known to increase blood pressure and should be used only with great caution in established hypertension [19].

2.12.6 What Are Some of the Drug Interactions of Antidepressants?

Degree of CYP450 enzyme inhibition of antidepressant drugs at their usual therapeutic dose (Table 2.5).

Table 2.5 Drug interactions of antidepressants

	Cytochrome P450 enzyme inhibition				
Drug	2D6	1A2	3A4	2C9	2C19
Nortriptyline	+	0	0	0	+
Desipramine	+	0	0	0	+
Amitriptyline	+	++	0	+	+++
Imipramine	+	++	+	+	+++
Dothiepin	+	+?	0?	+?	+++?
Doxepin	+	+?	0?	+?	+++?
Clomipramine	+?	++?	0	+?	+++
Sertraline	+	0	0	0	0
Fluoxetine	+++	0	+	++	+++
Fluvoxamine	+	+++	++	+++	+++
Paroxetine	+++	0	0	0	0
Citalopram	++	0	0	0	0
Escitalopram	++	0	0	0	0
Venlafaxine	+	0	0	0	0
Duloxetine	++	0	0	0	0

Guide to approximate ranking of effect:
+ measurable, but likely to be clinically insignificant
++ clinically significant, possibly serious with other drugs with narrow safety margins
+++ large, often clinically significant, serious interactions highly predictable with certain drugs
"?" indicates an estimate from structurally related drugs because there are no data available for that specific drug
No data known for lofepramine [20] and http://medicine.iupui.edu/flockhart/clinlist.htm

2.12.7 Describe the Differences Among Antidepressants with Respect to Their Effect on Sexual Function (Table 2.6)*?*

Post-SSRI sexual dysfunction has been recently identified as a potential, although rare, adverse effect of SSRIs and SNRIs. Consider the possibility of post-SSRI sexual dysfunction in patients in whom sexual dysfunction was absent before starting antidepressants but develops during or soon after antidepressant treatment and persists after remission from depression and discontinuation of the drug [21].

Table 2.6 Sexual function and antidepressants

Greatest risk of sexual dysfunction: • Selective serotonin reuptake inhibitors (SSRIs) • Serotonin and noradrenaline reuptake inhibitors (SNRIs)
Less risk with • Tricyclic antidepressants (except clomipramine) • Mirtazapine • Vilazodone
Least with • Moclobemide • Agomelatine • Reboxetine • Bupropion

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Chapter 3
Electroconvulsive Therapy

3.1 Describe a Brief History of ECT?

Electroconvulsive therapy (ECT) is the oldest among the early biological treatments introduced in psychiatry, and the only one still in use.

- In 1934, Ladislas von Meduna (1896–1964) injected camphor into a person with schizophrenia with the intention of inducing convulsion; this was the first modern convulsive therapy. Sakel used insulin to induce convulsions through hypoglycemia leading to convulsions in 1935.
- Seizure induction by camphor in oil injection then metrazol (pentylene tetrazol) was found to be easier to administer and more effective.
- In Rome, in 1938, stimulated by the success of von Meduna, **Ugo Cerletti** (1877–1963) assisted by Lucio Bini (1908–1964) supervised the first ECT treatment. The first patient, SE, was a 39- year- old engineer from Milan who was found wandering the streets of Rome in a psychotic state. He received 11 treatments, obtained a good response, and wrote to the doctors the following year thanking them for their treatment [1].
- In the 1950s ECT trend started declining (meds, media).

3.2 What Is the Mechanism of Action of ECT?

Older studies suggested that ECT potentiates serotonergic function and that changes in G-protein levels may play a role in the mechanism of ECT. Some studies suggested a role for brain-derived neurotrophic factor (BDNF).

ECT may increase GABA concentration and enhance serotonergic function. It also affects the hypothalamic-pituitary-adrenal axis, normalizing the results of the dexamethasone suppression test. Functional brain activation is altered. Some authors reported significant increases of gray matter volume in medial temporal

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lobes following ECT, suggesting that a neurotrophic effect of ECT could play a role in its therapeutic effect ([2, 3].

3.3 What Are the Indications of ECT?

Royal Australian and New Zealand clinical professional guidelines (RANZCP) for the administration of ECT published in 2019 suggest that ECT is an appropriate and effective treatment for a number of psychiatric indications such as depressive disorders including major depression and major depression with psychotic features, major depression with melancholic features, and major depression with peripartum onset. ECT can be used in both unipolar and bipolar disorders for both mania and depression. Electroconvulsive therapy (ECT) proved to be effective in two-thirds of the patients with severe and drug-resistant mixed states. It can be used in schizoaffective disorder bipolar or depressed type, acute and chronic treatment-resistant schizophrenia schizoaffective disorder, acute psychosis, puerperal psychosis, and neuroleptic malignant syndrome.

The guidelines also suggested that ECT may also have a role in the treatment of severe and repetitive self-injurious behaviors in autism and in the treatment of agitation and aggression in patients with dementia.

ECT can be helpful in acute psychosis: particularly when there are catatonic features or with limited food and fluid intake and when other psychotic symptoms are unresponsive to medication.

Other indications for ECT among patients with depression are lack of a response to or intolerance of antidepressant medications, a good response to previous ECT, and the need for a rapid and definitive response (e.g., because of psychosis, catatonia, or a risk of suicide).

Electroconvulsive therapy (ECT) remains an essential treatment of geriatric patients. ECT is indicated in the treatment of severe depression, mania, psychosis, catatonia, and comorbid depression and agitation in dementia or in behavioral and psychological symptoms of dementia (BPSD).

ECT also serves an essential role in treating urgent illness requiring expedient recovery, such as catatonia and food refusal, or in patients with severe suicidal ideation or intent. ECT is even more effective in the elderly than in mixed-age adult populations [4].

ECT can be used in pregnancy and postpartum disorders.

3.4 Other Indications

- Parkinson's disease
- Neuroleptic malignant syndrome
- Intractable status epilepticus
- Delirium

- Catatonia
- Refractory patient to other therapies
- Children and adolescents and congenital and acquired brain injury
- Patient preference [5].

3.5 Describe Some of the Research Findings on the Use of Maintenance ECT in Schizophrenia?

Maintenance electroconvulsive therapy combined with medication may be an efficient alternative to pharmacological treatment alone in refractory schizophrenia [6].

A study of maintenance ECT (M-ECT) in patients with treatment-resistant schizophrenia on clozapine had interesting findings. Thirty-eight patients were followed for over 2 years. The patients were divided into three groups: (1) clozapine alone (CZP, $n = 15$), (2) acute ECT only (A-ECT, $n = 11$), and (3) acute ECT with M-ECT (M-ECT, $n = 12$). The study suggested that electroconvulsive therapy A-ECT augmented the effect of clozapine, but M-ECT was required for sustaining symptom improvement. No persistent or serious adverse effects were observed [7].

A retrospective cohort study on the clinical effectiveness of maintenance electroconvulsive therapy in patients with schizophrenia found that maintenance electroconvulsive therapy (M-ECT) was able to maintain clinical response in 48 (77%) treatment courses. Significant cognitive adverse effects were reported only in 7 (11%) of the courses. Use of antipsychotic, antidepressant, or benzodiazepine medications; psychiatric disorder; and sex were not associated with response. The study showed meaningful clinical effectiveness and good tolerability of M-ECT in patients with resistant schizophrenia over extended periods [8].

Several studies used M-ECT weekly for the first month and then biweekly.

3.6 What Is the Response Rate of ECT in Depression?

A meta-analysis showed ECT to be more effective than antidepressant medications alone in treating the psychotic subtype of depression, and it showed a trend for ECT to be better than combination pharmacotherapy. Effect size for ECT was 0.91 in several studies. Response rate in medication resistant population is 60–70%.

3.7 How Many Treatments Should Be Considered for a Usual Course of ECT?

ECT is administered three times weekly for approximately 6–12 treatments, depending on the severity of the patient's symptoms and the rapidity of the response.

3.8 List the Workup Suggested Prior to ECT?

- Determine if ECT is indicated
- Establish psychiatric and cognitive baselines to serve as a reference point from which to assess response/side effects
- Identify and treat any medical issues which may be associated with increased risk
- Initiate the process of informed consent.

3.9 Patient Evaluation

- Medical and psychiatric history
- Physical exam with special focus on neurological, cardiovascular and pulmonary exam
- Mental state exam
- Lab battery: CBC, electrolytes, LFTs, Ca++, Mg++, TSH, and patient-specific tests
- EKG
- CXR
- Consider neuroimaging, EEG, anesthesia consultation if indicated.

3.10 How Do you Manage Medications and Medical Conditions Prior to ECT?

According to RANZCP, tricyclic antidepressants (TCAs) may lower the seizure threshold and may increase the risk of cardiac arrhythmias, particularly in elderly people and those with cardiac disease. However, a balanced approach should be considered as nortriptyline has been shown to be relatively safe and may improve cognitive outcomes.

-Lithium has been reported to increase the risk of post-ECT delirium during a course of acute index ECT in some patients. Higher serum levels (above 0.6) are particularly associated with risk, and lower serum levels during an acute course of ECT are recommended in situations where it is essential to continue lithium treatment during acute index ECT (e.g., in patients at high risk of manic switch and in whom other mood stabilizers are ineffective and cannot be used). This can be achieved by lowering the regular dose of lithium and withholding it the night before and morning of the treatment.

Consideration should be given to ceasing benzodiazepines and anticonvulsants (when used as mood stabilizers) before ECT treatment. Some authors suggested that benzodiazepines decrease seizure duration, but rarely increase seizure threshold—and reduce response in RUL ECT but not bilateral ECT—while anticonvulsants can

increase, or have no effect on seizure threshold and seizure duration. Hydroxyzine/benadryl or methotrimeprazine 10 mg can be used in agitation.

Antipsychotics for psychosis have been shown to improve acute positive symptoms and work synergistically with ECT. The combination of ECT with clozapine may be of particular benefit for people who have an inadequate response to clozapine alone:

- NPO after midnight the night before ECT.
- Give cardiovascular drugs with sips of water at least 2 h before ECT.
- Give beta- blocker drops for glaucoma as pretreatment.

3.11 Management of Medical Conditions

- CVS: Give meds before TTT, fixed- mode pacemaker to prevent inappropriate deactivation, consult cardiology.
- DM: Adjust insulin dose, early morning ECT, IV glucose if long wait before ECT. Hypoglycemia increases the risk of seizure; check glucose 30 min before ECT.
- Asthma: Minimize theophylline (increase seizure duration).
- Epilepsy: Give meds after ECT. Check levels.

3.11.1 Coronary Artery Disease

- More common complications with CAD than any other cardiac disease.
- Require optimal stabilization of cardiac status before treatment.
- Careful use of lidocaine (high anticonvulsant properties) and diuretics (full bladder can rupture during seizure).

3.11.2 Pacemakers and Dysrhythmias

- Bundle branch block (BBB), first- degree heart block and atrial fibrillation can be safely treated with ECT. Conversion to sinus rhythm occurs during ECT, so pretreatment with anticoagulant is considered optimal.
- Patients with malignant ventricular arrythmia are at high risk for hemodynamic instability during ECT.
- Pacemakers usually do not need special attention except old ones that need change demand mode to fixed mode.

3.11.3 Hypertension

- Pre-ECT antihypertensive medications indicated especially short acting drugs during anesthesia. Oral antihypertensives should be given 2 h prior to ECT with sip of water except diuretics for risk of bladder rupture.

3.11.4 Vascular Malformation and Anticoagulation

- Continue anticoagulant. Assess the risk of rupture during ECT (one case report).

3.11.5 Dementia

- Two- thirds of depressed and demented patients obtain noticeable antidepressant benefit.
- Half show greater than usual confusional states.
- Some will have tardive seizure post-ECT.

3.11.6 Parkinson's Disease

- Highly effective for severe depression so often seen in such patients.
- In a substantial proportion of patients, a variety of EPSE may improve often faster than depression.
- Benefit from days to years.
- Maintenance ECT may extend period of cognitive improvement.
- Treatment emergent dyskinesias and delirium are common.

3.11.7 Neuroleptic Induced Movement Disorder

- ECT may aggravate TD.
- ECT may be a lifesaving option for NMS.
- Some improvement in tardive dystonia noted with ECT.

3.11.8 Cerebrovascular Disease

- Several isolated case reports indicated significant improvements with ECT.

- Location of the lesion and time since stroke was not associated with clinical response.
- Basal ganglia lesion predisposes to ECT- related delirium.

3.11.9 Intracranial Tumors

- In absence of focal neurologic finding, mass effect, brain edema, increase ICP or papilledema, risks probably are relatively small.
- Use risk reduction strategies as dexamethasone and furosemide.

3.11.10 Pulmonary Disorders

- Patients with COPD and asthma should receive bronchodilator prior to treatment.
- Theophylline should be discontinued prior to ECT because of risk of prolonged seizure.

3.12 Describe the Agents Used in Anesthesia in ECT?

RANZCP guidelines state that "general anaesthetic induction should be used. Typically used agents are propofol, thiopentone methohexital, etomidate and ketamine. The most commonly used agents, propofol and thiopentone, are potent anticonvulsants so the lowest effective anaesthetic dose should be used.

The addition of remifentanil or other short acting opiates enables the reduction in dose of the induction agent and thus potentially lowers seizure threshold.

This technique carries a risk that the patient is too lightly induced and may be aware of the procedure so careful monitoring is essential.

Ketamine has been used successfully as an anaesthetic agent in some clinics alone, or in combination with remifentanil, thiopentone or propofol (reducing the dose of ketamine to minimize the risk of psychotomimetic side-effects). It has less effect on the seizure threshold compared to propofol and thiopentone, enabling a lower ECT stimulus dose to be administered. Use of ketamine in ECT anaesthesia may lead to earlier improvement, but evidence to date suggests that overall improvement over the ECT course is not increased. If ketamine is used, it may prolong recovery time and can be associated with a psychomimetic emergence delirium with patients experiencing illusions, hallucinations and dissociative symptoms.

Side-effects of repeated dosing with ketamine should also be monitored; for example, cystitis, liver function abnormalities, dissociative symptoms and development of dependency".

- Propofol yields the shortest seizures by duration of 40% but has less cardiac toxicity than barbiturates.
- Etomidate and ketamine + propofol 1:1 seem to yield the seizures with best quality.
- Manual hyperventilation with 100% O_2 may increase the pO_2/pCO_2 ratio, which may be correlated with better seizure quality.
- Methohexital and thiopental (ultrashort barbiturates), shorten seizure duration.
- Ketamine is more cardiotoxic, and can produce emergent psychosis.

3.13 Muscle Relaxants

- Patients are not typically intubated, but mask ventilation with supplemental oxygen is used. Neuromuscular blocking agents are administered to prevent skeletal muscle contraction and possible injury during tonic-clonic activity. To decrease intensity of ictal motor movement
- Succinyl choline (suxamethonium) depolarizing agent is preferred 0.75–1.25 mg/kg
- Serious concern would be patients with homozygous pseudocholineestrase defiency since they will have prolonged apnea
- Avoid if patients had neuroleptic malignant syndrome (NMS), malignant hyperthermia. Can cause hyperkalemia, interaction with lithium and digoxin
- Atracurium or mevacurium (non-depolarizing) can be used instead of succinyl choline. They are also metabolized by pseudocholineestrase enzyme.
  - RANZCP suggests that a small dose of rocuronium, or vecuronium, may be administered before suxamethonium to minimize the suxamethonium-induced myalgia. The effect of rocuronium can be reversed using sugammadex, but the combination is presently very expensive.

3.14 Other Agents

- Anticholinergics: Decrease risk of bradycardia, asystole, salivation and aspiration related to. Examples are atropine or glycopyrrolate. Glycopyrrolate is preferred since it does not cross blood brain barrier BBB therefore less linked to delirium)
- Sympatholytics: Beta blockers (BB) as labetolol or esmolol ultrashort acting beta blockers can be given in some patients.
- Oxygen is important because of 200% increase cerebral demand during seizure
- Flumazenil (benzo agonist) reverse action of benzo for people on high levels of benzo [9, 10].

3.15 What Are the Contraindications of ECT?

There are no absolute contraindications. However, it is considered a high-risk procedure for patients with increased intracranial pressure, space-occupying cerebral lesion, recent myocardial infarction, recent cerebral hemorrhage or stroke, vascular aneurysm, retinal detachment, and pheochromocytoma. Attention should also be paid to patients with high anesthetic risk [9].

3.16 What Are the Adverse Effects of ECT?

- Muscle pain: usually due to the fasciculation reaction to succinylcholine. Usually worse initially; can pre-medicate with ibuprofen.
- Headache—tension-type, usually mild and does well with Tylenol or NSAID
- Nausea—some patients may experience this.
- Fatigue.
- Acute postictal confusional state.
- Anterograde memory dysfunction, AMD.
- Retrograde memory dysfunction, RMD.
- <7% of bipolar patients can switch to manic.
- Clenching of the jaw (remove dentures, use soft bite block).

3.17 Postictal Confusion

- All patients have this to some degree. Initial disorientation and confusion will subside within 10–20 min, and typically resolve within the hour.
- Few will develop marked agitation and restlessness or "emergent delirium." Midazolam 1-4 mg IV can be used.

3.18 Anterograde Memory Dysfunction (AMD)

- Impaired ability to record new memories
- Worse immediately after ECT, and subsides within days to weeks
- More marked after a course of ECT than a single maintenance treatment
- Anterograde and retrograde memories are variably affected. Anterograde memory changes generally return to normal or may be improved compared to pre-ECT levels within 2–4 weeks.

3.19 Retrograde Memory Dysfunction (RMD)

- The most common persistent adverse effect of ECT.
- Impaired memory from the pre-ECT period
- Most often limited to the weeks or few months before the start of ECT. "Last in is first out."
- The vast majority of patients consider such gaps acceptable given the benefits.
- Most patients have gaps in the memory of events that occurred before the treatment, and retrograde amnesia may extend back several months or years.
- The memory of autobiographical information is less affected by ECT than the memory of events of an impersonal nature.
- Although retrograde amnesia often improves during the first few months after ECT, for many patients, recovery is incomplete, with prolonged amnesia regarding events that occurred close to the time of treatment.
- Retrograde memory changes, including autobiographical impairment, are more likely with BT placement and can persist for weeks to months after ECT. It is also possible that long-term autobiographical memory impairment may persist permanently [11].
- Preexisting cognitive impairment is predictive of amnesia after ECT, and amnesia is more likely in older adults. Variations in ECT technique (e.g., right unilateral electrode placement with ultrabrief pulse width) can reduce the incidence and severity of retrograde amnesia substantially [9].

3.20 What Factors Are Associated with Delirium or Cognitive Impairment Post-ECT?

Some authors suggested that catatonic feature, cerebrovascular disease, Parkinson's disease, older age, dementia, bitemporal electrode placement, high stimulus intensity, or longer seizure length are associated with an increased risk of post-ECT delirium. Moreover, dexmedetomidine and ultrabrief pulse ECT seem to have preventive effects of post-ECT delirium [12].

3.21 What Are the Autonomic Nervous System Changes that Occur While Delivering the Electric Stimulation in ECT?

- Parasympathetic stimulation then sympathetic stimulation then parasympathetic stimulation.
- Parasympathetic response through vagal nucleus: bradycardia, hypotension or sinus asystole, and bronchoconstriction. Avoid by giving anticholinergics

- Sympathetic stimulation lead to tachycardia, increase blood pressure, increase myocardial oxygen demands, ventricular arrhythmia, transient ischemic changes in susceptible individuals (risk diminished by premedication and O_2). Absent in missed seizures which leads to unopposed parasympathetic stimulation.
- Parasympathetic stimulation: arrhythmias, bradycardia, premature ventricular contractions or sinus arrest.

3.22 What Are the Stimulus Characteristics in ECT?

The ECT stimulus depends on several characteristics, including electrode placement and stimulus parameters that describe the electrical pulse (e.g., shape, width, and amplitude) and the pulse train (e.g., frequency, directionality, polarity, and duration). ECT machines are designed to adjust the pulse width, frequency, and duration.

Initially, the summary dose metric was described by the total energy of the stimulus train (in joules, J) and then later replaced by the total charge (in millicoulombs, mC) which is the current description.

Modern ECT devices, such as the MECTA Spectrum (MECTA Corp., Tualatin, OR) and the Thymatron System IV (Somatics LLC, Lake Bluff, IL), produce trains of rectangular, constant-current pulses with alternating polarity, as listed in Fig. 3.1.

The brief pulse is characterized by

(a) *Amplitude* (the current strength during the pulse) reported in milliamperes (mA)
(b) *Pulse width* (PW, the duration of each pulse) and reported milliseconds (ms)
(c) Frequency (pulse pairs per second both positive and negative) and reported in hertz (Hz)
(d) *Duration of the stimulus* reported in seconds (s)

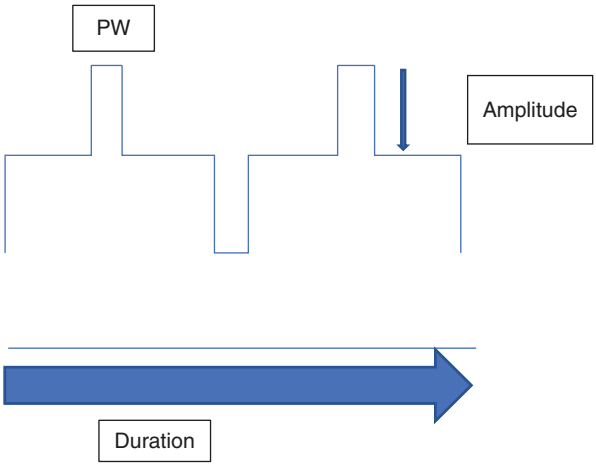

Fig. 3.1 Brief pulse. *PW* pulse width

3.23 List the Equations Used in ECT?

Number of pulses = (train duration) × 2 × (pulse-pair frequency) = (train duration) × (pulse frequency)

Charge = (current amplitude) × (PW) × 2 × (pulse-pair frequency) × (train duration)

Charge = current × duration at peak pulse amplitude

Charge = current × (pulse width × #of pulses/second × duration of the entire train)

Energy = (charge) × (current amplitude) × (dynamic impedance)

Energy = $current^2$ × dynamic impedance × duration@ppa/1000

- MECTA; Medcraft B25 doses by energy, fixed current
- Thymatron: higher peak current with EEG monitoring

3.24 What Are the Problems Associated with Sine Wave in ECT?

- Sine wave practice stopped many years ago because of the severe cognitive impairment associated with it. Sine wave had been replaced by brief pulse.
- Brief pulse is recommended because of rapid rise and fall and the typical pulse width is similar to the neuroelectric activity of the brain [9]

3.25 Describe the Selection of the Dosing of the Electric Stimulus in ECT?

The ECT dose is measured in millicoulombs of charge delivered; the dose administered must be sufficient to induce seizure activity. You can deliver fixed current or fixed voltage. Most centers deliver fixed current.

Generalized seizure with appropriate duration is suggested for therapeutic response. Barley suprathreshold stimulus are diminished in efficacy and marked suprathreshold level associated with severe cognitive side effects.

One approach in selecting the ECT dose is called seizure threshold titration. It involves giving progressively higher doses during the initial ECT session until the seizure threshold (ST) is reached, and then selecting a dose at 500% above the seizure threshold equivalent of six times the ST in unilateral treatment or 1.5 × ST in bilateral treatment.

Another accepted approach involves the use of an age-based dosing algorithm in bilateral treatment, although this technique has some limitations, since age accounts for only a small percentage of the variance in the seizure threshold.

Table 3.1 ECT dosage parameter setting for age-based titration

Age	Pulse width (ms)	Frequency (Hz)	Duration (s)	Total energy (J)
15	1	30	1.75	14.8
20	1	30	2.25	19
25	1	30	3	24.3
30	1	30	3.5	29.6
35	1	35	3.5	34.5
40	1	35	4	39.4
45	1	40	4	45.1
50	1	40	4.5	50.7
55	1	50	4	56.3
60	1	35	6	59.1
65	1	65	3.5	64.1
70	1	45	5.5	69.7
75	1	45	6	76
80	1	45	6.5	82.4
85	1	40	7.5	84.5
90	1	40	8	90.1
95	1	45	7.5	95
100	1	45	8	101.4

Some authors criticized the use of a "summary metric" (charge) to describe the dose of ECT. They provide theoretical and empirical evidence that stimulus parameters (pulse amplitude, shape, width and time frequency, directionality, polarity, and duration) exert unique neurophysiological effects. Electrode size has been shown to influence the physiological response; therefore, the optimal dosing paradigms remain to be determined, and will depend on more than the oversimplified "summary metric" of charge (Table 3.1) [9].

3.26 Describe the Impedance or Resistance in ECT?

- Skin can be a source of dynamic impedance encountered during ECT. Dynamic impedance decreases when the stimulation voltage of ECT increases. "One of the causes of such changes is the mechanism of electroporation of the skin, which is the phenomenon where the membrane permeability to ions and macromolecules is increased when exposed to a high electric field. In other words, the skin conductivity changes with the applied electric field or the stimulation voltage" [13].
- Very important measure, vary from patient to patient and from treatment to treatment

- Primary source is the SCALP
- High impedance: poor contact with the skin
- Low impedance: too close electrodes or gel or sweat forms short circuit and non pass to brain tissue
- Higher for women than man
- Higher for unilateral than bilateral
- Inversely proportional to electrode size big electrodes, low resistance
- Most common cause for high static impedance is failure to connect electrodes to cable then insufficient preparation of the scalp gel or too little pressure

3.27 How to Select an ECT Administration Technique or Protocol?

RAZNCP states that there is a range of valid treatment approaches, and no single "protocol" for administering ECT. The treatment approach needs to be individualized to the patient, their disorder, and response to ECT. The choice of ECT technique will be dependent on the balance of effectiveness, need for speed of recovery, and relevance of possible cognitive adverse effects.

The critical consideration is the combination of dosing, electrode placement, pulse width, session frequency, concomitant medication, and anesthetic approach. The treatment approach should be selected based on the needs of the individual patient and characteristics of the illness episode.

3.28 Describe the Different Electrode Placement Locations in ECT?

The electrode placements commonly in use are right unilateral (RUL), bitemporal (BT), and bifrontal (BF). There are also reports of the use of left anterior right temporal (LART). The relative efficacy of each is dependent on dose relative to the individual's seizure threshold. Right unilateral placement may be selected to reduce the burden of cognitive side effects particularly with small pulse width, whereas bitemporal placement carries the highest risk of cognitive side effects but may be selected if the right unilateral positions are unlikely to be effective. Some authors suggest that bifrontal placement is associated with less cognitive side effects than bitemporal placement.

It is also suggested that BF ECT has less impact on the cardiac rhythm (during the stimulus) than other forms of ECT.

RANZCP guidelines mentioned that psychiatrists considering the use of ultrabrief bilateral ECT should be aware of the limited evidence base and relatively low efficacy of this form of ECT.

The guidelines also mentioned that ultrabrief RUL ECT causes fewer cognitive effects than brief-pulse RUL ECT; these treatments also generally require more treatments over a longer period and in 25–50% of patients, this treatment may not lead to significant clinical improvement and there may be a need to switch to an alternative form of ECT. In general, the choice of electrode placements should be made on a case-by-case basis.

3.29 Describe Some of the Research Findings on the Relationship Between ECT Pulse Width and its Antidepressant Effect?

Increased pulse width is linked to more cognitive side effects.

The effect of electroconvulsive therapy (ECT) performed with ultrabrief pulse (UBP) stimulation with 0.25–0.3 ms has been found inferior to brief pulse (BP) 0.5–0.1 ms ECT in various studies [14].

A meta-analysis concluded that BP RUL ECT was significantly more efficacious in treating depression than UBP RUL ECT and required fewer treatment sessions but showed significantly more cognitive side effects in all cognitive domains examined (global cognition, anterograde learning and recall, retrograde memory). UBP had a lower remission rate [15].

Some authors suggested that pulse width of 0.5 ms or less (0.3 ms or 0.25 ms) should be considered ultrabrief (UB) RCT and pulse width above 0.5 should be considered brief ([9, 16].

3.30 What Are the Regular Procedures in ECT?

- NPO from midnight.
- Essential medications given with sips of water.
- Patient attends ECT suite *greeting*.
- Nurses attach cardiac monitor and O_2 saturation monitors.
- Anesthetist starts intravenous administration.
- Once asleep, EEG leads are attached, and electrodes applied after site preparation.
- Anesthetist continues to oxygenate, and inserts bite pad, saying “ready.”
- Psychiatrist says “treating” and delivers the stimulus.

Fig. 3.2 ECT machine

- Button is held until the beep stops.
- Seizure is observed, and note made of motor endpoint, EEG endpoint, and character of motor activity.
- Patient begins to wake up, and airway and oxygen supported until they are breathing on their own.
- Anesthetist decides when monitors can be discontinued.
- Patient's position is changed to the recovery position and then moved to the recovery room.
- Vitals and mental state are assessed and then back to their unit usually within a half-hour (Fig. 3.2).

3.31 How to Monitor the Seizure in ECT?

The electroencephalogram is monitored during ECT to confirm seizure activity and to document seizure duration.

Evidence of seizure motor activity is monitored. This technique involves the placement of a tourniquet around one of the patient's ankles before the administration of the muscle relaxant so that the potential for muscle contraction in the foot is maintained. It is monitored because EEG may be unreliable with artifacts.

Oxygen saturation and cardiac rhythm are monitored during the procedure.

EKG: Cessation of tachycardia is often a reasonable approximation of seizure end.

Some authors suggest that adequate seizure is 20 s motor response and 25 s EEG response. Data is lacking therefore clinical response is important.

Ictal EEG response can be helpful because it reflects the brain action and it is 10–20 s longer than motor response (which may not be observed) and prolonged seizure may be detected only by EEG.

The ictal EEG below starts after the electric stimulation with peri-ictal activity.

Then recruitment which is a very rhythmic activity of low-to-moderate amplitude then goes to polyspike activity, then termination, and postictal suppression.

3.32 Example of EEG Response (Fig. 3.3)

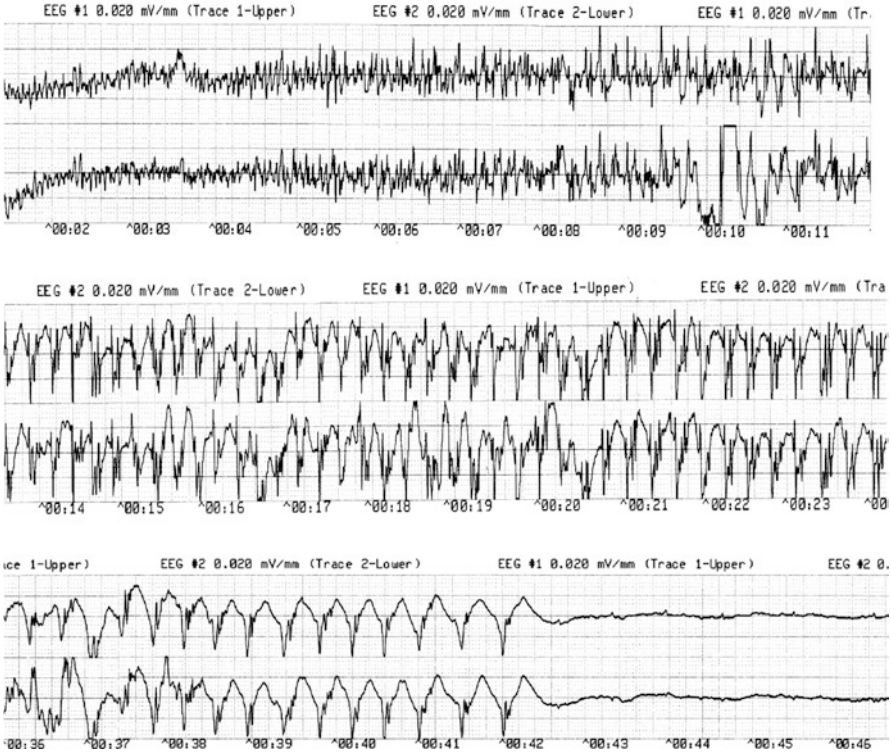

Fig. 3.3 EEG response

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Chapter 4
Mood Stabilizers

4.1 Introduction

Bipolar disorder is a severe and disabling mental illness characterized by periods of elevated expansive or irritable mood (mania or hypomania), depression, and mixed episodes. It affects 1–2% of the population worldwide, transcending nationality, ethnicity, and socioeconomic status. Lithium and other mood-stabilizing treatments do not cure mood disorders but can reduce the frequency, severity, and duration of relapses and improve long-term stability.

Bipolar disorders are classified mainly into bipolar I in which there is at least one manic episode with or without depressive episodes. In bipolar II, there should be at least one hypomanic episode plus depression. Other types are suggested.

Mood stabilizers for bipolar mania are lithium and valproate and for bipolar depression are lithium and lamotrigine ([1, 2]).

People living with BD experience significant functional impairment. Many domains are affected including work, physical health, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, independence, identity, and academic achievements.

4.2 Is Bipolar Disorder (BD) Underdiagnosed or Overdiagnosed?

According to the canadian network for mood and anxiety treatments (CANMAT) guidelines there are common situations when BP is underdiagnosed and others when it is overdiagnosed.

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The most frequent misdiagnosis happens when depressed patients come for the treatment of depressive symptoms and may not recall periods of hypomania or mania, or may not interpret them as being a problem.

BD may be overdiagnosed in patients presenting with symptoms of borderline personality disorder, substance-use disorder (SUD), and attention-deficit hyperactivity disorder (ADHD). Patients with these conditions often get misdiagnosed with BD. These conditions also are often comorbid with BD, which makes the diagnosis of this condition often challenging.

4.3 What Are some of the Guideline Recommendations for the Treatment of Acute Mania?

First-line therapy includes several agents with comparable efficacy (small-to-medium effect size). Approximately 50% of patients will respond to monotherapy with significant improvement in manic symptoms within 3–4 weeks. Lithium, divalproex, quetiapine, asenapine, aripiprazole, paliperidone (for doses >6 mg), and risperidone are all recommended as first-line treatment options and they have level 1 evidence. Carbamazepine, olanzapine, ziprasidone, and haloperidol also have level 1 evidence for efficacy but they are downgraded to second-line options due to safety/tolerability risks with these agents.

4.3.1 Combination Therapy

Combination therapy is preferred to monotherapy. Combination with the atypical antipsychotics quetiapine, olanzapine, aripiprazole, risperidone, or asenapine and lithium or divalproex can be a valuable treatment option.

If no response is observed within 2 weeks with therapeutic doses of antimanic agents, and other contributing factors for nonresponse are excluded, then switch or add-on strategies should be considered. The next step is to switch to or add on an alternate first-line agent except paliperidone and ziprasidone due to lack of evidence for additional efficacy.

Second-line choices include ECT, monotherapy with olanzapine, carbamazepine, ziprasidone, and haloperidol or combination therapy with olanzapine plus lithium or divalproex. The combination of lithium and divalproex is also recommended as a second-line choice.

Third-line options for the treatment of acute mania include monotherapy with chlorpromazine, clonazepam, or monotherapy or adjunctive therapy with clozapine. Combination treatments are with carbamazepine or oxcarbazepine, haloperidol, and repetitive transcranial magnetic stimulation (rTMS) in the right prefrontal cortex at 110% motor threshold.

4.4 ICD 10 Classification of Mood Disorders

F30	Manic Episodes
F30.0	Hypomania
F30.1	Mania without psychotic symptoms
F30.2	Mania with psychotic symptoms
*.20	with mood-congruent psychotic symptoms
*.21	with mood-incongruent psychotic symptoms
F30.8	Other manic episodes
F30.9	Manic episode, unspecified
F31	Bipolar affective disorder
F31.0	Bipolar affective disorder, current episode hypomanic
F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms
F31.2	Bipolar affective disorder, current episode manic with psychotic symptoms
*.20	with mood-congruent psychotic symptoms
*.21	with mood-incongruent psychotic symptoms
F31.3	Bipolar affective disorder, current episode mild or moderate depression
*.30	without somatic syndrome
*.31	with somatic syndrome
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
*.50	with mood-congruent psychotic symptoms
*.51	with mood-incongruent psychotic symptoms
F31.6	Bipolar affective disorder, current episode mixed
F31.7	Bipolar affective disorder, currently in remission
F31.8	Other bipolar affective disorder
F31.9	Bipolar affective disorder, unspecified
F32	Depressive Episode
F32.0	Mild depressive episode
*.00	without somatic syndrome
*.01	with somatic syndrome
F32.1	Moderate depressive episode
*.10	without somatic syndrome
*.11	with somatic syndrome
F32.2	Severe depressive episode without psychotic symptoms
F32.3	Severe depressive episode with psychotic symptoms
*.30	with mood-congruent psychotic symptoms
*.31	with mood-incongruent psychotic symptoms
F32.8	Other depressive episodes
F32.9	Depressive episode, unspecified

F33	Recurrent depressive disorder
F33.0	Recurrent depressive disorder, current episode mild
*.00	without somatic syndrome
*.01	with somatic syndrome
F33.1	Recurrent depressive disorder, current episode moderate
*.10	without somatic syndrome
*.11	with somatic syndrome
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
*.30	with mood-congruent psychotic symptoms
*.31	with mood-incongruent psychotic symptoms
F33.4	Recurrent depressive disorder, currently in remission
F33.8	Other recurrent depressive disorders
F33.9	Recurrent depressive disorder, unspecified
F34	Persistent mood (affective) disorders
F34.0	Cyclothymia
F34.1	Dysthymia
F34.8	Other persistent mood (affective) disorders
F34.9	Persistent mood (affective) disorder, unspecified
F38	Other mood (affective) disorders
F38.0	Other single mood (affective) disorders
.00	Mixed affective episode
F38.1	Other recurrent mood (affective) disorders
.10	Recurrent brief depressive disorder
F38.8	Other specified mood (affective) disorders
F38	Unspecified mood (affective) disorder

Individual mood stabilizers that are the recommended treatment of bipolar affective disorder

4.5 Lithium

4.5.1 What Is the History of Using Lithium in Bipolar Disorder?

Lithium was discovered in 1817. Because lithium urate is highly soluble, lithium salts were used later that century for the treatment of gout. It was suggested that the beneficial effects obtained from the healing spas such as the waters at Lourdes may have been because they contain higher than usual levels of lithium. But recent analyses have not supported this theory.

In 1949, John Cade (1929–1996), an Australian psychiatrist, serendipitously initiated a new era in psychiatric treatment by using lithium carbonate to treat mania.

He was studying the effect of lithium urate on the renal function of guinea pigs. Coincidentally, he observed that the substance had a calming effect. Subsequently, he used lithium salts in the treatment of acute mania in humans, and published his observations in the Medical Journal of Australia, 1949 ([3, 4].

4.5.2 What Is the Mechanism of Action and Pharmacokinetics of Lithium?

The mechanism of action of lithium on the CNS remains unclear. It is rapidly absorbed, has a small volume of distribution, and is excreted in the urine unchanged (there is no metabolism of lithium). Lithium modifies sodium transport in nerve and muscle cells. It alters the metabolism of neurotransmitters, specifically catecholamines and serotonin. It may alter intracellular signaling via second messenger systems by inhibition of inositol monophosphate. This inhibition, in turn, affects neurotransmission through the phosphatidylinositol secondary messenger system. Lithium also decreases protein kinase C activity, which alters genomic expression associated with neurotransmission. Lithium appears to increase cytoprotective proteins and possibly activates neurogenesis and increases gray matter volume.

The half-life of lithium is 18–30 h. It has lower absorption on an empty stomach.

Lithium ions interact with the transport of cations across the neuron membrane, resulting in a smaller resting voltage gradient. This has been interpreted as evidence that lithium makes the neuron "less excitable" and less liable to discharge. There is evidence that lithium modulates glutamate release, and the actions of the enzymes inositol monophosphate and glycogen synthase kinase-3 [5, 6].

4.5.3 What Are the Psychiatric Indications for Lithium?

- Treatment of acute mania (3–4 days for therapeutic effect)—75% response rate (lithium is usually not sufficient as the sole agent and is usually supported by an antipsychotic); best for euphoric mania—may not be effective for rapid cycling and mixed episodes
- In acute treatment-resistant depression, as augmentation of antidepressants
- Prophylaxis in schizoaffective disorder (usually in combination with an antipsychotic)
- Reported to have a beneficial effect in reducing suicide risk
- Prophylaxis of mania
- Prophylaxis of depressive episodes (both bipolar and unipolar)
- Prophylaxis in impulse control disorders (the evidence is not strong) [3].

4.5.4 What Is the Dosing and Monitoring Requirements for Lithium?

4.5.4.1 Preliminary Workup

Lithium may impact thyroid (hypothyroidism) and renal function (nephrogenic diabetes insipidus; rarely nephritis, renal failure) and the ECG (benign, reversible depression of the T wave). It is necessary to have baseline thyroid and renal function estimates and ECG in addition to CBC, Ca, and electrolytes.

Assess the reproductive plans of females.

4.5.4.2 Blood Concentrations of Lithium

Measuring the blood level of lithium is very important. CANMAT guidelines suggest that lithium monitoring is particularly important for those who may be nonadherent to treatment. Measurement of serum levels should be repeated at the trough point, which is approximately 12 h after the last dose. It should be done about 1 week after the first dose, then weekly in the first month, at least once a month in the next 3–6 months, and every 3–6 months thereafter. Blood sampling should be done reliably at a consistent interval (optimally about 12 h after the last dose of the day) and about a week after any dose change.

The target serum level for lithium in acute treatment is 0.8–1.2 mEq/L (0.4–0.8 mEq/L in older adults) while in maintenance treatment, serum levels of 0.6–1 mEq/L may be sufficient; serum levels should be obtained about 5–7 days after the most recent dose titration. It is important to avoid toxic levels as these are associated with an increased risk of kidney damage in the long term.

Some patients may require higher concentrations, whereas for others, lower concentrations may suffice and can be better tolerated.

Other blood tests: Blood levels of creatinine and BUN (for kidney function), sodium, potassium, calcium, thyroid, and parathyroid hormones should be measured before starting the treatment and at least once or twice a year thereafter.

Factors that Can Alter Blood Levels

Fever above 38 °C (100.4 °F), dehydration, or diarrhea, or when a low-sodium diet is required (not recommended during lithium therapy). Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) is not recommended with lithium (acetaminophen/paracetamol is preferred for pain). ACE inhibitors, metronidazole, and thiazide diuretics should not be used with lithium.

4.5.4.3 Dosing

For acute treatment 600–1800 mg/day will be needed, usually given in divided doses, 2–4 times per day. Maintenance will require lower doses, around 900 mg/day.

Lithium remains unique in not being dosed adequately by the mg dose of drug given per day, but instead by achieving serum concentrations 10–14 h after the last dose taken (most stable range of the day) in the range of 0.5–1.0 mEq/L, while being aware that earlier, daily peak concentrations can be 2–3 times higher.

Low doses are required by the elderly and those with renal impairment.

It takes about 1–3 weeks for lithium to show the effects and remission of symptoms.

Safety is not established below age 12 [3].

4.5.5 What Patient Features Would Suggest Benefits of Lithium Therapy Versus Poor Response?

- Patients with typical bipolar disorder that includes an episodic clinical course before treatment
- Family history of the disorder
- Favorable response by a family member
- Lack of other co-occurring psychiatric illnesses
- Illness course sequence characterized by mania or hypomania followed by depression and then a stable or euthymic interval ("MDI" pattern) rather than the opposite (depression-mania-euthymic interval ("DMI"))

Moreover, as for all maintenance treatments, a favorable clinical response is associated with faithful adherence to the treatment regardless of current lack of symptoms, absence of early or current adverse life events, adult age at onset, good social support, and absence of substance abuse or other co-occurring psychiatric disorders including personality disorders.

4.5.6 Responsiveness to Lithium Has Been Inferior Among the Following

Patients with relatively complicated forms of bipolar disorder, such as with rapid cycling, psychotic features, co-occurring anxiety syndromes or substance abuse, depression-prone cases, or those following the DMI course pattern, and lithium is less effective in preventing recurrences of bipolar depression than mania [2].

4.5.7 What Are the Adverse Effects of Lithium?

- Nausea, vomiting, and diarrhea, with 35–45% of patients experiencing these side effects. It is particularly common during treatment initiation, or rapid dose increases. Gradual dose titration, taking the medication at bedtime, taking medications with food, and slow-release preparations may reduce nausea and other side effects. These adverse effects often settle after a few weeks. Other strategies to decrease them in the early stages include taking small doses four times per day, and moving to twice-daily doses at a later stage.
- Metallic taste.
- Weight gain.
- Cardiac: Bradycardia, flattened or inverted T waves, heart block, sick sinus syndrome, and risk of abnormal QT prolongation. Elderly are at high risk.
- Fine tremor: Experienced by up to 10% of those treated with lithium; propranolol is usually helpful.
- Hematologic: Leukocytosis and aplastic anemia.
- Cognitive: Complaints of slowing of thinking/poor memory/tiredness/lack of energy.
- Dermatological: Acne, psoriasis, eczema, hair loss, nail dystrophy, mucosal lesion, rash, and psoriasis may be made worse.
- Hypothyroidism: Lithium may substitute for iodine and interfere with the production of thyroid hormone. If lithium has been beneficial, add thyroxine. If lithium has been of no or little benefit, consider ceasing (the hypothyroidism is reversible) and commencing another mood stabilizer. Lithium may also cause hyperparathyroidism. Calcium should also be monitored.
- Nephrogenic diabetes insipidus (NDI) is an extreme form of interference with the action of antidiuretic hormone and reported in 20–40% of patients. Endocrinology consultation is appropriate. This condition corrects with the cessation of lithium therapy.
- More than 65% of patients on chronic lithium treatment will experience polyuria, which can cause impairment in work and daily functioning. This side effect is commonly underreported, unless it is directly inquired about. It may be irreversible, especially if the treatment has been prescribed for more than 15 years.
- Increased thirst and drinking of more fluid than previously.
- Disturbance of diabetes control may be a complication of lithium therapy, and adjustment of insulin dosage may be indicated.
- Some treatment guidelines explain that lithium has a well-recognized potential for renal toxicity, including nephrogenic diabetes insipidus (NDI), chronic tubulointerstitial nephropathy, and acute tubular necrosis. Long-term administration (i.e., 10–20+ years) is further associated with decreased glomerular filtration rate and chronic kidney disease. A chronic renal failure is observed in patients treated for more than 10–20 years. Its prevalence is estimated at 12% after 19 years of treatment. Some patients (0.5%) may reach end-stage renal disease. The major risk factor is the duration of exposure to lithium.

- Factors that may increase susceptibility to chronic renal failure include higher plasma lithium levels, multiple daily lithium doses (vs. once daily), concurrent medications (e.g., NSAIDs, ARBs, ACEIs, and diuretics), somatic illnesses (e.g., hypertension, diabetes mellitus, and coronary artery disease), and older age. Instances of lithium toxicity will also greatly increase the risk of renal dysfunction. Lithium use is associated with a twofold higher risk of chronic kidney disease in older adults (>66 years). While the overall risk for progressive renal failure is low, plasma creatinine concentrations and ideally estimated glomerular filtration rate (eGFR) for these patients should be measured at least every 3–6 months. Since 37% of patients aged >70 years have an eGFR <60 mL/min per 1.73 m^2, a strict eGFR cutoff for lithium discontinuation is difficult. The UK National Institute for Healthcare and Excellence (NICE) guidelines for chronic kidney disease (CKD) recommend nephrologist consultation if there is rapidly declining eGFR (>5 mL/min per 1.73 m^2 in 1 year, or >10 mL/min per 1.73 m^2 within 5 years), if the eGFR falls below 45 in two consecutive readings, or if the clinician is concerned [2, 7].

4.5.8 Lithium Toxicity

Toxicity occurs at high serum levels. In extreme cases, convulsions, acute renal failure, coma, and death may result. Toxicity can occur with intentional or unintentional overdose.

The most common cause is unintentional dehydration that may happen with excessive exercise in hot weather, urinary tract infection, kidney disease, concomitant diarrhea and vomiting, and drugs reducing renal clearance of lithium (predominantly thiazide diuretics, and anti-inflammatory drugs, including nonsteroidal anti-inflammatories).

Early signs

Nausea, vomiting, diarrhea, unsteady gait, clonus, mental confusion

Severe signs

Coarse tremor, abdominal pain, slurred speech, ataxia, stupor, delirium/coma, renal failure

Management includes immediate cessation of lithium, determination of blood level (interpreted with knowledge of the time of last ingestion), and medical review for dialysis and ICU admission if required. Treatment for lithium toxicity is primarily hydration and to stop the drug. Give hydration with normal saline, which will also enhance lithium excretion. Avoid all diuretics. If the patient has severe renal dysfunction or failure, or severely altered mental status, then start with hemodialysis [2, 7].

4.5.9 What Are Some of the Examples Where Lithium Should Not Be Used or Used with Great Caution?

4.5.9.1 Use in Medical Conditions

Lithium may not be used by patients who have or have had acute myocardial infarction, acute kidney failure, or certain rare disorders of heart rhythm. It can be used cautiously and with close medical monitoring with cardiac arrhythmia, reduced kidney function, psoriasis, myeloid leukemia, Addison's disease, hypothyroidism, and certain neurological disorders, including abnormalities of posture and movement, tremors, myasthenia gravis, and epilepsy. Lithium should be stopped 48–72 h before surgery requiring general anesthesia, and during periods of low fluid intake.

4.5.9.2 Use in the Elderly

At ages over 60 years, doses and blood levels of lithium are at the low end of the therapeutic range (e.g., 0.4–0.6 mEq/L). Undesirable effects in the elderly in addition to those already described can include confusion or worsening of cognitive functions, unsteady balance (ataxia), restless movements (akathisia), declining kidney function, hypothyroidism, possible worsening of diabetes, and leg swelling (peripheral edema).

4.5.9.3 Pregnancy

It is highly important that clinicians inform and advise women about the risks and benefits of remaining on lithium in pregnancy, if possible before pregnancy.

Lithium is used cautiously in pregnancy, with at least monthly monitoring of blood concentrations. If possible, lithium should be discontinued slowly or the dose lowered during the first trimester because of the association between lithium use and two- to threefold increase of significant congenital malformation. Ebstein's anomaly is a cardiac defect in infants associated with lithium treatment during pregnancy. Discuss risks and benefits of continuing, lowering, or interrupting lithium treatment during pregnancy and after childbirth with the treating doctor.

During the third trimester, lithium blood levels should be monitored weekly. It is not necessary to stop lithium before delivery.

Some authors recommend a high-resolution ultrasound with fetal anomaly scanning at 20 weeks. Ideally, delivery should take place in a specialized hospital where psychiatric and obstetric care for the mother is provided and neonatal evaluation and monitoring of the child can take place immediately after birth.

If a mother receives lithium during delivery, it is essential to monitor the infant for hypotonia and floppy baby syndrome for at least 48 h [2].

4.5.9.4 Postpartum

Most clinical guidelines discourage breastfeeding in women treated with lithium. The thyroid function of the newborn may be temporarily impaired. Lithium passes into the breast milk, and bottle feeding is recommended.

If lithium is discontinued during pregnancy, it should be restarted immediately after delivery, due to increased risk of relapses then. Target lithium levels should be relatively high (0.8–1.0 mEq/L) temporarily during the first month after delivery to minimize relapse risk, and checked twice weekly during the first 2 weeks after delivery. Do not breastfeed while taking lithium [2].

4.5.9.5 Discontinuation

Interrupting lithium should be done gradually and under medical supervision to avoid relapse into mania or depression, unless an acute medical problem requires rapid discontinuation under close medical supervision. Dose -reduction of lithium can be done safely by lowering the daily dose by 20–25% every 2 weeks [8].

4.5.10 What Are Some of the Key Points in Educating Patients on Lithium?

- Diuretics contraindicated.
- Drink 6–8 glasses of H2O daily (1500–3000 mL).
- Do not restrict sodium—4 to 5 g daily.
- Take with food.
- Report nausea, vomiting, diarrhea, or other side effects.
- Monitor blood levels as ordered.
- Monitor weight.
- Check renal and thyroid function.
- Do not take over-the-counter meds without consulting your doctor.
- Consider support group.
- Avoid excessive use of caffeine and colas.
- Monitor cardiac status.
- Driving and heavy machinery with caution.
- Avoid activities that cause sodium depletion.
- Use contraception if you are female in childbearing age.
- Lithium levels should be drawn 12 h after last dose.

4.6 Valproate (Divalproex Sodium)

Sodium valproate was initially marketed as an anticonvulsant. Following the success of carbamazepine as a mood stabilizer, sodium valproate was found to be effective.

In both acute mania and long-term maintenance, sodium valproate is as effective as lithium and carbamazepine. It may be superior to lithium in the treatment of rapid cycling and mixed mania. In comparison to lithium, sodium valproate treatment provides comparable medical costs, and clinical and quality-of-life outcomes.

Pharmacokinetics: T½ = 9–16 h.

4.6.1 What Is the History of Using Divalproex Sodium in Bipolar Disorder?

Beverly S. Burton in the USA was the first person who synthesized valproic acid in 1881. It was only used as an organic solvent at that time.

After WWII, valproic acid became a popular organic solvent in various industries in Western countries. It was commonly used as a diluent to solubilize other drugs.

In 1963, George Carraz and his colleagues working in Grenoble, France, studied the anticonvulsant activity of various khellin compounds. They used valproic acid as a diluent to dissolve the khellins. The results of their study showed that a correlation between anticonvulsant activity and different doses of the tested compound cannot be established but that the diluent has the anticonvulsant activity instead of the khellin derivatives. They recognized that all of the solutions containing valproic acid have to be effective anticonvulsants.

In Carraz' laboratory, the investigators showed that in animals, epileptic convulsions triggered by strychnine can be prevented by valpromide, not by valproate (Depakene®), another sodium-based derivative of valproic acid.

The first report of mood-stabilizing effects of valproate in patients with bipolar disorders appeared in 1966 in the French literature. Germany also independently discovered that valpromide has antimanic efficacy [4].

4.6.2 What Is the Mechanism of Action of Valproate?

The mode of action is uncertain. It may block sodium channels and potentiate gamma aminobutyric acid (GABA) effects on intracellular protein regulation. Animal studies show that sodium valproate is neuroprotective, protecting neurons against glutamate-induced excitotoxicity and promoting neurogenesis and neurite growth.

4.6.3 What Are the Suggested Psychiatric Indications for Valproate?

- Acute mania (patients with mixed affective disorder may do better than those with "pure" mania and in maintenance treatment for bipolar disorder and schizoaffective disorder)
- More effective at preventing mania than depression

4.6.4 What Is the Dosing and Monitoring Requirements for Valproate?

Before starting treatment

Check baseline labs (urine pregnancy, platelet counts, coagulation tests, liver function tests and blood count).

Ongoing monitoring

Platelet counts, coagulation tests, and liver function tests are recommended before initiating therapy and at least q6 months.

Dosing

The starting dose is 250–750 mg per day, in two divided doses. Dose can be increased every 2–3 days, depending on response and tolerance.

In acute mania, oral loading of 20 mg/kg can be given on the first day, to achieve rapid therapeutic levels. Patients who are not acutely manic may have difficulty tolerating this load. Usual max dosage: 60 mg/kg/day.

It is recommended that two consecutive serum levels be established in the therapeutic range during the acute phase for divalproex, and then measurement be repeated every 3–6 months or more frequently if clinically indicated. Blood should be drawn 12 h after the last dose.

The target serum level for divalproex is 350–700 mM/L (50–100 ug/mL) in the acute phase and should be obtained 3–5 days after the most recent dose titration. There is some evidence for a linear relationship between serum divalproex level and therapeutic efficacy in acute mania, with higher levels associated with greater efficacy.

No clear levels are suggested for maintenance treatment.

4.6.5 What Are the Adverse Effects of Valproate?

Headache (30%), somnolence (25%), fatigue (25%), tremor (10–25%), dizziness (25%), dyspepsia, nausea, diplopia, vomiting, diarrhea, abdominal pain, ataxia, nystagmus, weight gain, alopecia (6–12%) (reversible on discontinuation of valproate), cognitive impairment, and amnesia. Excessive weight gain plays an important

factor in valproate discontinuation and poor treatment adherence. New-onset oligomenorrhea or hyperandrogenism could happen more often in divalproex sodium users.

Pregnant females serve as important contraindication.

Contraindications to the administration of valproate due to the risk of fetal malformations: Valproate is believed to exert its teratogenic effect through inhibition of fetal histone deacetylase (HDAC), a key enzyme involved in the storage of DNA. Other contraindications to valproate include severe hepatic failure and hematological malignancies.

4.6.6 Warnings and Precautions

- Acute hemorrhagic pancreatitis.
- Agranulocytosis, thrombocytopenia.
- Hepatotoxicity, liver failure.
- Polycystic ovarian syndrome (mixed evidence).
- Suicidal behavior or ideation.
- Hypothermia.
- Multi-organ hypersensitivity, Stevens-Johnson syndrome (1:5000).
- Hyperammonemia and hyperammonemic encephalopathy: This condition is characterized by a raised plasma ammonia level, falling GCS, and vomiting and is thought to be attributable to the inhibition of urea cycling by valproate metabolites. Early treatment with L-carnitine has been shown to improve outcomes in patients with valproate-induced encephalopathy. It can be fatal.

4.6.7 Toxicity

Toxicity occurs with overdose and may take the form of heart block, coma, and death. Hemodialysis may be necessary to eliminate the drug.

4.6.8 What Are the Recommendations of Valproate Use in Pregnancy and Lactation?

Category D evidence of risk to human fetus.

Sodium valproate is associated with a 1% risk of neural tube defects, such as spina bifida and lower cognitive test scores in children when taken during the first trimester of pregnancy. Other congenital malformations have been reported, and the overall risk may be as high as 11%. Some authors suggest that the risk to the unborn

is unacceptable. Sodium valproate can cause significant harm to the fetus; the presence of a "fetal valproate syndrome" characterized by specific facial characteristics, cardiovascular and limb abnormalities, and valproate "is associated with the highest rate of major congenital malformations."

Sodium valproate passes into the breast milk at less than 10% of the serum concentration. The effects on the nursing child are uncertain, but the risk is considered to be low [9, 10].

4.6.9 What Are Some of the Drug Interactions with Valproate?

Amitriptyline (TCA), fluoxetine (SSRI), and erythromycin may increase valproate concentration, possibly by inhibiting valproate metabolism.

Aspirin may elevate the free fraction of valproate, by displacing from protein-binding sites, thereby increasing the effects on the central nervous system.

Valproate can displace diazepam, carbamazepine, and warfarin, thereby increasing the activity of these drugs.

The AEDs carbamazepine, eslicarbazepine acetate, ethosuximide, lamotrigine, methsuximide, phenobarbital, phenytoin, primidone, tiagabine, and topiramate enhance the elimination of valproic acid and decrease plasma concentrations.

Plasma valproic acid concentrations are also decreased by several nonepilepsy drugs including amikacin, cisplatin, diflunisal, doripenem, efavirenz, ertapenem, imipenem, meropenem, methotrexate, naproxen, oral contraceptives, panipenem, rifampicin, and ritonavir. By contrast, the AEDs clobazam, felbamate, and stiripentol and the nonepilepsy drugs bupropion, chlorpromazine, cimetidine, erythromycin, guanfacine, isoniazid, lithium, sertraline, and verapamil inhibit the metabolism of valproic acid and increase plasma concentrations ([6, 11, 12]

4.6.10 What Are the Possible Predictors of Response to Valproate?

(a) Rapid cycling illness
(b) Mixed episodes
(c) Closed head injury
(d) EEG abnormalities
(e) Learning disability
(f) Later age of onset
(g) Shorter duration of illness

4.6.10.1 Comment on the Treatment of Mania with Valproate in Children and Adolescents?

Recent Cochrane review suggested that there is evidence that valproate is an efficacious treatment for acute mania in adults when compared to placebo. By contrast, there is no evidence of a difference in efficacy between valproate and placebo for children and adolescents. Valproate may be less efficacious than olanzapine in adults, and may also be inferior to risperidone as a monotherapy treatment for pediatric mania [13].

4.7 Lamotrigine (LAM)

Lamotrigine is one of the most recent anticonvulsants to be found to have mood-stabilizing effects. Lamotrigine is a first-line drug in the treatment of bipolar depression.

4.7.1 What Is the History of Using Lamotrigine in Bipolar Disorder?

Lamotrigine was synthesized in the early 1980s at Wellcome Research Laboratories (Beckenham, Kent, England) as part of a program to develop new antiepileptic agents that could be better tolerated than those available at that time. Lamotrigine was finally approved in 1990 in Ireland for use in epilepsy and in 1994 in the USA.

The first author who produced scientific data on the efficacy of lamotrigine in bipolar disorder was Richard H. Weisler (University of North Carolina Chapel Hill School of Medicine at Chapel Hill, North Carolina, USA) in 1994 [4].

4.7.2 What Is the Mechanism of Action of Lamotrigine?

Mechanism of action: voltage-gated sodium and calcium channel blockade, antiglutamate and anti-aspartate, antikindling, weak 5-HT3 antagonism, and neuroprotective (Fig. 4.1).

4.7.3 What Are the Psychiatric Indications for Lamotrigine?

- Sound evidence supports the use of LAM for acute bipolar depression and prophylaxis, treatment-resistant schizophrenia, treatment-resistant obsessive-compulsive disorder, post-traumatic stress disorder, depersonalization disorder, and affective dysregulation and behavioral dyscontrol domains of borderline personality disorder.

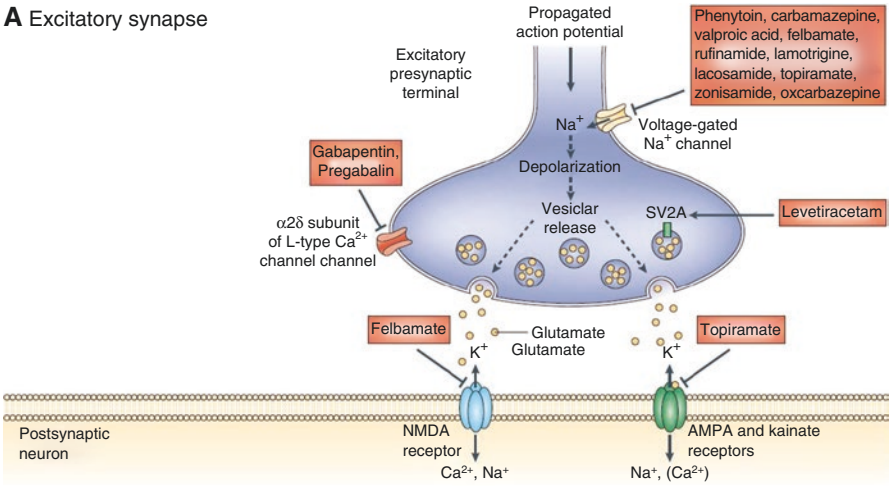

Fig. 4.1 Excitatory synapse (Source: Nature.com/reviews/drugdisc, January 2010, volume 9)

- Less compelling evidence is present for use in behavioral and psychological symptoms of dementia and neuropsychiatric sequelae of traumatic brain injury.
- No evidence supports use in autism spectrum disorder or acute unipolar depression [14].

4.7.4 What Are the Potential Advantages of Lamotrigine?

It is weight-neutral and procognitive, and possibly does not interfere with sexual functioning. Lamotrigine is not associated with excessive changes in body mass [14].

4.7.5 Describe the Pharmacokinetics of Lamotrigine?

The pharmacokinetics of lamotrigine are linear.

Absorption: After oral ingestion, lamotrigine is rapidly absorbed, with a T_{max} of 1–3 h and a bioavailability of >95%. It is 66% bound to plasma proteins and its V_d is 0.9–1.3 L/kg.

Metabolism: Lamotrigine is extensively metabolized in the liver, primarily by UGT1A4, but UGT1A1 and UGT2B7 also contribute, to form 2-N (76%) and 5-N glucuronides (10%).

The $t_{1/2}$ is 15–35 h in adults.

4.7.6 What Is the Dosing and Monitoring Requirements for LAM?

Initiation: Weeks 1 and 2: 25 mg daily at bedtime. Weeks 3 and 4: 50 mg daily. Week 5: 100 mg daily. Week 6: 200 mg daily. Dosage will need to be adjusted for patients taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate. Estrogen-containing oral contraceptives increase the metabolism of lamotrigine such that target dose may need to be increased.

Typical target dosage: 150–200 mg daily. No published data support greater efficacy in bipolar disorders above 200 mg/day.

Ongoing monitoring: Typically drug levels are not measured.

Restarting therapy after discontinuation: If lamotrigine has been withheld for 3 days, restart according to initial dosing recommendations.

Nonurgent discontinuation: Decrease by 50% per week.

The current reference range for lamotrigine in plasma is 2.5–15 mg/L (1). The drug is secreted into saliva where concentrations reflect nonprotein-bound concentration in plasma; thus, saliva can be used as an alternative matrix for lamotrigine TDM [11].

4.7.7 What Are the Adverse Effects, Warning, and Contraindications of Lamotrigine?

Dizziness (31%), headache (29%), double vision (24%), nausea (18%), somnolence (14%), blurred vision (11%), unsteadiness/ataxia (10%).

Approximately 10% of patients being treated with lamotrigine will experience a non-serious rash, with 0.3–1% developing a serious rash with mortality such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), although for those initiated on a dose of 25 mg with a gradual titration increasing the dose by 25 mg biweekly, the risk of developing serious rash may be as low as 0.02% or 1 in 5000 [2].

Both SJS and TEN form a continuum of disease, with SJS being characterized by mucosal blistering lesions with 10% cutaneous desquamation while TEN is defined by a 30% detachment of the skin. The pathogenesis of these type IV hypersensitivity reactions remains to be fully elucidated; however it is postulated that aberrant lymphocytic activity plays a crucial role in their etiology [15].

The Food and Drug Administration (FDA) is warning that lamotrigine (Lamictal) for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's infection-fighting immune system. This can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune system. HLH typically presents as a persistent

fever, usually greater than 101°F, and it can lead to severe problems with blood cells and organs throughout the body such as the liver, kidneys, and lungs.

Warnings and Precautions: Suicidal ideation, blood dyscrasias, multi-organ failure, HLH, aseptic meningitis, withdrawal seizures.

Black Box Warning: [1] Aseptic meningitis and [2] for serious, life-threatening rashes requiring hospitalization and discontinuation of treatment (Stevens-Johnson syndrome at approx. 1:1000 to 2000). The risk of rash may also be increased by coadministration of lamotrigine with Depakote (valproic acid) exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine. Nearly all cases of life-threatening rashes associated with lamotrigine have occurred within 2–8 weeks of treatment initiation. Lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related.

Contraindications: Known hypersensitivity reaction to the product. Lamotrigine has as a relative contraindication in patients with Brugada syndrome, largely due to its ability to inhibit cardiac sodium channels at high doses. Clinicians should therefore be aware of the risks of lamotrigine in patients with a familial history of sudden death [16].

4.7.8 List Some of the Drug-Drug Interactions of Lamotrigine?

The medications that inhibit the metabolism of lamotrigine and therefore increase blood lamotrigine concentrations include aripiprazole, isoniazid, and sertraline felbamate and valproic acid, which is particularly potent.

Drugs that induce lamotrigine metabolism and decrease lamotrigine blood concentrations include acetaminophen, atazanavir, ethambutol, olanzapine, oral contraceptives (estrogen component), rifampicin, ritonavir carbamazepine, eslicarbazepine acetate, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide.

Carbamazepine decreases the level of LAM by 40–50% (oxcarbazepine-inducing effect is almost half that of carbamazepine). Estrogen-containing oral contraceptive pills decrease LAM level by up to 64% [11].

4.7.9 What Are the Features Suggestive of Malignant Rash with Lamotrigine?

Purpuric and tender rash.

Widespread and confluent rash.

Associated fever, lymphadenopathy, malaise, anorexia, or pharyngitis.

Prominent involvement of neck and upper trunk.

Involvement of eyes, lips, mouth, or other mucous membranes.

4.7.10 What Are the Recommendations of Lamotrigine Use in Pregnancy and Lactation?

Pregnancy: Category C; North American Antiepileptic Drug Pregnancy Registry (NAAED) suggests an increased incidence of cleft lip and/or cleft palate following first-trimester exposure. Lamotrigine has not been established as safe during pregnancy.

Breastfeeding: Enters breast milk/not recommended. American Academy of Pediatrics Committee on Drugs considers the use of lamotrigine "of concern" in breastfeeding [10].

4.8 Carbamazepine

Carbamazepine has a structure similar to the TCA, imipramine. It was initially developed as an antidepressant, in the 1950s, but was found to be useful and marketed as a treatment of epilepsy and neuropathic pain. Over recent decades carbamazepine has been used in bipolar disorder.

4.8.1 What Is the Mechanism of Action of Carbamazepine?

The mode of action is uncertain; the blockade of voltage-dependent sodium channels with reduction of membrane excitability may play a role. Recent work suggests the modulation of prefrontal dysfunction (Schneider et al. 2014).

4.8.2 Describe the Pharmacokinetics Carbamazepine?

The pharmacokinetics of carbamazepine are nonlinear because of autoinduction that completes within 3 weeks and can result in a threefold increase in elimination.

Absorption: After oral ingestion, the absorption of carbamazepine is erratic and variable with T_{max} being formulation dependent (range 0.5–9.0 h), bioavailability being 75–85%, and V_d being 0.8–2.0 L/kg.

Carbamazepine is 75% bound to plasma proteins and its pharmacologically active metabolite, carbamazepine-epoxide, is 50% protein bound.

Metabolism: Carbamazepine is extensively metabolized in the liver, primarily by CYP3A4, to carbamazepine-epoxide, which accumulates in plasma and is pharmacologically equipotent to carbamazepine. Carbamazepine-epoxide is further metabolized, by epoxide hydrolase, to the pharmacologically inactive 10,11-diol, which is eliminated in urine partly unchanged and partly as a glucuronide conjugate.

The $t_{1/2}$ is 8–20 h in adults, whereas in children and the elderly, it is 10–13 h and 30–50 h, respectively. The $t_{1/2}$ of carbamazepine-epoxide is ~34 h.

4.8.3 What Are the Psychiatric Indications for Carbamazepine?

Acute mania (usually in combination with an antipsychotic).

Prophylaxis in bipolar disorder—particularly where there is "rapid cycling," failed response to lithium, inability to tolerate side effects of other mood stabilizers, and a "mixed affective state".

Schizoaffective disorder.

Depressive phase of bipolar disorder.

Other indications:

- Trigeminal neuralgia and other pain syndromes.
- Epilepsy.
- Impulsivity.
- Alcohol, benzodiazepine withdrawal.

4.8.4 What Is the Dosing and Monitoring Requirements for Carbamazepine?

4.8.4.1 Preliminary Workup

A preliminary ECG, a full blood count, and liver function test should be done before treatment is commenced. These are often repeated every 2 weeks for the first few months, and then every 3–6 months.

Assess the reproductive plans of females. Risk to the unborn is greater than with carbamazepine than lithium.

Carbamazepine can decrease the blood concentration of other medications including the oral contraceptive. If there is evidence of breakthrough bleeding, another form of birth control should be considered.

4.8.4.2 Dose and Monitoring

The starting dose is 100–200 mg/day, and increased over 1–2 weeks. This slow start reduces the risk of side effects (including rash). The dose/blood level should be checked after a few weeks, because the drug induces metabolizing liver enzymes which may cause a reduction in the blood level, after a stable initial period. The effective dose is usually in the range of 600–1200 mg/day.

The optimal therapeutic carbamazepine plasma concentration for mood stabilization is yet to be established. Some psychiatrists use the levels recommended for epilepsy prophylaxis (17–50 μmol/L). Others increase the dose until side effects intervene, and then reduce the dose such that the side effects are tolerable.

4.8.5 Why Therapeutic Drug Monitoring of Carbamazepine Can Be Useful?

To ensure that the levels are not in the toxic range.

To check for treatment adherence.

Carbamazepine has nonlinear pharmacokinetics (due to autoinduction).

Carbamazepine efficacy and adverse effects can in part be attributable to its pharmacologically active metabolite carbamazepine-epoxide.

Carbamazepine is the target of many drug-drug pharmacokinetic interactions resulting in large differences between individuals in the dose-to-plasma concentration relationship.

There is considerable interpatient variability in the carbamazepine concentration that is associated with an optimal therapeutic response (which may in part be due to the variation in carbamazepine-epoxide concentration). In practice, both carbamazepine and carbamazepine-epoxide concentrations should be monitored.

The current reference range for carbamazepine in plasma is 4–12 mg/L, whereas that of carbamazepine-epoxide is up to 2.3 mg/L. Carbamazepine and carbamazepine-epoxide may also be determined in saliva, where the salivary concentration of each is similar to the pharmacologically active, nonprotein-bound free concentration in plasma.

There is no established relationship between efficacy and serum level; thus, monitoring for serum carbamazepine levels may be done at 6–12 monthly intervals and as clinically indicated.

Patients who are treated with concurrent carbamazepine or other hepatic enzyme-inducing agents should have serum levels of all psychotropic medications monitored, particularly in cases of inadequate response or nonresponse, to determine whether efficacy has been compromised because of reduced serum levels [11].

4.8.6 What Are the Adverse Effects, Warning, and Contraindications of Carbamazepine?

4.8.6.1 Adverse Effects

Adverse effects are more common during the initiation phase; they often subside over time. They include dizziness, dry mouth, dyspepsia, ataxia, sedation, nausea/vomiting, and diplopia. Weight gain is less common than with several other agents.

Hematological: Carbamazepine is also associated with increased risk of rash and SJS, especially in the first 8 weeks of therapy. Carbamazepine may be a risk factor for leukopenia, although this finding is not robust. This side effect is generally reversible with dose reduction or discontinuation. There is also some concern about rapidly developing bone marrow suppression resulting from hypersensitivity, particularly in older patients.

Carbamazepine has been associated with suppression of the white blood cells (which is considered clinically unimportant) and rarely with potentially fatal, severe blood dyscrasias, including agranulocytosis, pancytopenia, and aplastic anemia.

Hepatic: Carbamazepine has been associated with benign elevations of hepatic transaminases and rarely with potentially fatal non-dose-related idiosyncratic hepatic failure.

Cardiac: Carbamazepine slows intracardiac conduction, and is relatively contraindicated in heart block.

Dermatological: Rashes (benign) occur in 5–15% of patients. However, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrosis have been reported. In view of the potentially fatal outcome, the recommendation is that carbamazepine be discontinued if rash occurs.

Hair loss (reversible on discontinuation of carbamazepine).

Endocrine: Carbamazepine can exert antidiuretic effects, resulting in clinically insignificant hyponatremia in up to 40% of patients.

4.8.6.2 Carbamazepine Lab Changes

- Mild reversible leukopenia
- Potential for cardiac conduction delay (similar to TCAs)

4.8.7 Toxicity

Overdose can be fatal: atrioventricular block, coma, seizure, and respiratory depression. Early signs include nystagmus, tremor, ophthalmoplegia, and myoclonus.

4.8.8 What Are the Possible Dose-Related Adverse Effects?

Sedation *(dose related)*
Cognitive impairment *(possibly dose related)*
Balance and motor-ocular disturbances *(possibly dose related)*
Weight gain: unknown
Nausea and vomiting: unknown
Hyponatremia: SIADH and/or increased sensitivity to ADH
↑ Liver enzymes: unknown

Leukopenia: unknown

PR interval prolongation: ↓ activity of cardiac voltage-dependent sodium channels

SJS/TEN: immunological mechanisms

Induction of Endogenous Compounds

Osteoporosis: induction of vitamin D metabolism

Thyroid disturbances: induction of thyroid hormone metabolism

Hyperlipidemia: induction of enzymes involved in lipid metabolism

Sexual disturbances: induction of enzymes involved in sexual hormone metabolism

4.8.9 What Are the Important Drug Interactions of Carbamazepine?

Induction of P450 system, incl. autoinduction. Universal inducer

Medications that inhibit the metabolism of carbamazepine and thus increase carbamazepine blood concentrations include clobazam and stiripentol, clarithromycin, cimetidine, ciprofloxacin, danazol, diltiazem, erythromycin, fluconazole, fluoxetine, flurithromycin, grapefruit juice, haloperidol, isoniazid, isotretinoin, josamycin, ketoconazole, metronidazole, miconazole, nefazodone, nelfinavir, nicotinamide, ponsinomycin, propoxyphene, ritonavir, ticlopidine, trazodone, troleandomycin, verapamil, and viloxazine. Cytochrome P450 3A4 inhibitors can inhibit carbamazepine metabolism.

Medications that induce carbamazepine metabolism and decrease carbamazepine concentrations include felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide, efavirenz, probenecid, rifampicin, St. John's Wort, and theophylline.

Carbamazepine may increase the metabolism of psychotropic drugs (valproate, lamotrigine, atypical antipsychotics olanzapine, quetiapine, risperidone, paliperidone, haloperidol, aripiprazole, and anxiolytics), and general medical drugs (analgesics, antibiotics, and steroids). Do not combine with sertraline, quetiapine, and lurasidone.

Some drugs do not alter carbamazepine concentrations per se, but can increase carbamazepine-epoxide concentrations, through the inhibition of epoxide hydrolase, and may cause typical carbamazepine toxicity. These drugs include brivaracetam, valproic acid, zonisamide, amoxapine, loxapine, and quetiapine [11].

4.8.10 What Are the Recommendations of Carbamazepine Use in Pregnancy and Lactation?

Use during pregnancy is associated with a 1% incidence of spina bifida. Craniofacial defects and developmental delay have been reported.

Carbamazepine passes into the breast milk, but this appears to be of little clinical importance. The baby should be monitored for jaundice, sedation, and weight gain [10].

4.8.11 What Is the Suggested Role for Pharmacogenomics Studies in Reducing Adverse Events of Carbamazepine?

Recent publication suggests "that pharmacogenomic studies have been pivotal in the identification of strong genetic risk associations between specific HLA class I alleles (*HLA-B*15:02*, *HLA-A*31:01* and *HLA-A*24:02*) and a range of AED-induced cutaneous (cADRs). The FDA recommendation of AED pre-treatment genetic screening for *HLA-B*15:02* in individuals of Asian descent led to a worldwide decreased incidence of carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

There is also evidence to suggest *HLA-A*31:01* genetic screening would be both cost effective and reduce disease burden. The concerning aspect of pre-treatment screening programs is that the HLA risk variants identified thus far are neither necessary nor sufficient (<5% PPV), thereby eliminating these individuals from otherwise efficacious treatment. Clearly, there is an immediate unmet clinical need to improve the predictability of AED-induced cADRs using novel biomarkers that extend beyond the HLA alleles" [17].

4.9 Oxcarbazepine

4.9.1 What Is the Mechanism of Action of Oxcarbazepine?

Blockade of voltage-sensitive sodium and calcium channels [18].

4.9.2 What Are the Psychiatric Indications for Oxcarbazepine?

There is some evidence in bipolar disorder as an alternative to carbamazepine but it is licensed for both monotherapy and adjunctive treatment of partial seizures with or without secondary generalization in patients aged 6 years and older [18].

4.9.3 Describe the Pharmacokinetics and Therapeutic Drug Monitoring (TDM) of Oxcarbazepine

Oxcarbazepine is a prodrug for the pharmacologically active 10-hydroxycarbazepine, which exhibits linear pharmacokinetics. After oral ingestion, oxcarbazepine is rapidly absorbed so that T_{max} for 10-hydroxycarbazepine is 3–6 h. Its bioavailability is 100% and its V_d is 0.75 L/kg. Plasma protein binding of 10-hydroxycarbazepine is 40%.

Oxcarbazepine is rapidly metabolized, by cytosolic aryl ketone reductase, to racemic 10-hydroxycarbazepine (also known as S-licarbazepine and monohydroxy derivative). The conversion of oxcarbazepine to 10-hydroxycarbazepine is stereoselective and concentrations of the S-enantiomer (which has slightly greater pharmacological activity) are a little higher than those of the R-enantiomer. 10-Hydroxycarbazepine is metabolized primarily by glucuronidation (51%) and it also undergoes hydroxylation by CYP isoenzymes to form a dihydrodiol metabolite (28%).

The $t_{1/2}$ of 10-hydroxycarbazepine in adults is 8–15 h.

Oxcarbazepine is rapidly metabolized to 10-hydroxycarbazepine resulting in very low, and often not detectable, blood concentrations; therefore it is important to monitor only 10-hydroxycarbazepine concentrations.

TDM is a valuable adjunct in individualizing treatment. The current reference range for 10-hydroxycarbazepine in plasma is 3–35 mg/L. 10-Hydroxycarbazepine is secreted into saliva and there is good correlation with plasma concentrations; thus, saliva can be used as an alternative matrix for 10-hydroxycarbazepine TDM [11].

4.9.4 What Is the Dosing and Monitoring Requirements for Oxcarbazepine?

Monotherapy in BPD: Initial dose 600 mg/day, divided into two doses; increase every 3 days by 300 mg/day; maximum dose 2400.

Adjunctive: I—600 mg/day divided, usually recommended 1200 mg/day.

Dose: 1.5 times higher than CBZ.

Converting: Titrate up over 2–4 weeks, concomitant Rx titrate down over 3–6 weeks.

Converting from CBZ—overnight possible.

Monitoring of Na required particularly in the first 3 months of treatment and elderly.

4.9.5 What Are the Adverse Effects, and Warnings of Oxcarbazepine?

They include dizziness, headache, somnolence, fatigue, and nausea.

Less common adverse effects include rash, vomiting, leukopenia, and parkinsonism.

- 25% of patients who have rash on CBZ will have it on OXCZ.
- Hyponatremia is more common and severe in patients taking OXC rather than CBZ. It is more common when SSRI or diuretics are used concomitantly.
- It may exacerbate narrow-angle glaucoma [18].

4.9.6 List Some of the Drug-Drug Interactions of Oxcarbazepine?

Carbamazepine, phenobarbital, and phenytoin enhance its metabolism, resulting in a 15–35% reduction in plasma 10-hydroxycarbazepine concentrations, whereas verapamil can also decrease plasma 10-hydroxycarbazepine concentrations by 20% and viloxazine can increase the concentrations by 11%. Do not combine with valproate due to complex DDI.

It mildly induces CYP450 3A4 and is not a self-inducer.

It has a tricyclic chemical structure, and is not recommended with MAOIs (+14 days).

It decreases the level of contraceptives [11, 19].

4.9.7 What Are the Specific Management Strategies of Adverse Effects of Mood Stabilizers?

The table reflects the opinion of Murru A and colleagues in their publication called Management of Adverse Effects of Mood Stabilizers (Table 4.1) [20, 21].

Table 4.1 Adverse effects of mood stabilizers

Cognitive side effects	Consider testing and add functional remediation program as adjunctive treatment
Acne	For mild-to-moderate acne treatment, topical salicylic acid, oral antibiotics, hormonal antiandrogens for female patients and oral isotretinoin, as well as other combination treatments
Alopecia	Discontinuation of the drug causing it (e.g., DVP, LMT, or CBZ) results in reversal of changes over time; hair growth may happen naturally
Stevens-Johnson syndrome or toxic epidermal necrolysis	Discontinuation of the drug; prescreening of the involved HLA alleles before starting treatment
Psoriasis	Topical steroids, keratolytics, vitamin D analogs, oral retinoids, combined psoralen and ultraviolet A therapy, and methotrexate. In case of a treatment-resistant psoriasis, Li discontinuation may be considered and the patient may be switched to another mood stabilizer
Parathyroid dysfunction	Calcium (and eventually PTH) should be added to routine lab tests
Thyroid dysfunction	Regular monitoring of serum TSH and FT4 in all patients receiving Li is recommended at intervals of 3–4 months for women over the age of 45, and every 6–12 months for all others. Patients already receiving treatment for hypothyroidism prior to starting lithium therapy, serum TSH, and FT4 should be checked after 4–8 weeks of Li treatment initiation. Substitution treatment is often indicated
Polycystic ovary syndrome	It is important that clinicians consider the association of PCOS in women treated with VPA, as is associated with metabolic disorders (such as obesity, glucose intolerance, hyperinsulinemia, and dyslipidemia) and endometrial carcinoma in the long term. PCOS should be monitored in women with VPA monotherapy/polytherapy. A careful multispecialist approach is required for evaluating the risks and benefits of this treatment in the presence PCOS and related conditions
Hyperammonemia	Symptoms generally reverse with abrupt discontinuation of valproate
Gastrointestinal	Clinician should monitor the liver function before prescribing high doses of an antiepileptic drug or before combining different antiepileptic drugs. Elder populations appear to be at increased risk of presenting with liver AEs *Nausea*, *diarrhea*, and *vomiting* are common and generally mild adverse symptoms related to Li treatment. Dose adjustment of Li may improve them, but they can also be symptoms of Li intoxication, so that dosing Li in serum has to be considered
Pancreatitis	Mild pancreatitis can be reversed with discontinuation of VPA
Hematological Starting CBZ treatment	Before CBZ initiation, a complete blood cell count should be performed and followed for the first 12 weeks of treatments in patients with a low or near-lower normal limit WBC count. CBZ should only be discontinued if the WBC count falls below $3000/mm^3$, when the neutrophil count is below $1000/mm^3$, or when infection occurs with any degree of leukopenia. Folic acid can reduce the development of some blood cell abnormalities linked to CBZ in children at doses of 1 mg/day irrespective of the patient's weight, but no optimal dose has been suggested in adults

Table 4.1 (continued)

Thrombocytopenia	In patients on VPA treatment, close monitoring of full blood count is required in women, particularly at serum levels above 80 mg/mL. This may be particularly important in older patients, for whom VPA dose reduction may be warranted
Serious rash	Most commonly the immediate discontinuation of the drug resolves the condition
Systemic erythematosus lupus-like syndrome	This condition, induced by treatment with CBZ, is fully reversible after CBZ discontinuation
Metabolic syndrome and weight gain	A constant monitoring of weight, BMI, and blood pressure for patients taking valproate is recommendable. Anyway, given the early age at which cardiovascular diseases manifest among people with BD, a systematic screening for and treating cardiovascular risk factors in this population should be performed irrespectively of the treatment used. For BD patients with comorbid obesity, first-line treatments should be approved medications with a neutral or negative profile on weight change. Unluckily, many effective treatment options are associated with weight gain. Behavioral weight management strategies should be implemented with these patients
Neurologic Hyperammonemic encephalopathy	In case of VPA-induced hyperammonemic encephalopathy, there is consensus on the need for withdrawal of the drug, and several approaches have been successfully used, namely supplementation with carnitine, lactulose, or neomycin and protein restriction. Ammonia levels greater than 400 μmol/L or significant clinical symptoms secondary to hyperammonemia require rapidly reducing blood ammonia levels with hemodialysis
Tremor	Beta-adrenergic blockers (e.g., propranolol) and vitamin B6 are effective in reducing tremor. As selective serotonin reuptake inhibitors may worsen the tremor and present with unclear benefits in most BD patients, their possible switch to other options should be carefully assessed
Renal	Close monitoring of the glomerular filtration rate is an essential part of Li safety measures. Older patients should be closely monitored and other concomitant risk factors for kidney impairment identified If polyuria-polydipsia syndrome happens, lithium serum levels should be maintained lower than 0.8 mEq/L with reintegration of liquids. If it is severe, diuretics as amiloride may be added (indomethacin in resistant cases). Real-time lithium levels can be obtained with a special point-of-care device which may help to close-monitor those patients that need extra caution
Erectile dysfunction	A 6-week, double-blind randomized clinical trial in men affected by bipolar disorder and with Li-related erectile dysfunction concluded that adjunctive treatment with aspirin 240 mg/day may improve this sexual AE. Symptomatic treatment with PDE5 inhibitors (sildenafil, tadalafil, vardenafil) seems to be the best option based on clinical experience

Case Vignette A 23-year-old woman with newly diagnosed bipolar disorder presents to your clinic to discuss treatment options. Which of the following has the LEAST evidence supporting its efficacy in bipolar disorder?

(a) Lamotrigine
(b) Modafinil
(c) Oxcarbazepine
(d) Risperidone
(e) Valproic acid

Answer
- (b) All of the agents **except modafinil** have been shown to be effective in various phases of BP disorder.

Rule Out the Other Options
- **Lamotrigine** has antidepressant properties and thus may be effective in **BP depression** and in preventing depressive episodes.
- **Oxcarbazepine** and **valproic acid** are **anticonvulsants** effective for **manic** and **mixed episodes**.
- **Risperidone** (like other atypical antipsychotics) is effective for mania, mixed episodes, depression, and maintenance treatment.

4.10 Topiramate

Topiramate has several possible mechanisms of action. It may stabilise the membranes of neurons by blocking sodium channels, block glutamate receptors, and increase the effect of gamma-aminobutyric acid (GABA) receptors. The practical usefulness of topiramate in clinical practice acute bipolar disorder remains questionable.

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Chapter 5
Antipsychotics

5.1 Introduction

The history of APs goes back to 1952 with the development of chlorpromazine. Several classes of first-generation antipsychotics (FGAs) were developed from 1952 to 1975 such as aliphatic phenothiazine (chlorpromazine, methotrimeprazine, trifluprom azine), piperazine phenothiazine (fluphenazine, trifluoperazine, perphenazine), piperidine (thioridazine, pipotiazine), butyrophenones (haloperidol), thioxanthenes (flupenthixol, zuclopenthixol), dihydroindolones (molindone), dibenzoxazepines (loxapine), and diphenylbutylpiperidine (pimozide).

5.2 What Are the Common Indications for Antipsychotics?

1. Schizophrenia and schizoaffective disorders
2. Acute mania
3. Major depressive disorder with psychotic features
4. Delusional disorder
5. Severe agitation
6. Tourette disorder
7. Borderline personality disorder: when patients develop psychotic symptoms
8. Dementia and delirium
9. Secondary psychotic disorder: in some cases of severe psychosis secondary to substance use, antipsychotics can be used to control agitation symptoms
10. Other indications such as Huntington's disease

J. Sadek, *Clinician's Guide to Psychopharmacology*,
https://doi.org/10.1007/978-3-030-60766-1_5

5.3 First-Generation (Typical or Conventional) Antipsychotics

5.3.1 Describe the Dopamine Hypothesis of Schizophrenia?

The earlier theory of schizophrenia etiology is related to increased release of dopamine and was called dopamine hypothesis. FGAs block dopamine receptors.

There are four dopamine pathways in the brain involved in schizophrenia:

1. The **mesocortical: involved in** negative symptom, cognitive symptoms, and executive functioning. The pathway extends from the ventral tegmental region of the midbrain to the frontal cortex. Those side effects of the antipsychotics known as the "secondary" negative symptoms are thought to be due to the further (drug-induced) disruption of this pathway.
2. The **mesolimbic involved in positive symptoms: It** extends from the ventral tegmentum to the nucleus accumbens—a limbic system structure. From the accumbens, impulses then pass to other components of the limbic system and temporal lobe structures (including the auditory cortex). Increased activity of this system compensating for the underactive mesocortical pathway produces hallucinations and other positive symptoms.
3. The **nigrostriatal** pathway is involved in movement disorder. It extends from the substantia nigra of the midbrain to the basal ganglia as part of the extrapyramidal system (EPS), which is involved in movement. APs block that pathway producing EPSE.
4. The **tuberoinfundibular** pathway is involved in prolactin elevation. It extends from the hypothalamus to the anterior pituitary. APs disrupt that system leading to elevation of serum prolactin (Pridmore 2018).

5.3.2 What Is the Mechanism of Action and Classification of Typical Antipsychotics?

Typical neuroleptic drugs such as haloperidol have been shown to produce their antipsychotic action by blockade of D2 receptors in the mesolimbic system, suggesting increased dopaminergic activity in these terminal areas of the ventral tegmental dopamine (DA) neurons. Striatal D2 receptor antagonism is the critical element in the EPSs produced by these drugs [1].

The antipsychotic effect of the first-generation antipsychotics FGAPs can be mainly attributed to strong antagonism of dopamine D_2 receptors. Potency is correlated with dopamine receptor occupancy. Dopamine receptor occupancy can be a predictor of antipsychotic response and adverse effects as follows: a striatal D_2 occupancy of 65–70% is associated with antipsychotic effects, and an occupancy of more than 80% increases the risk of EPS. A threshold between 65 and 80% D_2 occupancy would represent the therapeutic window with minimal risk of EPS.

Some patients however can show a different response, either by responding below this threshold or by having no response despite adequate receptor blockade. In addition to strong D_2 antagonism, each compound has distinct effects on other neuronal receptors [D_1 receptor, [alpha]$_1$ receptor, serotonergic (5-HT), histaminic, and muscarinic antagonism], attributing to variable adverse effects. The table below explains the adverse effects related to different receptor effects.

First-generation antipsychotics (FGAs) can be categorized based on the potency:

High potency

Medium potency

Low potency

Examples of high-potency antipsychotics include haloperidol, fluphenazine, perphenazine, and pimozide.

Medium-potency antipsychotics include loxapine and zuclopenthixol.

Low-potency antipsychotics include chlorpromazine and methotrimeprazine.

5.3.3 What Are the Major Adverse Effects of FGA Antipsychotics?

First-generation antipsychotics are associated with numerous adverse effects and the severity can be linked to the blockade of certain transmitters (see Table 5.1 below).

High-potency APs have the most significant extrapyramidal side effects (EPSE) and prolactin elevation while low-potency ones have the least EPSE and prolactin elevation.

EPSE include dystonia (first day), akathisia (first week), rigidity (first month), and parkinsonism. Tardive dyskinesia could happen with prolonged treatment.

Increased serum prolactin levels along with galactorrhea, breast enlargement, amenorrhea, impotence in men, and anorgasmia in women are known adverse effects due to the action of the dopamine receptor block in the tuberoinfundibular tract. It is also linked to osteoporosis and infertility.

Anticholinergic adverse effects include dry mouth, constipation, blurred vision, urinary retention, difficulty with micturition, and ejaculatory failure. Anticholinergic delirium is a toxic confusional state in extreme cases.

Table 5.1 Receptor type and adverse effects

Receptor type	Adverse effects
Dopamine (D_2)	EPS, prolactin elevation (galactorrhea, amenorrhea, gynecomastia)
Alpha$_1$	Orthostatic hypotension, sexual dysfunction
Muscarinic (M_1)	Urinary retention, constipation, blurred vision, dry mouth, tachycardia
Histamine (H_1)	Sedation, weight gain

Increased appetite and sedation are due to H1 histamine block. They are more common with low-potency APs such as chlorpromazine and methotrimeprazine (Nozinan) than high-potency APs. Chlorpromazine is the most sedating, while fluphenazine, haloperidol, and pimozide are less sedating.

Alpha-adrenergic blockade produces postural hypotension, cardiac arrhythmias, and impotence.

ALL APs also lower seizure threshold, and chlorpromazine and thioridazine are more epileptogenic than others. Haloperidol can cause abnormal heart rhythm, ventricular arrhythmia, and torsades de pointes. Other APs may cause prolongation of OTc interval, prolonged atrial and ventricular contraction, and other cardiac conduction abnormalities.

Thioridazine has a black box warning for sudden cardiac death.

Low-potency APs such as chlorpromazine commonly cause orthostatic hypotension. This adverse effect caused by alpha-adrenergic block usually occurs when starting treatment, and patients often develop a tolerance. It is important to avoid treating hypotension with epinephrine.

Blood-related adverse effects such as leukopenia, thrombocytopenia, and blood dyscrasia are rare side effects of treatment with FGAs.

Allergic dermatitis and photosensitivity can occur more with chlorpromazine. Chlorpromazine is also associated with blue-gray skin discoloration and benign pigmentation of the lens and cornea. Thioridazine can cause retinal pigmentation, which can continue even after discontinuing the drug.

Neuroleptic malignant syndrome is a rare but fatal adverse effect that can occur at any time during treatment with DRAs. The onset of symptoms is over 24–72 h with increased temperature, severe muscular rigidity, confusion, agitation, elevation in white blood cell count, elevated creatinine phosphokinase levels, elevated liver enzymes, myoglobinuria, and acute renal failure. The antipsychotic should be immediately discontinued, and dantrolene 0.8–2.5 mg/kg every 6 h up to 10 mg per day is the drug of choice. Lorazepam 2 mg q 2–4 h can be lifesaving before reaching the ICU. There should be adequate hydration, cooling, and close monitoring of vital signs and serum electrolytes. Though the risk of neuroleptic malignant syndrome is more with first-generation antipsychotics, second-generation antipsychotics are also known to cause this adverse effect.

Other adverse effects include fatigue, weight gain, nausea, insomnia, dizziness, anxiety, and tremor [2].

5.3.4 Describe the Extrapyramidal Side Effects with High-Potency Typical Antipsychotics?

Dystonia occurs secondary to D2 receptor blockade in the EPS. These can appear on the first day of treatment and can take various forms of involuntary muscle spasm, particularly involving the jaw, tongue, neck, and eyes.

A severe form is **oculogyric crisis**—in which the neck arches back and the eyes roll upward.

A potentially dangerous form is **laryngospasm. One of the early signs of laryngospasm** may be the patient's voice becoming higher pitched.

Treatment: Oral or intramuscular injection of an anti-ACh agent—such as benztropine (2 mg).

Akathisia usually occurs in the first week of treatment and involves either a mental and/or motor restlessness. Mental restlessness presents as increasing distress and agitation. Akathisia could progress from looking restless, nervous, impatient, and uncomfortable to needs to move at least one extremity to move one extremity almost constantly if sitting, or stamp feet while standing to inability to sit down for more than a short period of time to moving moves or walking constantly.

Treatment: Adding of lorazepam or diazepam or propranolol 10 mg BID to TID, and mirtazapine, has also been used in akathisia.

Rigidity (cogwheel) and parkinsonism usually occur some weeks after commencement of treatment. Rigidity could progress from some resistance to passive movements to difficulty to move the limb to marked resistance with definite difficulty to move the limb to limb nearly frozen.

Gait changes may progress with decreased pendula arm movements, stiff posture (neck, back), small step (shuffling gait), festination or freezing on turning, and finally inability to walk.

Postural stability could be affected with hesitation when pushed to retropulsion to inability to stand without assistance.

Expressive automatic movements (facial mask/speech) could progress from decrease in facial expressiveness to rare or no spontaneous smile, decreased blinking, voice slightly monotonous to marked facial mask, inability to frown, and slurred speech to severe facial mask with unintelligible speech.

Bradykinesia with difficulty in initiating movements and tremors can be evident.

Treatment: Lowering the dose of the antipsychotic (if possible) and adding an anticholinergic agent.

Abnormal movements and tics may happen during the course of the treatment.

Dyskinetic movements may involve:

- Lingual movements (slow lateral or torsion movement of tongue), occasional partial or complete protrusion of the tongue
- Jaw movements (lateral movement, chewing, biting, clenching)
- Bucco-labial movements (puckering, pouting, smacking)
- Truncal movements (involuntary rocking, twisting, pelvic gyrations)
- Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)
- Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)
- Other involuntary movements include swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc.

Tardive dyskinesia (TD) usually happens after years of treatment. It manifests as continuous choreoathetoid movements of the mouth and tongue, frequently

with lip smacking, and may also involve the head, neck, and trunk. TD may continue after cessation of the antipsychotic and could get worse with ECT. Tetrabenazine has emerged as a potential treatment.

Extrapyramidal symptom rating scale (ESRS) has a reasonable measurement of these side effects [3].

5.3.5 What Are the Possible Contraindications of First-Generation Antipsychotics?

First-generation antipsychotics are contraindicated in the following situations:

1. History of severe allergy
2. With anticholinergic medication like scopolamine or use of phencyclidine
3. Severe cardiac abnormalities
4. History of seizure disorder
5. Narrow-angle glaucoma or prostatic hypertrophy
6. History of or ongoing tardive dyskinesia
7. Comatose state
8. Lewy body dementia except in rare cases [4]

5.3.6 List Some of the Warning and Precautions with FGAs?

Neuroleptic malignant syndrome, agranulocytosis, priapism, sudden cardiac death, cerebrovascular accident, tardive dyskinesia, lowered seizure threshold, orthostatic hypotension, QTc prolongation, hyperprolactinemia, body temperature dysregulation.

Black box warnings: Increased mortality in elderly patients with dementia-related psychosis.

5.3.7 Describe the Suggested Monitoring Prior to and during Treatment with FGAs?

Prior to starting treatment: Assess baseline weight, waist circumference, blood pressure, fasting plasma glucose, fasting lipid profile, CBC (for baseline WBC), EKG (to assess QTc), and AIMS test.

Ongoing monitoring: EKG at target dose (at least once to assess QTc). At 4 weeks: weight. At 8 weeks: weight. At 12 weeks: weight, blood pressure, fasting plasma glucose, and fasting lipid profile. Quarterly thereafter: weight. Annually/ongoing: Waist circumference, weight, blood pressure, fasting plasma glucose, fasting lipid profile, and AIMS test.

5.3.8 *What Are the Dosing Recommendations of Typical Antipsychotics* (Table 5.2)*?*

5.3.9 *Compare FGA Equivalent Doses?*

Antipsychotic equivalent doses of oral daily dose (range, wider range = less certainty) (Table 5.3).

Table 5.2 Dosing recommendations of typical antipsychotics

First-generation agents	Recommended dose range	Chlorpromazine equivalents (mg/day)[b]	Half-life (h)[c]	Potency
Chlorpromazine	300–1000	100	6	Low
Methotrimeprazine	50–1000	70	16–78	Low
Fluphenazine	5–20	2	33	High
Mesoridazine	150–400	50	36	High
Perphenazine	16–64	10	10	High
Thioridazine	300–800	100	24	High
Trifluoperazine	15–50	5	24	High
Haloperidol	5–20 range 1–30 mg	2	18	High
Loxapine	30–100	10	4	Medium
Pimozide	2–20	2	29	High
Zuclopenthixol	15–60	15	12–28	Medium
Flupenthixol	3–6, range 3–12	3	26–36	High

Table 5.3 FGA equivalent doses

Chlorpromazine	100 mg
Fluphenazine	2 mg (1.25–5 mg)
Levomepromazine	not established
Pericyazine	24 mg
Perphenazine	8 mg (7–15 mg)
Prochlorperazine	15 mg (14–25 mg)
Promazine	100 mg (50–200 mg)
Thioridazine (to be discontinued)	100 mg (75–104 mg)
Benperidol	2 mg
Trifluoperazine	5 mg (2–8 mg)
Haloperidol	3 mg (1–5 mg)
Flupentixol	2 mg
Zuclopenthixol	25 mg (25–60 mg) up to 150 mg
Pimozide	2 mg (1–3 mg)

5.3.10 Long-Acting Injections of FGAs (Table 5.4)

5.4 Individual Medication Profile

5.4.1 Flupenthixol

5.4.1.1 How to Start and Maintain Patients on Oral Flupenthixol?

Start 1 mg TID

After 2–3 days, increase by 1 mg.

Usual dose 3–6 mg up to 12 mg daily in divided doses. Usually BID. Sometimes night dose can cause insomnia so switch to earlier time.

5.4.1.2 How to Switch from Oral to Depot Flupenthixol?

Multiply the oral daily dose by 4 if the IM will be given every 2 weeks.

Multiply the oral dose by 8 if the IM will be given every 4 weeks.

5.4.2 Haloperidol (Haldol)

5.4.2.1 How to Start and Maintain Patients on Oral Haloperidol?

Initiation for schizophrenia: Start haloperidol 1 mg BID. Dose could increase to 2 mg BID in 4–7 days while assessing for side effects and consider further increases weekly if required. Dose could be shifted to HS if a patient experiences sedation in the morning.

Typical target: 5–10 mg. **Max dosing:** 20 mg.

Table 5.4 Long-acting injections of FGAs

Name	Dose and frequency of administration	Test dose	Duration of oral supplementation
Flupenthixol decanoate (Fluanxol) 20 mg/mL or 100 mg/mL	20–100 mg q2–4 weeks Start with 20 mg IM	5 mg	7 days
Haloperidol decanoate (Haldol LA) 50 mg/mL or 100 mg/mL	50–300 mg q 4 weeks	10 mg	7 days
Fluphenazine decanoate 25 mg/mL or 100 mg/mL	12.5–100 mg q 4 weeks	5 mg	Up to 14 days
Zuclopenthixol decanoate Clopixol depot (zuclopenthixol) 200 mg/mL	200–400 mg q 2–4 weeks	20 mg	Up to 14 days
Zuclopenthixol acetate	50–150 mg q 3 days	No	Not required; use only in emergency situations

Small doses (e.g., 0.5–1.0 mg BID) are used for brief periods for management of agitated or aggressive behavior in delirium in elderly patients.

There might be a need to prescribe an anticholinergic medication to deal with parkinsonian side effects (Benadryl 25 mg or Benztropine (Cogentin) 1–2 mg po or IM PRN or scheduled). Lorazepam 1 mg BID can be helpful in akathisia or propranolol 10 mg twice daily.

5.4.2.2 How to Switch from Oral to Depot Haloperidol?

Multiple the oral daily dose by 10 or 15
Maximum starting IM dose is 100 mg q 4 weeks
Adjust by 50 mg q 4 weeks
Maximum dose 300 mg q 4 weeks

5.4.3 Perphenazine (Trilafon)

Dosing information: Initiation for schizophrenia: Week 1: Start perphenazine 4 mg BID. Week 2: Assess for side effects and increase to 8 mg BID. Week 3 and beyond: Assess for side effects and consider further increases to 12 mg BID if still symptomatic. If QAM dosage is excessively sedating consider consolidating more of the dose to QHS. Typical target: 12–24 mg/day. Max dosing: 24 mg/day as an outpatient.

Pharmacokinetics: *T*½ = 9–12 h.

5.4.3.1 Describe the Challenge of the Classification of First- Versus Second-Generation Antipsychotics?

A study published in the Lancet in 2013 by Leucht et al. suggested that their findings challenge the straightforward classification of antipsychotics into first-generation and second-generation groupings. Rather, hierarchies in the different domains should help clinicians to adapt the choice of antipsychotic drug to the needs of individual patients.

5.4.4 Atypical Antipsychotics (Second Generation)

5.4.4.1 List Some of the Second-Generation or Atypical Antipsychotics?

Aripiprazole
Amisulpride
Asenapine

Olanzapine
Risperidone
Quetiapine
Iloperidone
Lurasidone
Paliperidone
Ziprasidone
Clozapine (used in refractory schizophrenia)

5.4.4.2 What Are the Proposed Mechanisms of Action of Atypical Antipsychotics that Were Modified by Horacek et al., in 2006?

"The model suggested that atypical antipsychotics or second generation antipsychotics may have a role in dopaminergic modulation by:

Blockade D2—blockade of 65–75% leads to effectiveness with preserved safety (EPS and hyperprolactinemia).

Blockade D1—is localized in PFC: therapeutic effect on negative and cognitive symptoms. D1 and modulate activity of D2 (potentiation of efficiency).

Blockade D4—decreases catalepsy and induces dopamine release in the basal ganglia and PFC. D4 and D1 antagonism alone no antipsychotic effect.

Blockade of D2/D3—preferential antagonism of inhibitory D2 auto receptors; increased striatal dopamine (lower risk of EPS) and neocortical dopamine release (cognitive and negative symptoms).

Blockade of D3 receptors in temporal cortex, leads to stereoselectivity and efficacy on positive symptoms without induction of EPS

Rapid dissociation from D2 ('fast OFF')—shorter duration of drug binding to D2 is sufficient for an antipsychotic action but insufficient to induce EPS and hyperprolactinemia (particularly quetiapine and clozapine)

Partial D2 agonism—aripiprazole, 30–40% of intrinsic D2 receptor agonism in connection with high D2 blockade exerts an antipsychotic effect with a low risk of EPS and hyperprolactinemia.

Serotonergic modulation: blockade of 5-HT2A—5-HT2A receptors integrate cortical and subcortical inputs. Antagonism of 5-HT2A blocks the effect of NMDA antagonists and induces striatal and neocortical dopamine release.

5-HT1A agonism—induces dopamine release into the striatum and neocortex (analogous to 5-HT2A blockade) and also into limbic structures.

Blockade of 5-HT2C—induces neocortical dopamine release

Modulation of 5-HT2A, 5-HT1A and 5-HT2C alone no antipsychotic effect

Induction of neuroplasticity: phosphorylation of receptors, potentiation of glutamate/glycine and induction of neuronal growth factors (nerve growth factor (NGF) and brain-derived neurotrophic factor or BDNF): reinforcement of NMDA receptor activity and development of new synapses or their remodeling" (Horacek et al. 2006).

5.4.4.3 Describe Some of the Differences in the Mechanism of Action of Some Atypical Antipsychotics?

Aripiprazole partial agonist effect at presynaptic D2 receptors and an antagonist at postsynaptic D2 receptors. It has little affinity for D3-, D4-, and D1-like receptors, and its affinity for 5HT-2A receptors is low. It has some affinity to serotonin 5-HT_{1a} receptors.

Amisulpride: high affinity for D_2 and D_3 dopamine receptors, with lower affinity for serotonergic, adrenergic, and cholinergic receptors.

Asenapine shows antagonism at dopaminergic (D_2, D_3, D_4), serotonergic (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, 5-HT_7), [alpha]-adrenergic ([alpha]$_{1A}$, [alpha]$_2$), and histamine (H_1) receptors.

Ziprasidone: low affinity for dopamine D2 receptors and a much higher affinity for serotonin ($5HT_2$) receptors; the serotonin/dopamine ratio is one of the highest among the atypical.

5.4.4.4 Describe the Proposed Criteria for Remission and Recovery in Schizophrenia?

- **Response:** Percentage decrease in symptoms by 50% or more in non refractory patients
- **Remission (APA consensus):** SAPS-SANS global rating 2 or less or PANSS item ratings of 3 or less
- **Recovery:** Independent functioning (work, school, social relationships, independent living); requiring minimal or no support (societal perspective) and personal sense of well-being (personal perspective) [5]

5.4.4.5 Describe the Suggested Monitoring Prior to and During Treatment with Atypical Antipsychotics?

Prior to starting treatment: Assess baseline weight, waist circumference, blood pressure, fasting plasma glucose, fasting lipid profile, CBC (for baseline WBC), EKG (to assess QTc), and AIMS test.

Ongoing monitoring: EKG at target dose (at least once to assess QTc). At 4 weeks: Weight. At 8 weeks: Weight. At 12 weeks: Weight, blood pressure, fasting plasma glucose, fasting lipid profile. Quarterly thereafter: Weight. Annually ongoing: Waist circumference, weight, blood pressure, fasting plasma glucose, fasting lipid profile, AIMS test. Repeat CBC in patients with previous low WBC.

5.4.4.6 Describe the Dosage According to the Product Monograph of each Individual Atypical Antipsychotic?

Asenapine

Initiation for schizophrenia and bipolar mania:

Week 1: Start 5 mg BID under the tongue. This is sublingual medication and patient should not eat or drink for 10 min after administration. Week 2: 10 mg BID dosing as needed. Typical target: 5–10 mg BID. Maximum dose: 10 mg BID.

Lurasidone (LATUDA)

The recommended starting dose of LATUDA is 40 mg once daily. In placebo-controlled clinical trials, once-daily doses of 40, 80, 120, and 160 mg were shown to be effective. Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability, which is expected to be 40 mg or 80 mg once daily for most patients. Doses above 80 mg may be considered for certain patients based on individual clinical judgement.

In patients with hepatic and renal impairment, the dose should not exceed 40 mg/day.

Iloperidone (Fanapt)

1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets

The recommended target dosage of Fanapt tablets is 12–24 mg/day administered twice daily. This target dosage range is achieved by daily dosage adjustments, alerting patients to symptoms of orthostatic hypotension, starting at a dose of 1 mg twice daily, and then moving to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively, to reach the 12 mg/day to 24 mg/day dose range. Fanapt can be administered without regard to meals. Slower titration can be easier on some patients.

If medication has been stopped for greater than 3 days, the initial titration schedule should be followed.

Aripiprazole (ABILIFY)

2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets

Initiation for schizophrenia: Adult usual dose: The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule. Doses in the range of 10–30 mg/day have been established as effective in clinical trials. However, greater efficacy has not been demonstrated at doses higher than 10 mg/day. Dosage increases, if needed, should only be made after 2 weeks. Some

clinicians prefer to start at 5 mg and gradually increase to 10 mg in 4 days. Maximum dosage: 30 mg daily.

In adolescents, the recommended starting daily dose is 2 mg/day, titrated to 5 mg/day after 2 days and to the target dose of 10 mg/day after 2 additional days.

Initiation for bipolar manic/mixed episode: Start 7.5 mg daily and increase to 15 mg daily in 3–4 days. Maximum dosage: 30 mg daily. Typical target: 15 mg daily**.**

Initiation for major depressive disorder, adjunctive: The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2–5 mg/day. The efficacy of ABILIFY as an adjunctive therapy for the treatment of major depressive disorder was established within a dose range of 2–15 mg/day. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week

Olanzapine (Zyprexa)

Zyprexa tablets: Zyprexa tablets are available in 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg strengths.

Zyprexa Zydis: Zyprexa Zydis orally disintegrating tablets are available in 5 mg, 10 mg, 15 mg, and 20 mg strengths.

- Schizophrenia in adults, oral: start at 5–10 mg once daily; target: 10 mg/day within several days. Schizophrenia in adolescents, oral: start at 2.5–5 mg once daily; target: 10 mg/day.
- Bipolar I disorder (manic or mixed episodes) in adults, oral: start at 10 or 15 mg once daily.
- Bipolar I disorder (manic or mixed episodes) in adolescents, oral: start at 2.5–5 mg once daily; target: 10 mg/day.
- Bipolar I disorder (manic or mixed episodes) with lithium or valproate in adults, oral: start at 10 mg once daily.
- Agitation associated with schizophrenia and bipolar I mania in adults IM: 10 mg (5 mg or 7.5 mg when clinically warranted): Assess for orthostatic hypotension prior to subsequent dosing (max. three doses 2–4 h apart).
- Depressive episodes associated with bipolar I disorder in adults, oral in combination with fluoxetine: start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily.
- Depressive episodes associated with bipolar I disorder in children and adolescents, oral in combination with fluoxetine: start at 2.5 mg of oral olanzapine and 20 mg of fluoxetine once daily.
- Treatment-resistant depression in adults, oral in combination with fluoxetine: start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily.

5.4.5 Paliperidone (Invega): Oral Formulation

Dosage forms and strength: Tablets: 1.5 mg, 3 mg, 6 mg, and 9 mg

Paliperidone (Invega): Oral formulation

	Initial dose	Recommended dose	Maximum dose
Schizophrenia: adults	6 mg/day	3–12 mg/day	12 mg/day
Schizophrenia adolescents:			
Weight < 51 kg	3 mg/day	3–6 mg/day	6 mg/day
Weight ≥ 51 kg	3 mg/day	3–12 mg/day	12 mg/day
Schizoaffective disorder: adults	6 mg/day	3–12 mg/day	12 mg/day

5.4.6 Quetiapine (Seroquel (IR), Seroquel XR)

Quetiapine fumarate immediate-release tablets quetiapine 25, 100, 200, and 300 mg.

5.4.6.1 Dosing Information

Schizophrenia: The usual starting dose of Seroquel is 25 mg b.i.d., titrated with increments of 25–50 mg b.i.d. per day, as tolerated, to a target dose of 300 mg/day given b.i.d. within 4–7 days. Further dosage adjustments may be indicated depending on the clinical response and tolerability in the individual patient. Dosage adjustments should generally occur at intervals of not less than 2 days, as steady state for Seroquel would not be achieved for approximately 1–2 days in the typical patient. When adjustments are necessary, dose increments/decrements of 25–50 mg b.i.d. are recommended. Clinical trials suggest that the usual effective treatment dose will be in the range of 300–600 mg/day (see Part II: Clinical Trials). However, some patients may require as little as 150 mg/day. In schizophrenia, the safety of doses above 800 mg/day has not been evaluated.

In bipolar mania: Day 1100 mg/day, day 2200 mg/day, day 3300 mg/day, day 4400 mg/day, day 5 up to 600 mg/day, and day 6 up to 800 mg/day. All in divided doses as BID.

Approximately 85% of patients responded between 400 and 800 mg/day, while over 50% of patients responded between 600 and 800 mg/day (the average median dose for responders during the last week of treatment was approximately 600 mg/day). In bipolar mania, the safety of doses above 800 mg/day has not been evaluated.

In depression:

Day	1	2	3	4
Once daily HS	50 mg/day	100 mg/day	200 mg/day	300 mg/day

Patients in 300 mg fixed-dosage arms were continued on Seroquel 300 mg/day, from day 4 onward. In clinical trials that had a fixed 600 mg dosage arm, Seroquel was further titrated to 400 mg on day 5 and up to 600 mg by day 8, depending on

the clinical response and tolerability of individual patients. Antidepressant efficacy was demonstrated with Seroquel at both 300 mg/day and 600 mg/day; however no additional benefit was seen in the 600 mg group during short-term treatment. Thus, a usual target dose of 300 mg/day is recommended.

5.4.7 Risperidone (Risperdal)

Risperidone tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

5.4.7.1 Initiation for Schizophrenia

Risperidone can be administered on either a.o.d. or b.i.d. schedule, generally beginning with 1–2 mg per day. The dose should be adjusted gradually over several days based on clinical response to a target dose of 4–6 mg per day. Most patients respond between 4 and 6 mg daily. Doses above 10 mg daily were not beneficial.

Initiation for bipolar disorder: Risperidone should be administered on a once-daily schedule, starting with 2–3 mg per day. Dosage adjustments, based on clinical response and tolerability, should occur at intervals of not less than 24 h and in dosage increments or decrements of 1 mg per day. Risperidone doses higher than 6 mg per day were not studied in patients with bipolar disorder.

5.4.8 Ziprasidone (Geodon)

Give oral doses with food.

Schizophrenia: Initiate at 20 mg twice daily. Daily dosage may be adjusted up to 80 mg twice daily. Dose adjustments should occur at intervals of not less than 2 days.

Safety and efficacy have been demonstrated in doses up to 100 mg twice daily.

Acute treatment of manic/mixed episodes of bipolar I disorder: Initiate at 40 mg twice daily. Increase to 60 mg or 80 mg twice daily on day 2 of treatment. Subsequent dose adjustments should be based on tolerability and efficacy within the range of 40–80 mg twice daily.

Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate: Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40–80 mg twice daily.

Acute treatment of agitation associated with schizophrenia (intramuscular administration): 10–20 mg up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 h.

5.5 Individual Medication Profile

5.5.1 Lurasidone (LATUDA)

- LATUDA is an atypical antipsychotic indicated for the acute treatment of patients with schizophrenia.
- It has been suggested that the efficacy of LATUDA in schizophrenia is mediated through a combination of central dopamine type 2 (D2) and serotonin type 2 (5HT2A) receptor antagonism unknown.
- The recommended starting dose of LATUDA is 40 mg once daily.
- Doses above 80 mg may be considered for certain patients based on individual clinical judgement.
- Patients should be treated at the lowest effective dose that provides optimal clinical response and tolerability.
- LATUDA should be taken with food (at least 350 calories independent of fat content).
- In placebo-controlled clinical trials, doses of 40 mg, 80 mg, 120 mg, and 160 mg were shown to be effective (Fig. 5.1).

Before starting: Assess baseline weight, waist circumference, blood pressure, fasting plasma glucose, fasting lipid profile, CBC (for baseline WBC), EKG (to assess QTc), and AIMS test.

Dose: The recommended starting dose of LATUDA is 40 mg once daily. In placebo-controlled clinical trials, once-daily doses of 40, 80, 120, and 160 mg were shown to be effective. Patients should be treated with the lowest effective dose that provides optimal clinical response and tolerability, which is expected to be 40 mg or 80 mg once daily for most patients. Doses above 80 mg may be considered for certain patients based on individual clinical judgement.

In patients with hepatic and renal impairment, the dose should not exceed 40 mg/day.

Safety and efficacy in pediatric patients have not been evaluated and its use is not recommended.

LATUDA is not indicated in elderly patients with dementia. The safety and efficacy of LATUDA in patients 65 years of age or older have not been established.

Pharmacokinetics: *T*½ = 18 h.

- Pharmacokinetics
  - Following administration of 40 mg of LATUDA the mean (%CV) elimination half-life was 18 (7) h.

Fig. 5.1 Lurasidone dose

  - Steady-state concentrations are reached within 7 days of starting LATUDA.

- Absorption: Lurasidone is absorbed and reaches peak serum concentrations in approximately 1–3 h.
- Dose should be proportional within a total daily dose range of 20–160 mg.
  - It is estimated that 9–19% of an administered dose is absorbed.

5.5.1.1 Side Effects

Common: Somnolence (22%), akathisia (13%), nausea (10%), parkinsonism (10%), agitation (6%), anxiety (6%).

Warnings and Precautions: Seizures, orthostatic hypotension/syncope, neuroleptic malignant syndrome, hyperprolactinemia, leukopenia/neutropenia/agranulocytosis, hyperglycemia/diabetes/weight gain, tardive dyskinesia, sudden cardiac death, cardiovascular accident, body temperature dysregulation. Contraindications: Known hypersensitivity reaction to the product. Coadministration with a strong CYP3A4 inhibitor (e.g., ketoconazole) and inducer (e.g., rifampin).

- The use of LATUDA should be avoided in combination with drugs known to prolong QTc including class 1A antiarrhythmics (e.g., quinidine, procainamide) or class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin).[1]
- LATUDA should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia, hypokalemia, or hypomagnesemia, and presence of congenital prolongation of the QT interval.[1]

Black Box Warnings: (1) Increased mortality in elderly patients with dementia-related psychosis.

Pregnancy: Category B. **Breastfeeding:** Unknown if enters breast milk/not recommended.

5.5.1.2 Significant Drug-Drug Interactions

LATUDA is metabolized mainly via the CYP3A4 pathway:

- LATUDA is contraindicated in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole).
- LATUDA dose should not exceed 40 mg/day concomitant with a moderate CYP3A4 inhibitor (i.e., diltiazem).
- LATUDA is contraindicated in combination with a strong CYP3A4 inducer (i.e., rifampin).

5.5.2 Asenapine (Saphris) Sublingual

Atypical antipsychotic with dibenzoxepinopyrrole structure.

Pharmacokinetics: *T*½ = 24 h.

Oral bioavailability is less than 2%, and sublingually as maleate 35%. Steady state is achieved after 3 days.

Metabolism of asenapine consists of direct glucuronidation by UGT1A4 and oxidation by CYP1A2 and to a lesser extent by CYP3A4 and CYP2D6. Consequently, possible interactions with inducers or inhibitors of CYP1A2 and CYP2D6 can be expected.

TDM: A therapeutic range of 2–5 ng/mL. TDM is potentially useful but should be restricted to special indications because plasma concentrations of asenapine do not correlate with clinical effects.

Side effects: Common: Somnolence (13%), extrapyramidal symptoms (12%), akathisia (11%), dizziness (11%), weight gain (5%), mouth numbness (4%), dyspepsia (4%). It has a lower weight gain and lower metabolic side effects. It does not significantly increase prolactin but has moderate EPSE.

5.5.3 Iloperidone (Fanapt)

*T*½ = 14 h. Iloperidone is well absorbed orally, with a bioavailability of 96%, and is extensively metabolized in the liver via CYP2D6 and CYP3A4. Peak serum iloperidone values were seen within 2–4 h of administration. It reaches a steady-state concentration within 3–4 days of initial administration.

Side effects: Common: Dizziness (20%), fatigue/somnolence (15%), tachycardia (12%), dry mouth (10%), increased weight (9%), nasal congestion (8%), orthostatic hypotension (5%).

Significant drug-drug interactions: Fanapt dose should be reduced by one-half when administered concomitantly with strong CYP2D6 inhibitors such as fluoxetine or paroxetine, in known slow CYP2D6 metabolizers, and in patients taking strong CYP3A4 inhibitors. Caution with centrally acting antihypertensives (due to its α1-adrenergic receptor antagonism). Medications that prolong QTc.

5.5.4 Aripiprazole (ABILIFY)

*T*½ = 75 h.

Side effects: Common: Akathisia (19%), insomnia (18%), constipation (11%), sedation/fatigue (8%), tremor (6%), extrapyramidal symptoms (5%).

Severe weight gain is not encountered.

5.5.5 *Olanzapine (Zyprexa)*

*T*½ = 30 h.

Side effects:[1] **Common:** Somnolence (35%), dry mouth (22%), dizziness (18%), fatigue (15%), dyspepsia (11%), constipation (9%), tremor (6%), weight gain/increased appetite (6%), akathisia (5%), postural hypotension (5%).

It has an advantage of over some other SGAs in being available in an IMI form for acute administration. A preparation which dissolves in the mouth is available. A long-acting depot form is available but because physiological response is variable, the patient must be observed for 3 h following every injection. Patients might develop postinjection sedation, delirium, or in rare cases coma.

5.5.6 *Paliperidone (Invega): Oral Formulation*

*T*½ = 23 h. **Side effects: Common:** Somnolence/fatigue (26%), extrapyramidal symptoms (23%), akathisia (17%), headache (14%), tachycardia (14%), constipation (4%), orthostatic hypotension (4%), salivary hypersecretion (4%), weight gain (4%), gynecomastia (3%).

Significant drug-drug interactions: Caution with antihypertensives, Tegretol, Epival.

5.5.7 *Quetiapine (Seroquel (IR), Seroquel XR)*

*T*½ = 6 h. (IR); 7–12 h (XR).

Side effects: Common: Seroquel IR: Headache (21%), somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), dyspepsia (5%), rash (4%), abdominal pain (4%), postural hypotension (4%). Seroquel XR: Somnolence (50%), dry mouth (34%), constipation (10%), dizziness (10%), dyspepsia (7%), weight gain (7%), fatigue (7%), dysarthria (5%), nasal congestion (5%), weight gain (5%), ALT/AST increased (5%), increased appetite (4%).

5.5.8 *Risperidone (Risperdal)*

*T*½ = 20 h.

Side effects: Common: Insomnia (32%), extrapyramidal symptoms (parkinsonism (25%), akathisia (10%)), anxiety (16%), nausea (9%), dizziness (7%), sedation/fatigue (6%), weight gain, dry mouth (4%), tremor (3%), orthostatic hypotension

[1] Side effects could vary among different studies. The percentages should be interpreted with caution.

(2%). **Significant drug-drug interactions:** Caution with antihypertensives (because of orthostatic hypotension).

5.5.9 Ziprasidone (Geodon)

*T*½ = 7 h. **Side effects:**[2] **Common:** Somnolence (14%), extrapyramidal symptoms (14%), dizziness (8%), akathisia (8%), respiratory tract infection (8%), abnormal vision (6%), asthenia (5%), vomiting (5%).

Contraindications: Known hypersensitivity reaction to the product. Do not use in patients with a known history of QT prolongation. Do not use in patients with recent acute myocardial infarction. Do not use in patients with uncompensated heart failure. Do not use in combination with other drugs that have demonstrated QT prolongation. **Significant drug-drug interactions: Contraindicated:** Methadone, many others including any medications that prolong QTc.

5.5.10 Clozapine

5.5.10.1 Is Clozapine Used Equally Around the World?

No. There is significant variations among different countries despite its clinical superiority and its advantage in the treatment of resistant schizophrenia (TRS) in comparison with other antipsychotic drug. Its use varies from 10 to 20% in the USA to 31.9% in China and 54% in the UK. Popularity of clozapine has increased over the recent years, and it is still suggested that access to clozapine should be facilitated.

Clozapine was the first of the atypical antipsychotics to be developed. It was introduced in the early 1970s with enthusiasm due to its demonstrated low incidence of negative and extrapyramidal effects, but this was followed by voluntary withdrawal from the market in 1974 due to its association with agranulocytosis. However, in 1989, as a result of studies demonstrating it to be superior to other antipsychotic drugs in the treatment of refractory schizophrenia, the FDA reapproved the use of clozapine. Clozapine remains a unique agent in both its therapeutic benefit and adverse effects. It is effective in treating the "negative" symptoms of schizophrenia, such as anhedonia, avolition, blunted affect, and lack of emotion.

5.5.10.2 List the Adverse Effects of Clozapine

Nevertheless, clozapine has several unwanted clinical effects that have led to discontinuation in about 8% of patients. The adverse effects include the following:

Orthostatic hypotension, tachycardia, and syncope

Gastrointestinal symptoms such as constipation and nausea

[2] Side effects could vary among different studies. The percentages should be interpreted with caution.

Sedation, dizziness, tremors, and headache

Sialorrhea or hypersalivation, weight gain, sweating and visual disturbances, and dysarthria

Pruritis, eczema, erythema, and pallor

Grand mal seizures may be observed in higher therapeutic doses usually >600 mg and in overdose.

The 1% risk of agranulocytosis and decreased white blood cells.

Rare adverse effects include anemia, diabetes and hyperglycemia, dyslipidemia, fever, QTc prolongation, agitation, dysphonia, delirium, thromboembolism, arrythmia, paralytic ileus, myocarditis, cardiomyopathy, and vasculitis.

Extrapyramidal side effects are uncommon.

Very rare side effects include thrombocytopenia, ketoacidosis, tardive dyskinesia, swelling of salivary gland, priapism, hepatic fibrosis, liver injury, CPK increase, and sudden death.

5.5.10.3 Describe the Suggested Regular Clozapine Monitoring Schedule?

In the United Kingdom, both white blood count (WBC) and absolute neutrophil count (ANC) monitoring frequency were weekly for 18 weeks, biweekly in weeks 19–52, and then monthly thereafter.

In Canada and the USA, it is recommended to monitor only ANC weekly throughout the initial 6 months, every 2 weeks between 6 and 12 months, and monthly after 12 months of treatment [6].

5.5.10.4 Describe Clozapine Monitoring Based on Lab Results?[3]

In the United Kingdom, clozapine treatment is limited to patients who have initially normal leukocyte findings [white blood cell count ≥ 3500/[μ]L (≥3.5 × 10^9/L), and ANC ≥ 2000/[μ]L (≥2.0 × 109/L)] (green).

WBC less than 3000/[μ]L or ANC less than 1500/[μ]L at any time during treatment is an indication for clozapine discontinuation without further re-exposure of the patient to the drug (red).

Clozapine is continued with monitoring occurring twice a week when either WBC is between 3500 and 3000/[μ]L or ANC is between 2000 and 1500/[μ]L (amber).

US Federal and Drug Administration (FDA) modified the requirement, lowered the threshold for ANC to 1000 μ/L, and removed the requirement for WBC count.

Patients with benign ethnic neutropenia (BEN) should be consulted by a hematologist and given especial consideration [6].

List some possible strategies to mitigate the risk of blood dyscrasias with clozapine:

- Add lithium since it may increase ANC by 88% of baseline values.
- Add granulocyte colony-stimulating factor (GCSF) [7].

[3] Side effects could vary among different studies. The percentages should be interpreted with caution.

5.5.10.5 What Factors Are Associated with Clozapine Response?

No unequivocal factors to clozapine response were found despite a relatively rich body of the literature, which calls for more works on this important topic. Clozapine level of 350 ng/mL appears to be useful in case of nonresponse (Suzuki, T) schizophrenia Bulletin.

5.6 Summary of Second-Generation Long-Acting Injectable Antipsychotics

Agent	US FDA approval date	Indication	Formulation design technology	Oral dosing initiation
Risperidone (Risperdal Consta)	October 2003	Schizophrenia	Microspheres	Yes, 21 days
	May 2009	Bipolar I		
Olanzapine pamoate (Zyprexa Relprevv)	December 2009	Schizophrenia (210–405 mg)	Pamoic acid crystal	Not needed
Paliperidone palmitate, 1 month (Invega Sustenna)	August 2009	Schizophrenia	Nanocrystals	Not needed
	November 2014	Schizoaffective		
3 months (Trinza)	May 2015	Schizophrenia	Nanocrystals	Not needed
Aripiprazole (ABILIFY MAINTENA)	February 2015	Schizophrenia	Polymorphic	Yes, 14 days
	July 2017	Bipolar I		
Aripiprazole Lauroxil	October 2015	Schizophrenia	Pro-drug; 2-step hydrolysis	Yes, 21 days
Iloperidone (Fanapt)		Schizophrenia	Crystalline	Yes, 21 days

(Zyprexa Relprevv) has regulations about supervising patients for 3 h after each injection due to the possibility of postinjection sedation or delirium [8].

5.7 Describe the Product Attributes of Paliperidone Palmitate?

It is an aqueous solution-based nanosuspension. Can be given deltoid and gluteal IM. No reconstitution or refrigeration required. Initiation injections on day 1 (150 mg loading) and day 8 with no requirement for oral supplementation. Dose range in day 8 is 50, 75, 100, and 150.

- Time to maximum plasma concentration (t_{max}):
  - Median t_{max} = 13 days
  - Drug release starts as early as **day 1**, lasting up to 126 days

- A 28% higher maximum plasma concentration (C_{max}) observed with IM injection of single doses (50–150 mg eq.) in the deltoid muscle, compared with the gluteal muscle.
- Two initial deltoid IM injections of 150 mg eq. on day 1 and 100 mg eq. on day 8 help attain therapeutic concentrations rapidly.

5.8 List the Recommendations of Managing Missed Doses of Paliperidone Palmitate?

Month to 6 weeks: Administer previous maintenance dose ASAP followed by injections at monthly intervals.

>6 weeks to 6 months: Maintenance doses of 25–100 mg eq.

1. Deltoid injection ASAP at the same maintenance dose
2. Another deltoid injection (same dose) 1 week later (day 8)
3. Resumption of the normal monthly cycle of injections in either the deltoid or the gluteal muscle of 25–150 mg eq.

>6 weeks to 6 months: Maintenance dose of 150 mg eq.

1. Deltoid injection ASAP at the 100 mg eq. dose
2. Another deltoid injection 1 week later (day 8) at the 100 mg eq. dose

Resumption of the normal monthly cycle of injections in either the deltoid or the gluteal muscle of 25–150 mg eq.

>6 months: 150 mg eq. on day 1 and 100 mg eq. on day 8 (deltoid) followed by monthly maintenance doses in either the deltoid or the gluteal muscle of 25–150 mg eq.

5.9 Adverse Events Associated with Atypical Antipsychotics (Table 5.5)

5.10 List the Warning and Precautions Associated with Atypical Antipsychotics?

Seizures, QTc prolongation, orthostatic hypotension, neuroleptic malignant syndrome, agranulocytosis, hyperglycemia/ diabetes, tardive dyskinesia, sudden cardiac death, cerebrovascular accident, and body temperature dysregulation. **Contraindications**: Known hypersensitivity reaction to the product.

Table 5.5 Adverse events associated with atypical antipsychotics

	Cl	Ol	Ri	Qu	Zi	Ar	Il	As
Neurological somnolence	++++	+++	++	+++	+	+	+	++
Sedation	++++	+++	++	+++	+	+	±	++
EPS DD = dose dependent	+	DD	DD++	+/0	DD	DD	±	+/0
Seizure risk	DD	±	±	±	±	±	±	±
Neuroleptic malignant syndrome	+	+	+	+	+	+	+	+
Metabolic weight gain	++++	+++	++	++	+/0	+/0	++	+
Dyslipidemia	+++	+++	++	++	±	±	±	+/0
Glucose dysregulation	+++	+++	+	++	±	±	+	+/0
Cardiovascular myocarditis/cardiomyopathy	+/0	ISF	ISF	ISF	ISF	ISF	ISF	ISF
QTc prolongation	±	±	±	±	+/0	±	+/0	+/0
Hormonal prolactin elevation	±	±	DD++	±	±	±	±	±
DD: Dose-dependent ISF insufficient data								

Black Box Warnings: (1) Increased mortality in elderly patients with dementia-related psychosis. (2) If the antipsychotic is indicated in depression, increased risk of suicide thoughts is a warning.

5.11 What Is the Impact of Antipsychotics on the Risk of Thromboembolism?

Patients with schizophrenia are predisposed toward developing cardiovascular disease for several reasons:

Patients with psychotic disorders may have additional risk factors such as lower physical activity due to sedentary lifestyle and effect of the illness, inadequate nutrition, in addition to increased rate of smoking and substance abuse.

Patients receiving typical antipsychotic drugs have been reported to have elevated concentrations of antiphospholipid antibodies, including anticoagulants and anticardiolipin antibodies. The presence of both antibodies is associated with an increased risk for thromboembolism.

Patients with psychotic disorders in acute phase may have a statistically significant increase in the concentrations of D-dimer and P-selectin, and in the expression of platelet glycoprotein IIb/IIIa receptors.

Researchers suggest that before starting atypical antipsychotics to hospitalized patients, all possible risk factors for thromboembolism should be considered to allow the application of lower risk drugs. They also suggest that other preventive measures should be considered such as hydration, compression stockings, regular exercise of lower extremities, and low-molecular-weight heparin injections [9].

5.12 Describe the Risk of Osteoporosis and Fracture Incidence in Patients on Antipsychotic Medication?

"Typical antipsychotics, in addition to the atypical antipsychotics risperidone and amisulpride, have been shown to increase serum prolactin levels in in vivo human studies. Researchers suggested that high concentrations of prolactin have been shown to adversely affect bone cell metabolism and accelerate the rate bone mineral density loss, thereby increasing fracture risk. It might be helpful to screen patients at high risk of antipsychotic-induced osteoporosis and provide them with treatment, which may reduce the incidence of potentially avoidable fractures" [10].

5.13 Describe the Possible Mechanism of Sialorrhea During Treatment with Antipsychotics and Possible Pharmacological Management Strategies?

There are two theoretical mechanisms:

1. Sympathetic α-adrenergic receptor antagonism.
2. Parasympathetic cholinergic (muscarinic) receptor (M1-M5) agonism: This mechanism has more evidence:
   - When muscarinic cholinergic receptors are stimulated, salivary flow increases almost fivefold.
   - It was hypothesized that selective stimulation of the M_4-muscarinic receptors in salivary glands leads to an increase in secretions (clozapine and olanzapine).
   - Another study indicated that muscarinic induction of salivation is mediated by M_3 receptors.
   - An association was found between the adrenoreceptor alpha 2A gene (ADRA2A) and clozapine-induced sialorrhea ($P = 0.0215$); the α2 receptors also appear to be involved in the swallowing movement-respiratory coordination [11].

Pharmacological management strategies include the following:

Anticholinergics such as atropine, trihexyphenidyl, benztropine, procyclidine, glycopyrrolate, propantheline.

Alpha-2-adrenergic receptor agonists such as clonidine, guanfacine, α-methyldopa (Chen 2019).

5.14 What Are the Ocular Side Effects of Antipsychotics? [12] (Table 5.6)

5.15 Describe the Metabolic Syndrome with Atypical Antipsychotics?

There are several definitions of metabolic syndromes. Some of the most common definitions for the metabolic syndrome include the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program, and the adapted Adult Treatment Panel (ATP III-A) proposed by the American Heart Association and the International Diabetes Federation (IDF) definitions.

ATP III definitions require three out the following five:

Waist circumference Men >102 cm (>40 in) and women >88 cm (>35 in)
Blood pressure ≥ 130/≥85 mmHg
HDL cholesterol Men <40 mg/dL (1.04 mmol/L), women <50 mg/dL (1.29 mmol/L)
Triglycerides ≥ 150 mg/dL (1.7 mmol/L)
Fasting glucose ≥ 110 mg/dL (6.1 mmol/L

Table 5.6 Ocular side effects of antipsychotics

Disorder	Antipsychotic associated with the side effects
Eyelid and keratoconjunctival disorders	Chlorpromazine when used in high doses sometimes more than 2 g/day may result in abnormal pigmentation (reversible) of the eyelid, conjunctiva, and cornea Secondary corneal edema can causa visual impairment and be associated with phenothiazine
Uveal tract (iris, ciliary body, and choroid)	Antipsychotic with a strong anticholinergic and antiadrenergic effect such as phenothiazine can lead to mydriasis and cycloplegia
Glaucoma	Antipsychotic with a strong anticholinergic and antiadrenergic effect such as phenothiazine can be a risk for angle closure glaucoma
Cataract	Most common offending agent is thioridazine And some reports of chlorpromazine Little association with trifluoperazine, fluphenazine, and perphenazine Reported in animal studies with quetiapine but not in humans but the manufacturer mentions changes to the lens and recommend routine eye examination Atypical antipsychotics may affect the lens due to the effect of hyperglycemia on the eye
Dystonia of ocular muscle	High-potency typical antipsychotics such as haloperidol. Some reports with risperidone. Oculogyric dystonia was also reported with aripiprazole
Accommodation interference	Antipsychotic with a strong anticholinergic and antiadrenergic effect such as phenothiazine can decrease ocular accommodation

5.16 The Metabolic Syndrome with Antipsychotics

Metabolic syndrome is more common in people with schizophrenia than the general population. It is more common in chronic than first-episode schizophrenia.

A study found that the rate of metabolic syndrome for those taking clozapine is 51.9%, 28.2% for olanzapine, and 27.9% for risperidone and in patients with schizophrenia not taking medications, the rate was 20.2% [13].

5.17 Weight Gain

Clozapine and olanzapine are consistently associated with greater weight gain risk. They have the greatest affinity for H 1 and 5-HT 2C receptors.

A meta-analysis estimated that over a 10-week period the mean increase was as follows:

1. Clozapine 5 kg
2. Olanzapine 4.15 kg
3. Risperidone 2.1 kg (quetiapine probably similar)
4. Ziprasidone 0.04 kg

Aripiprazole, asenapine, and lurasidone probably have neutral metabolic side effects.

CATIE study found that rates of >7% of increase in baseline weight at 12 and 24 weeks are as follows:

Medication	12 weeks	24 weeks
Olanzapine	60%	80%
Quetiapine	29%	50%
Risperidone	32%	58%

Other studies mentioned additional findings: Patients on paliperidone extended release gained 1.5 kg in 3–6 weeks after initiation of treatment. Patients on iloperidone gained average of 4.8 kg in a 52-week duration trial. Weight gain may be dose related. Majority of weight gain occurred in first 6 weeks of treatment. Weight gain on asenapine was noted to be 23% vs. olanzapine, and 57.1% in patients with initial BMI 23. Weight gain was not dose related [14].

5.18 Type 2 Diabetes

The prevalence of type 2 diabetes in people with schizophrenia is double that of the general population. An association between schizophrenia and diabetes has been recognized for many years. Many APs are associated with weight gain, but there is no evidence for an intrinsic role for the antipsychotics in the etiology of diabetes.

FDA's database analysis in terms of diabetes reported the following adjusted ratio hierarchy for diabetes mellitus-related adverse outcomes:

Clozapine increases the risk of diabetes more than any other antipsychotic as follows:

Olanzapine 9.6 (95% CI 9.2–10.0)
Risperidone 3.8 (3.5–4.1)
Quetiapine 3.5 (3.2–3.9)
Ziprasidone 2.4 (2.0–2.9)
Aripiprazole 2.4 (1.9–2.9)
Haloperidol 2.0 (1.7–2.3) 0.72

5.19 List Some of the Cardiac Adverse Effects of Atypical Antipsychotics?

5.19.1 QTc Interval Prolongation

Many psychotropic drugs can delay cardiac repolarization and thereby prolong the rate-corrected QT interval (QTc). QTc interval prolongation is a matter of concern. It can be followed, in rare cases, by the life-threatening polymorphic ventricular tachyarrhythmia called torsade de pointes (TdP).

The average QTc interval in healthy adults is about 400 ms.

It is suggested that in males QTc below 450 is considered normal, between 451 and 470 considered borderline, and above 470 ms considered prolonged.

In females QTc below 430 is considered normal, between 431 and 450 considered borderline, and above 450 ms considered prolonged.

A QTc interval of 500 ms or a change from baseline of 60 ms or more is a risk factor for torsade de pointes (a ventricular arrhythmia which can lead to syncope, ventricular fibrillation, and sudden death). Additional risk factors include age over 65 years, preexisting cardiovascular disease, bradycardia, female sex, hypokalemia, hypomagnesemia, and toxic serum concentration One study found the following prolongations:

1. Thioridazine 30 ms
2. Ziprasidone 20.3 ms
3. Quetiapine 14.5 ms
4. Risperidone 11.6 ms (3% of patients on risperidone had prolonged QTc during CATIE study)
5. Olanzapine 5.8 ms
6. Haloperidol 4.7 ms

Other studies suggested that sertindole and amisulpride are associated with significant increase of QTc.

5.19.2 Myocarditis and Cardiomyopathy

There are rare (0.015–0.188%) side effects of clozapine therapy.

Myocarditis occurs mainly in the first 2 months of initiation of clozapine.

Cardiomyopathy was found after 6–12 months of treatment [15].

5.20 What Are the Manifestations of Overdose of Atypical Antipsychotics? (Table 5.7)

Table 5.7 Manifestations of overdose of atypical antipsychotics

Medication	Overdose
Risperidone	Characterized by tachycardia and dystonic reactions. Orthostasis has also been reported and generally responds to intravenous fluids. Dystonic reactions seem to be the most distinctive feature, occurring in 11% of risperidone overdoses in one series. All cases were treated with benztropine, and in all but one case, symptoms resolved soon after treatment. Delayed respiratory depression has been reported but is not a prominent feature in overdose
Olanzapine	Overdoses have been characterized by CNS depression and unpredictable fluctuation between sedation and agitation. Olanzapine ingestions have been associated with increased creatine kinase, although the mechanism by which this occurs remains unclear
Quetiapine	CNS depression is the most common adverse effect after quetiapine overdose. Tachycardia and hypotension are also common clinical manifestations in these cases. Quetiapine has a high affinity for histamine and adrenergic α-1 receptors, accounting for the clinical effects. Tachycardia has been reported to occur in about half of overdose patients and is likely from quetiapine's antimuscarinic effects, as well as a reflex response to α-1-inducted vasodilatation
Ziprasidone	Ziprasidone is more likely to cause QT prolongation compared to other agents, with a mean prolongation of 15–20 ms over baseline QT durations at peak plasma concentrations in therapeutic use. Although combined poisonings with ziprasidone and other agents have been linked to TdP, uncomplicated ziprasidone overdose has not yet been described to cause this dysrhythmia. Drowsiness is the most common symptom reported in overdose
Aripiprazole	Reports of overdose suggest that aripiprazole mainly causes sedation, which can be delayed. One report describes the onset of sedation in a patient occurring at 9 h after an intentional overdose. However, aripiprazole lacks clinically significant effects on cardiac conduction and is well tolerated in reported series thus far
Amisulpride	Amisulpride overdose has been characterized by cardiac effects, with CNS effects being less common In a recent prospective cohort, TdP occurred in 7% of overdoses, and more than two-thirds of patients developed prolonged QT interval
Paliperidone	Limited experience in overdose suggests that tachycardia is a common adverse event. Due to the unique design of this drug, delayed and sustained toxicity may occur [16]

5.21 Describe the Additional Risk of Antipsychotic Treatment in Patients with Schizophrenia during Pregnancy and Lactation?

Illness-related Factors
- Reduced antenatal attendance rates
- Reduced use of prenatal vitamins and thyroid hormone
- Increased rates of smoking, alcohol, and illicit drug use
- Increased rates of domestic abuse and homelessness

Risks Related to Medication Use Prior to Pregnancy
- Reduced predictability of fertility
- Increased rates of obesity and diabetes
- Increased rates of gestational hypertension, gestational diabetes, and thromboembolic events in pregnancy

Risk to the Babies of Mothers with Schizophrenia
- Vulnerability to prematurity and small-for-gestational-age weights, especially if they are exposed to typical antipsychotic medications in utero
- Vulnerability to both small- and large-for-gestational-age weights
- Vulnerability to neonatal abstinence syndrome and neonatal respiratory distress, especially if they are exposed to multiple psychotropics

For the above reasons, some researchers suggest that treatment with antipsychotic medications in pregnancy should prompt delivery of women in facilities with higher level neonatal care facilities [17] (Table 5.8).

Table 5.8 Risk of antipsychotic treatment in patients with schizophrenia during pregnancy and lactation

Lurasidone
Pregnancy: Category B. Breastfeeding: Unknown if enters breast milk/not recommended
Asenapine
Pregnancy: Category C. Breastfeeding: Not known if enters breast milk/not recommended
Iloperidone (Fanapt)
Pregnancy: Category C. Breastfeeding: Not known if enters breast milk/not recommended
Aripiprazole (ABILIFY)
Pregnancy: Category C. Developmental toxicity and teratogenic effects in animal studies. Breastfeeding: Enters breast milk/not recommended
Olanzapine (ZYPREXA)
Pregnancy: Category C. Breastfeeding: Enters breast milk/not recommended.
Paliperidone (Invega): Oral formulation
Pregnancy: Category C. Breastfeeding: Enters breast milk/not recommended. Significant

Table 5.8 (continued)

Quetiapine (Seroquel (IR), Seroquel XR)
Pregnancy: Category C. Breastfeeding: Enters breast milk/use caution
Risperidone (Risperdal)
Pregnancy: Category C. Breastfeeding: Enters breast milk/not recommended
Ziprasidone (Geodon)
Pregnancy: Category C. Breastfeeding: Enters breast milk/not recommended

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Chapter 6
ADHD Medications

Warning

This document does not include all of the medications, safety, efficacy infromation available. It is provided as a professional courtesy to provide pertinent data that will assist you in forming your own conclusions and making your own decisions. Please consult each Product Monograph of each product for detailed prescribing infromation.

6.1 Introduction

Medications should only be used when symptoms are pervasive across settings and are causing significant impairment in academic, social, or behavioral function, and after careful consideration of non-pharmacological approaches.

6.2 General Recommendations

A multimodal approach is advocated for the treatment of ADHD. Pharmacological treatment should be part of a comprehensive management plan that includes psychosocial treatment and education or vocational interventions.

Clinical practice is not always consistent with the indication stated in the product monograph. Clinicians are encouraged to know the product monograph recommendations, guidelines, and expert recommendations.

J. Sadek, *Clinician's Guide to Psychopharmacology*,
https://doi.org/10.1007/978-3-030-60766-1_6

Clinicians should discuss with their patient and the family (as appropriate) the indications for using the medication, the adverse side effects and their management, risk and benefit of treatment, alternative therapies, and any other information that would help the patient before obtaining consent for treatment. Clearly defined goals should be identified prior to commencing a trial of medication treatment.

Cost should be considered particularly when the patient has no medication coverage.

Family history of response and patient's prior early response to ADHD medications should be obtained. It can guide the clinician in their decision to select a medication.

Comorbid psychiatric or medical condition and current medications, and over-the-counter products, may also influence the selection of ADHD medication treatment.

When psychostimulant treatment is used, it should be continued for as long as it is of assistance to the person with ADHD and is not causing unacceptable side effects.

In school-age children, adolescents, and adults, methylphenidate (MPH)- or amphetamine-based products should be used as a first-line pharmacological treatment. Atomoxetine can be used as a first line in certain situations highlighted in the table below.

Extended-release formulation has the advantage of avoiding multiple dosing, and the stigma of taking medications during school for students.

In some cases the combined use of immediate-release and extended-release forms is required. This should only be considered if there is inadequate symptom control with the extended-release form.

6.3 Stimulant Medication

6.3.1 General Information About Stimulant Medications

Stimulants (either methylphenidate or amphetamine) are the most effective drug treatment for ADHD, with large effect sizes of about 1 when using rating scales in randomized controlled trials. Methylphenidate and mixed amphetamine salts are considered comparable in efficacy; 65–75% of children, adolescents, and adults achieved therapeutic response compared with 4% to 30% taking placebo in controlled studies. When one stimulant is ineffective, there is a 20–40% chance that the other stimulant will be effective, and it should be tried. When both methylphenidate and amphetamine salts have been tried, stimulant response rates are as high as 85%.

The following table explains the different options in ADHD treatment.

Stimulant medication

Methylphenidate-based products		Amphetamine-based products	
MPH IR (Ritalin®) 10 and 20 mg tablets	• Start with 5–10 mg b.i.d. to t.i.d. • Increase by 5–10 mg weekly • Maximum dose 60 mg for children and adolescents and 60 mg for adults (some experts recommend higher doses)	**Dexedrine®** (Dextroamphetamine) 5 mg tablet	• Start with 2.5–5 mg b.i.d. • Increase by 5 mg weekly • Maximum dose 40 mg for children, adolescents and adults
Ritalin® SR (MPH) 20 mg tablet	• Start with 20 mg in the morning • Increase by 20 mg weekly • **Maximum** dose 60 mg for children and for adolescents and 60 mg for adults (some experts recommend higher doses)	**Dexedrin® Spansule®** 10 and 15 mg spansule	• Start with 10 mg in the morning • Increase by 5–10 mg weekly • Maximum dose 40 mg for all ages
Biphentin® 10, 15, 20, 30, 40, 50, 60, 70, 80 mg capsule (**1st line**)	• Start with 10–20 mg in the morning • Increase by 10 mg weekly • Maximum dose 60 mg for children and 80 mg for adolescents and adults *40% immediate and 60% delayed release*	**Adderall XR®** (Amphetamine mixed salt) 5, 10, 15, 20, 25, 30 mg capsules **(1st line)** *Delivers 50% immediate and 50% delayed release*	• Start with 5–10 mg in the morning for children, 10 mg for adolescents and adults • Increase by 5–10 mg weekly • Maximum dose 30 mg for children and 30 mg for adolescents and adults
Concerta® 18, 27, 36, 54 mg tablets (**1st line**)	• Start with 18 mg in the morning • Increase by 18 mg weekly • Maximum dose 54 mg for children and 54 mg for adolescents, 72 mg and adults	**Vyyanse®** (Lisdexamfetamine dimeyslate) 20, 30, 40, 50, 60 mg capsules **(1st line)**	• Start with 20–30 mg in the morning • Increase by 10 mg weekly • Maximum dose 60 mg for children and 70 mg for adolescents and adults
MPH ER-C 18, 27, 36, 54 mg tablet	• Start with 18 mg in the morning • Increase by 18 mg weekly • Maximum dose 54 mg for all ages according to product monograph		

6.3.2 *Amphetamine-Based Psychostimulants*

Dexedrine® Tablets 5 mg

Dexedrine® Spansules 10, 15 mg

Adderall XR® Capsules5, 10, 15, 20, 25, 30 mg

Vyvanse® Capsules 10, 20, 30,40, 50, 60, 70* mg

Vyvanse® Chewable Tablets10, 20, 30, 40,50, 60 mg

6.3.3 Methylphenidate-Based Psychostimulants

Biphentin® Capsules 10, 15, 20, 30, 40, 50, 60, 80 mg

Foquest® Capsules 25, 35, 45, 55, 70, 85, 100 mg

Concerta® Extended ReleaseTabs 18, 27, 36, 54 mg

6.4 Additional Information About Medications (Alphabetical Order): Stimulants

6.4.1 Adderall XR® (Mixed Amphetamine Salts) (Source: CADDRA)

Adderall XR® is a controlled substance made up of a combination of different amphetamine salts that have effects on the noradrenaline and dopamine neurotransmitters. The mixed amphetamine salts in this medication are dextroamphetamine sulfate, dextro- and levoamphetamine sulfate, dextro- and levoamphetamine aspartate, and dextroamphetamine saccharate. Adderall consists of 25% levo- and 75% dextroamphetamine in four salts. It is used in the treatment of ADHD. The capsules can be opened and the beads inside the capsule can be sprinkled with no loss in efficacy. Adderall XR is a capsule with a 50:50 ratio of immediate- to delayed-release beads designed to release drug content in a long-acting time course. Adderall XR administered in once-daily doses of 20, 40, or 60 mg appears to be safe and efficacious for treating adults with ADHD. The treatment response rate and side effect profile of methylphenidate-based versus amphetamine-based products are similar.

6.4.2 *Biphentin® (Source: CADDRA)*

Biphentin® is a controlled-release methylphenidate (MPH) product and uses a multilayer release (MLRTM) delivery system that is long acting and produces 40% immediate and 60% delayed release. It can be opened and sprinkled on food, making it useful for children who cannot swallow pills, and since the beads within each capsule are all the same, there is no concern of pharmacokinetics problem in the body when it is poured. Patients can be switched from MPH easily (switching conversion rate: 10 mg t.i.d. MPH = 30 mg Biphentin). Biphentin was given once daily and produced equivalent improvements in behavioral and cognitive measures, and had a duration of effect at least as long as that of immediate-release MPH given twice daily (Fig. 6.1).

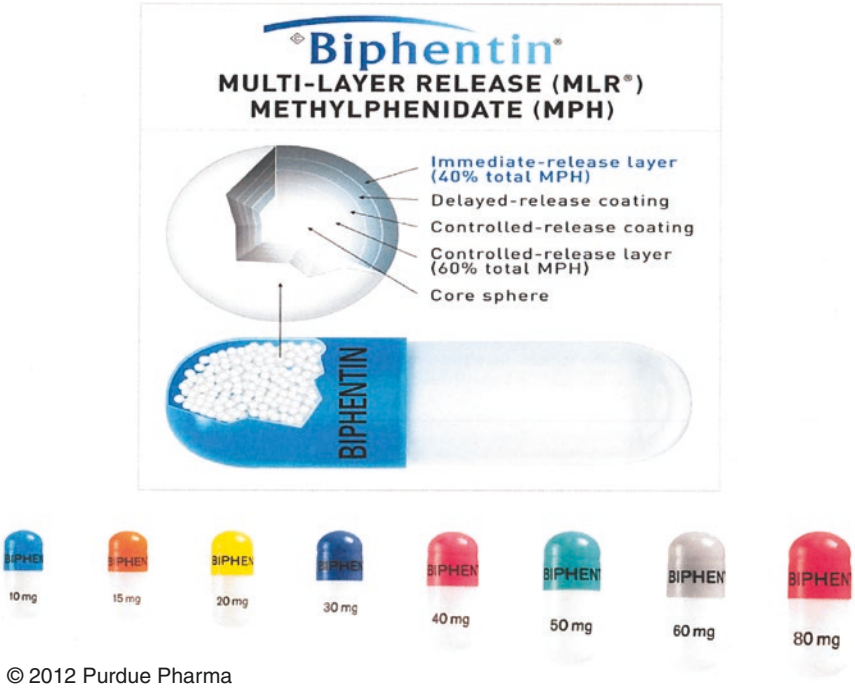

Fig. 6.1 Methylphenidate and amphetamine based stimulant medications

6.5 Concerta®

The information contained below is direct from the manufacturer, Janssen Ltd. (with permission) and does not include all of the Concerta® safety and efficacy information available. Please consult Concerta® Product Monograph for detailed prescribing information. Permission for reproduction has been received.

6.5.1 Product Summary

Concerta® (methylphenidate HCI) is indicated for the treatment of attention-deficit hyperactivity disorder (ADHD) in children (6–12 years of age), adolescents (13–18 years of age), and adults (>18 years of age).

Concerta® should not be taken by children under 6 years of age.

There is no data available for the use of Concerta® in patients over 65 years of age.

Concerta® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social). Effectiveness more than 4 weeks in children and adolescents, and for more than 7 weeks in adults, has not been systematically evaluated in placebo-controlled trials. Physicians electing to use Concerta® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

6.5.2 Warnings and Precautions

Theoretically, there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for sudden/cardiac death arising from the treatment with ADHD medications is lacking, prescribers should consider this potential risk, and Concerta® generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems.

Prior to initiating sympathomimetic treatments, a personal and family history and physical exam should be obtained to assess for cardiac disease. In patients with relevant risk factors, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram), based on the clinician's judgment. Patients who develop symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation.

Concerta® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior.

Concerta® should not be used in patients with preexisting gastrointestinal narrowing.

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with a prior history of seizures, in patients with prior EEG abnormalities in the absence of seizures, and, very rarely, in the absence of history of seizures and no prior EEG evidence of seizures.

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that Concerta® does not adversely affect their ability to engage in such activities.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring vision have been reported.

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder. Stimulants should be used with care to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode.

Treatment-emergent psychotic or manic symptoms, e.g.*, hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania, can be caused by stimulants at usual doses. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, these are often observed in children and adolescents with ADHD and have been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD.*

6.5.3 Adverse Events

The most common adverse events reported in children treated with Concerta®, regardless of causality, were headache (95), upper respiratory tract infections (8%), abdominal pain (7%), vomiting, anorexia, insomnia, increased cough, and pharyngitis (4% each).

The most common adverse events reported in adolescents treated with Concerta®, regardless of causality, were headache (9%), accidental injury (6%), insomnia (4%), fever, vomiting, and rhinitis (3%).

The most common adverse events reported in adults treated with Concerta®, regardless of causality, were decreased appetite (20–34%), headache (17–26%), dry mouth (7–21%), insomnia (12–17%), and nausea (8–16%).

6.5.4 Drug Interactions

Alcohol may exacerbate the CNS adverse effect of psychoactive drugs. Therefore, patients undergoing Concerta® therapy should be advised to avoid alcohol during treatment.

Because of possible increases in blood pressure and heart rate, Concerta® should be used cautiously with drugs with similar pharmacological actions.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants (e.g., warfarin), anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate.

Concerta® is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

6.5.5 Dosage and Administration

Concerta® tablets must be swallowed whole with liquids, and must not be chewed, divided, or crushed.

The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool.

The recommended starting dose of Concerta® for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily for all age groups. The maximum dosage for children and adolescents (6–18 years of age) is 54 mg once per day and 72 mg once per day for adults (>18 years of age).

References

1. *Concerta® (methylphenidate hydrochloride) extended-release tablets Product Monograph.*

6.6 Dexedrine® and Dexedrine® Spansules (DEX)

Dextroamphetamine (DEX) is classified as a psychostimulant which exact mechanism of action is not fully known but it is suggested that it blocks the reuptake of dopamine and norepinephrine, binds the dopamine transporter protein, and increases the release of dopamine making dopamine more available in the presynaptic neuron. That may explain its increased potency over MPH (i.e., only half the dose is required). Dexedrine® Spansules last for about 6–8 h. The drug has been available in Canada for decades.

DEX immediate release has a short half-life of 4–6 h, and requires multiple dosing of 2–3 times a day. DEX is quickly absorbed after oral administration and half the dose is eliminated unchanged and the other half goes through extensive metabolism mostly to benzoic acid. DEX can be used to supplement the long-acting medications if needed or when more flexibility in dosing is required.

6.7 Methylphenidate (MPH) Ritalin®, Ritalin® SR, and Generic Products

MPH is classified as a psychostimulant and is a controlled substance which exact mechanism of action is not fully known, but it is suggested that it blocks the reuptake of dopamine and norepinephrine, and binds the dopamine transporter protein. The efficacy and safety of MPH have been well established for decades with significant reduction in the core ADHD symptoms. MPH is rapidly and extensively absorbed after oral administration. After absorption, it undergoes significant first-pass metabolism in the liver by hydrolysis and 80% of the drug is excreted as ritalinic acid. MPH can be dissolved and injected. That can create some abuse potential, but remains much less than cocaine. Currently there are three pharmaceutical formulations of MPH: immediate release (IR), sustained release, and long acting. Ritalin® SR is an intermediate-acting sustained-release formulation but produces variable results due to pharmacokinetic changes, so it is less useful. An immediate-release or short-acting preparation can be used as a supplement to the long-acting preparation or when flexibility in dosing is required.

6.8 Vyvanse®

The information contained below is direct from the manufacturer, Shire PLC (with permission) and does not include all of the Vyvanse® safety and efficacy information available. Please consult Vyvanse® Product Monograph for detailed prescribing information.

6.8.1 Product Summary

VYVANSE® (lisdexamfetamine dimesylate capsules) is indicated for the treatment of attention-deficit hyperactivity disorder (ADHD). VYVANSE® is indicated as an integral part of a total treatment program for ADHD that may include other measures

(psychological, educational/vocational, and social) for patients with this syndrome (VYVANSE® Product Monograph).

VYVANSE® is a prodrug of d-amphetamine. A prodrug is an inactive compound that must undergo chemical or enzymatic transformation to an active form prior to exhibiting a pharmacological response.

After oral administration, LDX is rapidly absorbed from the GI tract and converted to d-amphetamine, which is responsible for the drug's activity, and L-lysine by hydrolysis in the blood (VYVANSE® Product Monograph). It was believed that conversion of LDX occurred by first-pass intestinal and/or hepatic metabolism. However, recent preclinical studies suggest that LDX is absorbed intact in the small intestine into the portal circulation and that the enzymatic hydrolysis of LDX to d-amphetamine occurs primarily in the blood by red blood cells, with a smaller amount converted in the gastrointestinal tract (Fig. 6.2).

The mode of therapeutic action of amphetamine in ADHD is not known (Vyvanse® Product Monograph). Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Unlike amphetamine, the parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro (Vyvanse® Product Monograph).

In patients who are either starting treatment for the first time or switching from another medication, 30 mg once daily in the morning is the usual starting dose. When in the judgement of the clinician a lower dose is appropriate, patients may begin treatment with 20 mg once daily in the morning. In clinical studies, doses of 20–70 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 30 mg/day, and adverse events and discontinuations were more frequent at higher doses. Doses greater than 70 mg/day of Vyvanse® have not been studied. If the physician, based on clinical judgment, decides that a dose increase is warranted for an individual patient, the maximum dose should not exceed 60 mg/day; dosage may be adjusted at approximately weekly intervals (Vyvanse® Product Monograph).

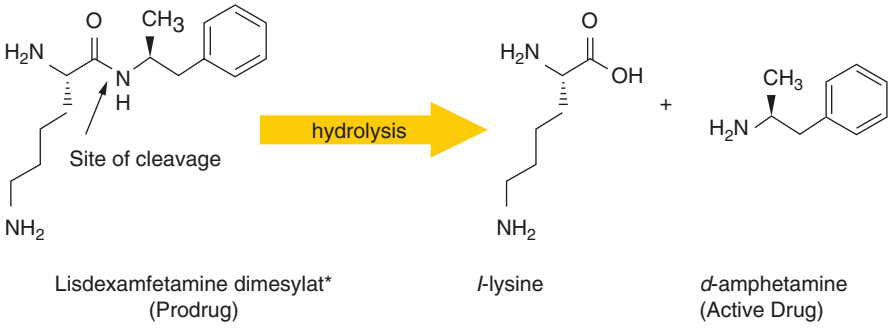

Fig. 6.2 Vyvanse conversion to active drug

Vyvanse® may be taken with or without food. Vyvanse® capsules may be taken whole, or the capsule may be opened and the entire contents dissolved in a glass of water. If the patient is using the solution administration method, the solution should be consumed immediately; it should not be stored. The dose of a single capsule should not be divided (Vyvanse® Product Monograph).

Vyvanse® is contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate-to-severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, allergy to amphetamines or to components of Vyvanse® or its container, glaucoma, agitated states, and a history of drug abuse during or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

Vyvanse® should not be used in patients with symptomatic cardiovascular disease including coronary artery disease and should generally not be used in patients with known serious structural cardiac abnormalities or other serious heart problems (e.g., cardiomyopathy, serious heart rhythm abnormalities) that may place them at increased vulnerability to the sympathomimetic effects of ADHD drugs.

Please consult the Vyvanse® Product Monograph for complete prescribing information, particularly in relation to preexisting psychosis, bipolar illness, emergence of new psychotic or manic symptoms, aggression, seizures, tics, growth suppression, and visual disturbances. The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.

Adverse events reported at a frequency ≥ 1% are as follows:

In the child clinical trials (patients 6–12 years old): Upper abdominal pain, vomiting, nausea, dry mouth, pyrexia, decreased weight, decreased appetite, anorexia, headache, dizziness, somnolence, psychomotor hyperactivity, insomnia, irritability, initial insomnia, affect lability, tic, obsessive-compulsive symptoms, agitation, aggression, rash, fatigue.

In the adolescent clinical trials (patients 13–17 years old): Palpitations, dry mouth, nausea, fatigue, decreased weight, increased blood pressure, decreased appetite, anorexia, headache, dizziness, tremor, insomnia, irritability, initial insomnia, affect lability, dyspnea, diarrhea, vomiting.

In the adult clinical trials (patients 18 years old and over): Palpitations, tachycardia, dry mouth, nausea, diarrhea, abdominal pain upper, feeling jittery, decreased weight, increased blood pressure, decreased appetite, anorexia, headache, tremor, insomnia, anxiety, initial insomnia, middle insomnia, agitation, restlessness, decreased libido, logorrhea, erectile dysfunction, dyspnea, hyperhidrosis, rash, dizziness, fatigue, irritability.

References

VYVANSE® Product Monograph. Shire Canada Inc. Stanczak A and Ferra A. Prodrugs and soft drugs. Pharmacol Rep. 2006;(58):599–613.

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AFT, Castellanos FX, eds. Stimulant drugs and ADHD: basic and clinical neuroscience. New York: Oxford University Press; 2001:332–52.

Nonstimulant medication

Atomoxetine (Strattera®) 10, 18, 25, 40, 60, 80, 100 mg capsules Use with ADHD patients who do not respond to, or are intolerant of, stimulant medication is contraindicated. **Consider as the first line if there is a comorbid substance abuse, severe tic disorder or anxiety disorder**	• Start with 0.5 mg per kilograms per day for children and adolescents, and 18 mg per day for adults • Increase gradually to reach a maintenance dose of 1.2 mg per kilograms per day in children and adolescents and 60–80 mg in adults • **Maximum** dose 60 mg per day for children and adolescents, and 100 mg for adults

6.9 Additional Information About Medications: Nonstimulants

6.9.1 Atomoxetine HCI: ATX Strattera® (ATX)

Atomoxetine, a highly selective norepinephrine reuptake inhibitor, is approved for the treatment of ADHD in children, adolescents, and adults. Unlike the stimulants, ATX is not a controlled substance; therefore, clinicians can provide samples and prescribe refills. ATX acts by blocking the norepinephrine reuptake pump on the presynaptic membrane, thus increasing the availability of intrasynaptic norepinephrine. FDA approved its use for ADHD patients over the age of 6 years. Atomoxetine is especially useful for ADHD patients who do not response or develop unacceptable side effects to stimulant use. It is also helpful in ADHD patients with comorbid tics, anxiety, and SUD. Atomoxetine has been shown to be effective in treating the core ADHD symptoms in children, adolescents, and adults. Several reported studies have shown improved functioning, better quality-of-life measures, and good long-term safety after two years of continuous atomoxetine use [1, 2]. Atomoxetine has also been shown to be an effective treatment for ADHD patients with comorbid anxiety and depression, and it may be a reasonable initial choice for those patients [1].

Atomoxetine is usually prescribed once daily, although twice-daily dosing can also be used. Atomoxetine should be initiated at doses of about 0.5 mg/kg body weight for about 2 weeks, and then titrated upward based on clinical response to 1.2 and 1.4 mg/kg, or a maximum total dose of approximately 100 mg/day. Higher doses have been used. It comes in seven doses (10, 18, 25, 40, 60, 80, and 100 mg). The capsules should never be opened as it may cause irritation of the gastric lining. It may take several weeks before the benefits from atomoxetine become apparent; therefore, it is important to inform patients about this to ensure continued compliance despite apparent little impact on symptoms during the initial stages of treatment. Measurements of

blood levels are not required. Atomoxetine undergoes extensive biotransformation, which is affected by poor metabolism by cytochrome P450 (CYP) 2D6 in a small percentage of the population; these patients have greater exposure to, and slower elimination of, atomoxetine than extensive metabolizers. Patients with hepatic insufficiency show an increase in atomoxetine exposure.

Common adverse effects with atomoxetine use include gastrointestinal upset, headaches, fatigue, and mild increase in heart rate and blood pressure. Rare, but important, adverse effects that should be discussed with patients include liver toxicity and increased suicidal thoughts. Two cases of liver toxicity were reported by the manufacturer, and in both these patients with liver damage, it was completely reversible after stopping the atomoxetine. ATX should be discontinued in patients who have jaundice and patients should contact their doctors if they develop pruritus, jaundice, dark urine, right upper quadrant tenderness, or unexplained flu-like symptoms. At this time, laboratory monitoring outside of routine medical care usually is not necessary [3]. An analysis of clinical trials by the manufacturer showed increased suicidal thoughts in 4 (0.4%) out of 1000 patients, but there were no attempted or completed suicides (Product Monograph). Nevertheless, the FDA warns clinicians to counsel patients about this potential risk.

6.10 Additional Information About Medications (Alphabetical Order): Other Medications

6.10.1 Bupropion HCI: Wellbutrin® SR Wellbutrin® XL

Bupropion hydrochloride is used as an antidepressant and in smoking cessation. It blocks the reuptake of noradrenaline and dopamine. It is not a controlled substance. Although it has been shown to be efficacious in the treatment of ADHD symptoms in children and adults, it is not currently approved for use in ADHD. Bupropion may be particularly useful in ADHD patients with comorbid SUD and depression, and/or nicotine use, and does not cause sexual dysfunction or risk of abuse or diversion. Side effects include insomnia, headache, weight loss, and a slightly increased risk of seizures. Wellbutrin® takes up to 4 to 6 weeks to show effect.

6.10.2 Clonidine

The main mechanism of action and therapeutic effects of clonidine and guanfacine for ADHD are not well understood. More research is needed, but animal studies suggest that alpha-2 adrenergic agonists may strengthen working memory by improving functional connectivity in the prefrontal cortex.

Clonidine has been used for the treatment of ADHD since the early 1990s. Systematic reviews of evidence from controlled clinical trials show that it is less

effective than stimulants and likely less effective than atomoxetine, tricyclic antidepressants, and bupropion. It is frequently used as an adjunct to stimulants to manage aggressive behavior or tics, or to improve sleep.

Common side effects include drowsiness, dry mouth, gastrointestinal upsets, hypotension, and dizziness. In children and adolescents with ADHD and comorbid ODD or conduct disorder, methylphenidate plus clonidine could be considered to treat the ADHD symptoms. In children and adolescents with ADHD and a comorbid tic disorder/Tourette syndrome, clonidine should be considered if ADHD symptoms show poor response to stimulants or atomoxetine. Discontinuation should be gradual to avoid rebound hypertension.

6.10.3 Guanfacine

Guanfacine is an alpha-2 adrenoreceptor agonist and is more selective for the alpha-2 receptor compared to clonidine. This selectivity imparts less sedation and less dizziness compared with clonidine. In a clinical trial, onset of therapeutic effect occurred between weeks 2 and 4. The most commonly reported treatment-emergent adverse events were dry mouth, headache, dizziness, gastrointestinal effects, constipation, abdominal pain, dry skin, fatigue, and sedation. Small to modest changes in blood pressure, heart rate, and ECG parameters were observed, but were not clinically meaningful [4]. It has been used in the treatment of ADHD, and is available in the USA.

Studies suggest that guanfacine in combination with psychostimulants does not produce a unique side effect pattern from that reported with monotherapy of either guanfacine or psychostimulants alone [5]. Guanfacine also demonstrated efficacy to reduce oppositional symptoms in children with combined ADHD and oppositional behaviors.

6.10.4 Modafinil (Alertec®)

Modafinil is a noncontrolled substance defined as a CNS stimulant. It is primarily indicated for narcolepsy, sleep apnea, and shift work sleep disorders. However, it is not approved for ADHD patients by Health Canada, nor the FDA. Modafinil at 4 mg/kg per day has been shown to improve cognitive and meta-cognitive functioning in healthy, non-sleep-deprived adults, and has been shown to have efficacy in the treatment of core ADHD symptoms in children.

Common side effects are headache, dry mouth, loss of appetite and weight, nausea, diarrhea, rhinitis, decreased effectiveness of hormonal birth control pills, and anxiety. Stevens-Johnson syndrome has been reported. There is a need for more research on modafinil use in ADHD.

6.10.5 Tricyclic Antidepressants (TCA)

Tricyclic antidepressants are older antidepressants that declined in use due to risk of death with overdose. The evidence for tricyclic antidepressants (TCAs) is largely from the early 1990s and is mainly based on imipramine/desipramine. The TCAs are more effective in addressing the behavioral symptoms (as measured by Conners' Teachers Rating Scale) than attention/concentration deficits.

Tricyclic antidepressants should not be routinely used in the treatment of ADHD, and when used, electrocardiographic monitoring should be conducted before and during treatment. Caution is warranted in patients with a personal or family history of cardiac problems.

6.11 ADHD Medication Contraindications and Drug Interactions

6.11.1 Contraindications to Stimulants

- Treatment with MAO inhibitors and for up to 14 days after discontinuation
- Glaucoma
- Advanced arteriosclerosis
- Untreated hyperthyroidism or thyroid dysfunction
- Known hypersensitivity or allergy to the products
- Moderate-to-severe hypertension (untreated)
- Pheochromocytoma
- Symptomatic cardiovascular disease or with potential to increase the risk of sudden cardiac death (e.g., coronary artery disease, structural heart disease, cardiomyopathy, history of arrhythmia).
- Acute psychiatric episodes of mania or psychosis

6.11.2 Contraindications to Atomoxetine (Strattera)

- Treatment with MAO inhibitors and for up to 14 days after discontinuation
- Glaucoma (narrow angle)
- Advanced arteriosclerosis
- Untreated hyperthyroidism or thyroid dysfunction
- Known hypersensitivity or allergy to the products
- Moderate-to-severe hypertension (untreated)
- Pheochromocytoma

- Symptomatic cardiovascular disease or with potential to increase the risk of sudden cardiac death (e.g., coronary artery disease, structural heart disease, cardiomyopathy, history of arrhythmia)

6.11.3 Contraindications to Guanfacine XR (Intuniv XR)

Known hypersensitivity or allergy to the products

Precautions are advised for those with a history of bradycardia, cardiovascular disease, heart block, hypotension, and syncope.

6.11.4 Main Potential Drug Interactions for Psychostimulants

- Monoamine oxidase inhibitors are contraindicated.
- SSRIs and SNRIs—possible increased risk of serotonin syndrome.
- TCAs—amphetamines and methylphenidate may interact with TCAs by different mechanisms.
- Antipsychotics (e.g., chlorpromazine, fluphenazine)—may reduce the effect of amphetamines.
- Anticonvulsants—methylphenidate may increase the level of phenytoin, primidone, and phenobarbital.
- Warfarin—methylphenidate may increase serum concentrations of warfarin.

6.11.5 Main Potential Drug Interactions for Atomoxetine (Strattera)

- Monoamine oxidase inhibitors are contraindicated.
- Inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, bupropion, quinidine)—may increase atomoxetine serum concentrations.
- Decongestants (e.g., pseudoephedrine)—possible increase in blood pressure and heart rate.
- QT-prolonging agents (e.g., quetiapine, quinidine)—may affect QTc interval, consider alternatives.

6.11.6 Main Potential Drug Interactions for Guanfacine XR (Intuniv XR)

- QT-prolonging drugs (e.g., quetiapine, quinidine)—since guanfacine XR may cause a decrease in heart rate, concomitant use with QT-prolonging drugs is not recommended.
- Beta-blockers—may increase the risk of rebound hypertensive effect if guanfacine XR is stopped abruptly.
- Anticonvulsants—guanfacine XR may increase serum concentrations of valproic acid. Carbamazepine, phenobarbital, and phenytoin may decrease serum concentrations of guanfacine XR through CYP3A4 induction.
- CYP3A4 inducers or inhibitors (e.g., rifampin, fluconazole, ritonavir)—inducers may reduce serum concentrations of guanfacine XR.
- CYP3A4 inhibitors may increase serum concentrations of guanfacine XR.

Source: Canadian ADHD Practice Guidelines 4th Edition, 2018, www.caddra.ca

6.12 General Contraindication of Psychostimulants

Mixed Salts of Amphetamines

- MAO inhibitors within 14 days, glaucoma, symptomatic cardiovascular disease, hyperthyroidism, moderate-to-severe hypertension

Dextroamphetamine and Methylphenidate

- MAO inhibitors within 14 days, glaucoma, and preexisting severe gastrointestinal narrowing

Caution with anticoagulants, anticonvulsants, and phenylbutazone and tricyclic antidepressants.

6.13 Drug Interactions

Markowitz and his group conducted a review that indicated that coadministration of MPH and imipramine could possibly result in increased concentrations of imipramine. However, it appears in all likelihood that metabolically generated desipramine concentrations are unaffected. There is also little involvement of MPH with CYP2D.

No clinically significant interactions occurred between desipramine and DEX.

Psychostimulants increase the level of phenytoin, carbamazepine, and phenobarbital. At the same time, these antiepileptics may lower the level of psychostimulants as they act as universal enzyme inducers.

Psychostimulants increase the level of MAO inhibitor, SSRI, and TCAs.

Psychostimulants may increase the effect of warfarin.

In the absence of schizophrenia, coadministration of antipsychotic agents with psychostimulants may be expected to result in only some mutual antagonism of central dopaminergic effects.

6.14 Management of Adverse Events

Adverse effects of stimulant medications include decreased appetite, sleep disturbance, headaches, irritability, nervousness, stomach upset, abdominal pain, nausea, abdominal discomfort, weight loss, tearfulness, stuttering, dizziness, and increased heart rate and blood pressure.

More severe side effects (rare) can include psychotic symptoms and sensitivity reactions that will require discontinuation of the medication.

Special consideration had been given to the impact of ADHD medications on growth, tics, seizure, cardiac events, and primary active psychotic disorders.

6.15 Contraindications of Psychostimulants

Stimulants are generally contraindicated in individuals with untreated thyroid dysfunction particularly hyperthyroidism, pheochromocytoma, glaucoma, known hypersensitivity or idiosyncrasy to the sympathetic amines and concurrent treatment (or treatment within 14 days) with monoamine oxidase inhibitors (MAO), and active substance use. Stimulants are also contraindicated in patients with significant heart disease hypertension and potential to increase the risk of sudden cardiac death (e.g., coronary artery disease, structural heart disease, cardiomyopathy, history of arrhythmia, and untreated hypertension).

6.16 Management of Adverse Events of ADHD Medications

Adverse effects of stimulant medications include decreased appetite, sleep disturbance, headaches, irritability, nervousness, stomach upset, abdominal pain, nausea, abdominal discomfort, weight loss, growth suppression, seizure, tearfulness, stuttering, dizziness, and increased heart rate and blood pressure.

More severe side effects (rare) can include psychotic symptoms and sensitivity reactions that will require discontinuation of the medication.

Special consideration had been given to the impact of ADHD medications on growth, tics, seizure, cardiac events, and primary active psychotic disorders and bipolar disorder.

6.17 Management of Side Effects

- **Cardiovascular risk**
  - In May 2006, Health Canada issued important safety information on ADHD medications and recommended that ADHD drugs should be started at the lowest possible dose, and increased slowly, as individual patient response to these drugs is known to vary widely. The recommendation also stated that:
  - ADHD drugs should not be used if a patient has:

    Symptomatic cardiac disease
    Moderate-to-severe hypertension
    Advanced arteriosclerosis, coronary artery disease
    Hyperthyroidism

  - Generally, ADHD drugs should not be used in patients with known structural cardiac abnormalities. Before prescribing an ADHD drug, it is important to be aware of whether the patient:

    Has a family history of sudden death, or death related to cardiac problems
    Participates in strenuous exercise
    Takes other sympathomimetic drugs

    These are thought to be additional risk factors. In patients with relevant risk factors, and based on the physician's judgment, further evaluation of the cardiovascular system may be considered before starting on the drug.

  - American Heart Association recommends that before beginning the therapy of stimulant medications, careful history should be obtained with special attention to symptoms, such as palpitations, syncope, or near syncope. Medication use, such as other prescribed and over-the-counter medications, should be determined. The family history should be reviewed with reference to the long QT syndrome or other causes of sudden, unexplained death. Detection of these symptoms, or risk factors, warrants a cardiovascular evaluation by a pediatric cardiologist before initiation of therapy.
  - Patients who are considered to need long-term treatment with ADHD drugs should undergo periodic evaluation of their cardiovascular status, based on the physician's judgment.
  - Patients taking drugs for the management of ADHD should be advised not to discontinue their medications without consultation with their physician.
  - At follow-up visits, patients receiving psychotropic drug therapy should be questioned about the addition of any drugs, and the occurrence of any of the above symptoms. The physical examination should include determination of heart rate and blood pressure.
  - ECG is not routinely recommended before starting stimulant medications.
  - Risk of sudden death is found to be similar to the general population.

- **Growth and appetite suppression**
  - Treatment with psychostimulant medications may result in a reduction in both height and weight. On average, the reduction in height amounts to approximately 1 centimeter per year during the first 1 to 3 years of treatment and 3 kilograms less than predicted for a period of over a year.
  - In the majority of cases, these effects are usually minor and the majority of patients fall within 95% of the population. The small group that suffer from significant growth suppression usually show a dose-dependent effect with doses over 1.5 mg per kilogram per day (given continuously) resulting in more problems; preschool children may be particularly vulnerable to growth effects.
  - Reduced caloric intake and suboptimal nutrition due to appetite suppression are the more likely causes of most growth suppression. Other hypotheses considered were the dysregulation of receptors in the growth system, effect of ADHD on growth hormone, prolactin, and possible increase or decrease in growth related to ADHD itself.
  - Monitor growth (weight and height) closely and use the growth charts.
    Simple strategies that might be helpful:

    Consuming additional meals, or snacks, early in the morning or late in the evening when the stimulant effects of the drug have worn off
    Obtaining dietary advice
    Consuming high-calorie foods of good nutritional value
    Changing the timing of the dose and/or meals
    Consuming high-energy snacks
    If growth is significantly affected by drug treatment (that is, the child or young person has not met the height expected for their age), the option of a planned break in treatment over school holidays may be considered to allow "catch-up" growth to occur. Drug holidays can be planned. Current data does not support specific guidelines indicating what magnitude of height or weight gain deceleration should trigger changes in the treatment regimen.
    In children, you can follow the medical criteria for referral to pediatric endocrinologist to consider growth hormone therapy in treatment of short stature, particularly if the height is more than 2 standard deviations below the population mean for the age, and a one-year decrease of more than 0.5 standard deviation in height. Consideration should also be given to the mother and father's height.

- **Jaundice, signs of liver disease, or biliary obstruction**
  - Stop medication immediately and seek the help of a specialist.
- **Agitation or mood disturbance**
  - Discern direct medication (emotional symptoms correlate with expected time of medication effect) as opposed to rebound effect (emotional symptoms occur later in day as medication is expected to wear off).

- If medication effect, discontinue medication.
- If rebound effect, add short-acting stimulant in the afternoon.

- **Psychotic symptoms**
  - New-onset psychotic symptoms that develop during the course of treatment of ADHD should be carefully evaluated. Development of psychosis as a side effect of psychostimulant is rare, and in most cases, the impact of psychotic adverse events is mild and mostly self-limiting. Several guidelines suggest that caution would be appropriate when prescribing ADHD drugs to children and young people with a family history of psychosis, or past history of psychotic episodes. A full psychiatric assessment should be conducted to determine if the psychotic symptoms are primary or secondary. A determination of starting an antipsychotic should be made at that point.

- **Seizures**
  - Despite the thin evidence of ADHD treatment in children with seizure disorder, it is not a contraindication to treat ADHD in the presence of seizure disorder.
    New-onset seizure has been observed after starting a few patients on ADHD medications, and ADHD patients have been shown to have incidence rates of unprovoked seizures and epilepsy two or three times greater than non-ADHD children. After careful evaluation, some patients who had documented seizure may start an antiepileptic medication.
  - If seizures are exacerbated in a child or young person with epilepsy, or de novo seizures emerge following introduction of stimulant or atomoxetine, another approach is to discontinue the drug and trial a different class.
  - It is important to rule out the possibility of substance abuse-inducing seizure in patients with ADHD.
  - Some studies support the lowering of seizure threshold with the use of psychostimulants but other studies found no evidence for an increase in relative risk for either MPH (0.8) or atomoxetine (1.1).
  - Fatal hepatotoxicity has been reported as an extremely rare event in young epileptic children with polypharmacy or inborn errors of metabolism, and the combination of atomoxetine with antiepileptic agents that might increase the risk of liver toxicity. It requires close clinical monitoring.
  - ADHD symptoms in epilepsy may be improved by nonspecific interventions, such as better seizure control, decreasing AED polypharmacy, reducing drug interactions, and switching to AEDs with fewer cognitive and behavioral effects of epilepsy.

- **Sleep disturbance**
  - Some clinicians concluded from several studies that the effect of ADHD medication on sleep may be beneficial, at least in some patients, but further research with more subjects, and with a variety of medication, is needed. Many patients treated with psychostimulants complain of insomnia, so an approach to manage this problem is necessary. Clinicians should document

sleep patterns and complaints before treatment to help interpret problems that may arise after medication has been prescribed.
  - Sleep hygiene, consisting of simple behavioral approaches that promote sound sleep (e.g., creating a restful environment and avoiding caffeine), is a primary approach for most patients with insomnia.
  - It might be helpful to look into shifting the dose to an earlier time or reducing an existing evening dose.
  - Atomoxetine may have an effect on sleep that is different from that of psychostimulants, including reduced sleep latency, but less efficiency. In a randomized, double-blinded, crossover trial, methylphenidate treatment for children with ADHD caused more initial insomnia, but fewer awakenings compared with atomoxetine treatment. Switching to atomoxetine may be considered for patients who prefer it, or who do not respond to adjunctive interventions for stimulant-associated insomnia.
  - Melatonin 3–6 mg at least half hour before sleep can be used. Other pharmacological options include trazodone 25–50 mg HS.

- **Suicide**
  - First, assess the suicide as a separate issue. Determine whether the patient is expressing suicidal ideation, intent, or plan or is there a history of chronic self-harm behavior as in a personality disorder. Evaluate if suicide developed after starting atomoxetine (more risk) or psychostimulant medications. Suicide prevention should be the first priority over any other consideration. You can use a tool, such as the Nova Scotia Suicide Risk Assessment Tool, to determine the risk level and management strategy. It is important to document all your findings about suicide and communicate them to others involved in the care of the patient. Caution is required when prescribing ADHD drugs to children and young adults with a past history of serious suicide attempts or depression. Families and caregivers should be advised of the need to recognize any emergence of emotional change, or self-injurious thinking, and to communicate well with the prescriber.
  - Patients being treated with ADHD drugs should be observed for the emergence of suicide-related events. If they do emerge in treatment, consideration should be given to dose reduction and/or other changes in therapeutic regimen, including the possibility of discontinuing medication, especially if symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.

- **Headache**: Typically self-resolves and use symptomatic care
- **Priapism** (rare): Medical emergency; discontinue medication
- **Tics:**
  - Tic disorder is not a contraindication for psychostimulant use; however, several patients may suffer from worsening of tics. Taking a history, and closely monitoring comorbid tics, is needed. It is important to note that several literature reviews suggested that stimulants are adequately safe in patients with both ADHD and tic disorder since tics are naturally waxing and waning. It is

often difficult to decide if worsening of tics is provoked by the ADHD medication. If no impairment, no action. If distressing, taper or discontinue stimulant medication and consider guanfacine ER monotherapy or augmentation.
– Treatment of both tics and ADHD symptoms can be treated together by adding antipsychotic medication to the psychostimulant or atomoxetine. The alpha-2 adrenergic agonist guanfacine or clonidine has been showing promise in the treatment of patients with ADHD and tic disorders.

6.18 Common Side Effects and Contraindications: Atomoxetine

- The common adverse effects associated with ATX include decreased appetite, drowsiness, abdominal pain, nausea and vomiting, dizziness, and increased heart rate and blood pressure.
- Less common side effects include dyspepsia and mood swings. There have been three published case reports of severe liver injury in children and adults using ATX. These individuals recovered when the drug was discontinued. Suicide-related behavior (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine.
- Atomoxetine is contraindicated for people with narrow-angle glaucoma and concurrent treatment (or treatment within 14 days) with monoamine oxidase inhibitors (MAO). It is also contraindicated in people with structural cardiac abnormalities, symptomatic cardiovascular disease, or other serious heart problems as it increases the heart rate and the blood pressure.

6.19 Child and Adolescent Dosing of ADHD Medications

6.19.1 Methylphenidate-Based Psychostimulants (Table 6.1)

6.19.2 ADHD Medication Effect Size

Stimulant medications = 1.0 and 0.4–0.8 in preschoolers.
a-Agonist medications, ER = 0.7
Atomoxetine = 0.7
0.2 = small effect size, 0.5 = moderate effect size, 0.8 = large effect size
Reference: Southammakosane C, PEDIATRICS Volume 136, number 2, August 2015

Table 6.1 Child and adolescent dosing of ADHD medications

Methylphenidate short-acting tablets 5 mg (generic) 10, 20 mg (Ritalin®), tablet pill can be crushed Duration of action: up to 3–4 h Starting dose: 5 mg b.i.d. to t.i.d. Dose titration: 5–10 mg at weekly intervals Max. dose/day: all ages = 60 mg
Biphentin® Extended release (capsules can be opened and contents dissolved) Capsules 10, 15, 20, 30, 40, 50, 60, 80 mg Duration of action: about 10 h Starting dose: 10–20 mg daily a.m. Dose titration 10 mg at weekly intervals Max. dose/day: children and adolescents = 60 mg and based on weight: 2 mg/kg
Concerta® Extended-release tabs 18, 27, 36, 54 mg Tablet needs to be swallowed whole to keep delivery mechanism intact Duration of action: up to 12 h Starting dose: 18 mg Dose titration: 18 mg at weekly intervals Max. dose/day: children = 54 mg Adolescents = 54 mg/adults = 72 mg Maximum dose based on weight: 2 mg/kg
Amphetamine-Based Psychostimulants
Dexedrine® (5 mg tablets short acting): high risk for diversion, abuse, and misuse Duration of action: lasts about 4 h Starting dose = 2.5–5 mg BID Dose titration by 2.5–5 mg at weekly intervals Maximum dose per day for children and adolescents = 20–30 mg
Intermediate acting **Dexedrine® Spansules** 10, 15 mg (cannot be crushed) Duration of action: lasts up to 6–8 h Starting dose = 10 mg daily in the morning Dose titration by 10 mg at weekly intervals Maximum dose per day for children and adolescents = 40 mg
Extended release **Adderall XR®** Capsules 5, 10, 15,20, 25, 30 mg and can be sprinkled Duration of action: lasts up to 12 hours Starting dose = 5–10 mg daily in the morning Dose titration by 5–10 mg at weekly intervals Maximum dose per day for children and adolescents = 30 mg Maximum dose based on weight: 1 mg/kg
Extended release **Vyvanse®** Capsules 10, 20, 30, 40,50, 60, 70 mg Capsule content can be diluted in water, orange juice, and yogurt Prodrug that may decrease the risk of recreational abuse Duration of action: lasts up to 13–14 h Starting dose = 10–20 mg daily in the morning Dose titration by 10 mg at weekly intervals Maximum dose per day for children and adolescents = 60 mg Maximum dose based on weight: 1 mg/kg

(continued)

Table 6.1 (continued)

Nonstimulants
Strattera (atomoxetine) Capsules 10, 18, 25,40, 60, 80, 100 mg Capsule needs to be swallowed whole to reduce GI side effects Duration of action: up to 24 h Starting dose for children and adolescents: 0.5 mg/kg/day Maintain dose for a minimum of 7–14 days before adjusting: Children = 0.8 then 1.2 mg/kg/day Max. dose per day: 1.4 mg/kg/day or 100 mg
Intuniv XR® (guanfacine XR) Extended-release tabs 1, 2, 3, 4 mg Pills need to be swallowed whole to keep delivery mechanism intact Duration of action: up to 24 h Starting dose for children and adolescents: 1 mg q.d. (morning or evening) Maintain dose for a minimum of 7 days before adjusting by no more than 1 mg increment weekly Maximum dose per day: monotherapy in ages 6–12 years = 4 mg Maximum dose per day: monotherapy in ages 13–17 years = 7 mg When used as adjunctive therapy to psychostimulants in ages 6–17, maximum dose 6–17 = 4 mg Maximum dose based on weight: 27–40.5 kg = 2 mg 40.5–45 kg = 3 mg Above 45 kg = 4 mg at bedtime

6.20 Pharmacological Management of ADHD Comorbidity

6.20.1 What Is the General Approach to Pharmacotherapy for Borderline Personality Disorder (BPD)?

Cochrane review of 27 trials stated that the current evidence from randomized controlled trials suggests that drug treatment, especially with mood stabilizers and second-generation antipsychotics, may be effective for treating a number of core symptoms and associated psychopathology, but the evidence does not currently support effectiveness for overall severity of borderline personality disorder. Pharmacotherapy should therefore be targeted at specific symptoms [6].

In adolescence, the risks of polypharmacy and iatrogenic harm are high [7].

One study shows some preliminary evidence for omega-3 fatty acids in adolescents with BPD and psychosis but no studies in BPD and ADHD [7].

6.20.2 What Are the Literature Recommendations for Pharmacological Therapy for Patients with ADHD and BPD?

There appears to be very limited data in relation to treatment of patients with comorbid ADHD-BPD [8].

Some reviewers argued that, while many patients with BPD receive "off-label" medications, no robust evidence of efficacy exists for pharmacotherapies in relation to "the core BPD symptoms of chronic feelings of emptiness, identity disturbance and abandonment."

Patients with BPD may have some tendencies to misuse or abuse controlled substances; therefore careful prescribing should take place particularly for short-acting stimulant medications [9].

With regard to the noradrenergic systems, clonidine treatment, which has been reported to effectively reduce impulsivity and hyperactivity in children and adolescents with ADHD, may also reduce aversive inner tension and the urge to self-harm in patients with BPD [10].

One author suggests that treating the core syndrome of ADHD may result in better functioning, less distress, and more control over behavior and possibly will have more engagement and benefit from psychotherapy [11].

6.20.3 What Are the Treatment Considerations in Comorbid ADHD and Anxiety Disorders?

Some authors raised concerns that stimulant medications may lead to exacerbation of anxiety disorders and sleep problems in patients with comorbid ADHD and anxiety disorders [12–14].

Some reports suggest that anxiety does not lessen response to ADHD stimulant treatment.

Combination of SSRI and stimulant medications has been combined successfully in the management of both conditions [15, 16].

Atomoxetine was found to be efficacious in reducing ADHD and anxiety symptoms in patients who had both conditions [17].

Non-pharmacological, psychosocial intervention may be a useful adjunct to pharmacotherapy in patients with ADHD and anxiety [18].

Anxiety disorders can present with symptoms consistent with ADHD. If there is no premorbid history of ADHD prior to onset of anxiety disorder it may be a primary anxiety disorder and not comorbid ADHD. Treatment should focus on anxiety disorder, and then once adequately treated can reassess for ADHD.

Multiple studies demonstrate the efficacy of a cognitive behavioral therapy intervention (CBT) in the treatment of anxiety disorders and OCD in children and adolescents. CBT outcomes are not as good if parental anxiety remains high and/or if paternal rejection and depression are present. Family therapy may be helpful to increase family awareness of how anxiety is influenced within the family dynamics and to improve communication and anxiety/distress tolerance within the family. Parent behavioral therapy (BT) focused on increasing positive parenting behavior support and reducing overprotectiveness and harsh discipline also has evidence of helping in ADHD [19].

Some guidelines recommend treating the most disabling disorder first. If clinicians start with ADHD treatment with a stimulant medication and the anxiety symptoms increase, then stimulant medication should be decreased or discontinued. Combination of SSRIs and stimulant medications is possible but frequent monitoring is required [20].

Results of a meta-analysis for comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders were recently published. It concludes that there is evidence supporting the effectiveness of CBT and SSRIs for reducing childhood anxiety symptoms. Serotonin-norepinephrine reuptake inhibitors also appear to be effective based on less consistent evidence. The review suggests that there is a need for head-to-head comparisons between various medications and comparisons with CBT [21].

6.20.4 What Are the Dosing Recommendations for Atomoxetine (ATX) in Children and Adolescents?

ATX can be started at 10–20 mg and titrated to optimal dose (80 mg) over 11 weeks. The maximum daily dose approved by the US FDA for children and adolescents who weigh less than 70 kg is 1.4 mg/kg/day; for children and adolescents who weigh 70 kg and adults, it is 100 mg/day.

Studies using up to 2.4 mg/kg/day and 3.0 mg/kg/day have not shown an improved overall response in children or adolescents who did not respond to lower doses of ATX (1.2–1.8 mg/kg/day) [1].

6.20.5 What Are the Specific Tapering Recommendations to Stop Atomoxetine and What Are the Withdrawal Symptoms?

When discontinuing ATX, tapering is not necessary as stopping the medication is not associated with acute discontinuation symptoms [3].

6.20.6 What Are the Dosing Reduction Requirements in Adolescents with Hepatic Impairment when Prescribing Atomoxetine?

For subjects with hepatic impairment, the dose should be reduced to 50% of the normal dose for those with moderate impairment, and to 25% of the original dose for those with severe impairment [1].

6.20.7 Does the Literature Recommend Fast Dose Titration or Slow Dose Titration when Starting Atomoxetine?

There is limited data. One study evaluated the effects of a daily dosing regimen and speed of titration in a post hoc analysis of 22 child/adolescent and found the following:

The time to the start of treatment-emergent adverse effects was significantly shorter in subjects who received once-a-day versus twice-a-day dosing. Time to onset of decreased appetite, abdominal pain, and somnolence significantly decreased with fast titration in children and adults.

Fast titration was defined as ATX 0.5 mg/kg/day × 7 days, then ATX 1.2 mg/kg/day versus slow titration ATX 0.5 mg/kg/day × 7 days, then ATX 0.8 mg/kg/day for 7 days, followed by ATX 1.2 mg/kg/day for children [1].

6.20.8 Describe Some of the Controversial Management Considerations that Clinicians Face when Using ADHD Medications in Individuals with ADHD and Addictions?

ADHD medications appear to have little to no efficacy in the treatment of comorbid addictive disorders but do not appear to exacerbate addictive disorders. Majority of the controlled clinical trials did not find enough evidence of exacerbation but it should be noted that a few cases of abuse and misuse have been reported in uncontrolled clinical studies.

ADHD medications appear less effective in ADHD patients with addictive disorders compared to patients without these comorbid disorders. It appears that although the various medications (both stimulants and nonstimulants) assessed in several studies can improve ADHD in the short term, they are less effective in ADHD patients with addictive disorders than in patients without these comorbid disorders. Researchers challenge the available evidence and consider it ambiguous in terms of whether differences in adherence affect clinical outcomes in patients treated for ADHD.

ADHD medications seem to exert a strong placebo effect on ADHD symptoms in patients with addictive disorders. Some studies report placebo response rates as high as 45–55% in adults. The high placebo response may be related to a nonspecific effect of addiction treatment on impulsivity and aggressiveness. Such an effect probably lessens the severity of some clinical manifestations of ADHD. Another possible explanation may be related to the high expectations of patients with addictions or their treating clinicians that medical treatment will improve ADHD symptoms.

Possibly the concomitant psychosocial treatment (mainly cognitive behavioral therapy) in many of the controlled studies may have contributed to the reported efficacy of the ADHD medications.

Some researchers suggest that ADHD- and SUD-related craving shares neurobiological similarities, and that treatment of ADHD may reduce craving for substances and subsequently reduce the risk for relapse to substance use. An aggregate of the literature seems to suggest that early stimulant treatment reduces, or delays, the onset of SUDs and perhaps cigarette smoking into adolescence; however, the protective effect is lost in adulthood. These issues remain unclear and further research is needed in these areas.

6.20.9 Describe Some of the Factors that Help Make the Decision of How Long to Wait for SUD to Be Under Control Before Initiating Pharmacological Treatment of ADHD?

The relationship between ADHD and SUD is bidirectional. The decision to treat or not treat ADHD in the context of active substance abuse depends on numerous factors. Among these are:

1. The type and severity of substance involved
2. The patient's opinion about the importance of ADHD in his/her particular case
3. The degree of diagnostic uncertainty for ADHD
4. The risk of exacerbating SUD and other mental disorders by treating ADHD
5. The experience of the treatment team in the management of SUD and ADHD comorbidity
6. The ability to closely monitor the patient's adherence and response to treatment

It is recommended to individualize the treatment decision due to the multiple challenges of ADHD and SUD comorbidity. The decision should be done on a case-by-case basis in which the arguments for and against immediate pharmacological treatment of ADHD are carefully weighed. The results of such an assessment will indicate when to initiate ADHD treatment and the most appropriate choice of medication.

6.20.10 Is There an Association Between Stimulant Medication and Substance-Use Disorder?

Stimulant medications not only lower concurrent risk but also lower long-term risk of substance-related events. ADHD medication is unlikely to be associated with greater risk of substance-related problems in adolescence or adulthood [22].

Patients who initiated treatment of ADHD at an early age (aged 9 or younger) had lower risk for substance use compared to those who initiated treatment in adolescence [23].

Longer duration of stimulant medication therapy for ADHD was associated with lower rates of substance use during late adolescence as compared to shorter duration of stimulant medication therapy for ADHD at all developmental periods, especially among those who initiated stimulant medication therapy for ADHD in preschool, elementary, and middle school. However, the length of duration of stimulant medication therapy for ADHD on substance use appeared to play a less pronounced role among those who initiated stimulant medication therapy for ADHD in high school [23].

6.20.11 What Are the Unique Needs of Adolescents with Substance-Use Disorders?

- Adolescent drug abusers have unique needs stemming from their immature neurocognitive and psychosocial stage of development. Research suggests that the brain areas most closely associated with aspects of behavior such as decision-making, judgment, planning, and self-control undergo a period of rapid development during adolescence and young adulthood; therefore adolescents need additional support during that period.
- Adolescent drug abuse is also often comorbid with ADHD, ODD, conduct disorder, and mood and anxiety disorders. Treatment of comorbid disorders is very valuable.
- Positive family involvement into the care of adolescents as well as integrating other systems in which the adolescent participates such as school and athletics, and recognizing the importance of prosocial peer relationships, is very important in effective treatment because adolescents are very sensitive to social cues.
- Medications for substance abuse among adolescents may in certain cases be helpful [24].

6.20.12 What Are the Treatment Recommendations for Substance-Abusing Patients with ADHD?

The strategy for caring for patients with SUD and ADHD should include consideration of both disorders. A complete assessment of the substance use and ADHD needs to be conducted prior to treatment. Once the substance use is better controlled

or in a harm reduction model, the uses of psychotherapeutic intervention such as motivational interviewing, family therapy, and CBT appear to be useful as a first step for addressing both the ADHD and SUD. They would incorporate structured and goal-directed sessions as well as active therapist involvement. Additionally, pharmacological agents can be used in conjunction with psychotherapy in order to alleviate ADHD symptoms and further substance use. Psychoeducation is also useful. Furthermore, young adults with SUD benefit from both family and individual intervention.

Several review studies have suggested that the use of nonstimulant agents (atomoxetine), extended-release or longer acting stimulants with lower abuse liability and diversion, and potential antidepressants (bupropion) is preferable when treating patients with comorbid ADHD and SUD ([25]; Griswold 2008; American family physician).

There have been some differences in the literature regarding response to atomoxetine depending upon the time the treatment was initiated (e.g., whether the study subjects were actively engaging in substance abuse or dependence versus being engaged in brief abstinence). Further research is also needed in these areas [26].

Psychotherapeutic interventions in addition to pharmacological treatment can be beneficial. Cognitive behavioral therapy (CBT) may be of particular interest, and neurofeedback (given preliminary evidence suggesting its possible efficacy in adolescents with comorbid ADHD and SUD) [27].

The family therapy models most commonly noted in the research literature for adolescent substance use include Brief Strategic Family Therapy (BSFT), Family Behavior Therapy, Functional Family Therapy (FFT), Multidimensional Family Therapy (MDFT), and Multisystem Family Therapy (MST).

Adolescent Community Reinforcement Approach (A-CRA) is designed to increase adolescents' access to reinforce through operant conditioning principles and skill training activities so that non-substance-using behaviors are rewarded and can replace substance-use behavior. It includes a combination of CBT (with an emphasis on behavioral procedures) and caregiver/family procedures. It uses a positive, nonconfrontational approach to promote abstinence, healthy social activities, positive peer relationships, and improved relationships with family. It has been successfully used for ADHD and SUD comorbidity in adolescents [28].

6.20.13 What Is the Relationship Between ADHD Medication and Suicide?

6.20.13.1 Atomoxetine

In 2005, both the US Food and Drug Administration and Health Canada warned of increased rates of suicidal ideation among patients taking atomoxetine in placebo-controlled trials. The latter published a meta-analysis that prompted the warnings after reviewing 12 studies comparing outcomes in children treated with atomoxetine

or placebo. Suicidal ideation was reported to have occurred in 5 (0.37%) of 1357 children given atomoxetine, but in none of the 851 children who received placebo [29].

As a result, health providers were advised to closely monitor children and adolescents treated with atomoxetine for aggravation of symptoms such as agitation, irritability, suicidal thinking or behaviors, and unusual changes in behavior.

A case report was published in 2008 of acute agitation and suicidal ideation in an 11-year-old boy after commencing atomoxetine [30].

6.20.13.2 Stimulant Medications

One study that examined the adult outcomes of childhood stimulant medication in a relatively small group of 32 subjects found that for 20 young adults, the childhood treatment had no lasting effect, but for 11 others, the positive effects lasted long after treatment was discontinued. Higher dosage of medication was associated with fewer diagnoses of alcoholism and with fewer suicide attempts [31].

There are seven comparator trials of atomoxetine and methylphenidate, five of which were randomized double blind and included in the analysis of suicide risk while receiving ADHD medications. In total there were 5 events using FDA coding 1–4, atomoxetine 3/559 and methylphenidate 2/465. All events using FDA coding 1–4 were suicidal ideation: there were no suicide attempts nor completed suicides and there was no difference in risk between atomoxetine and methylphenidate with a Mantel-Haenszel risk ratio of 0.52 (95% CI; 0.06, 4.54). Mantel-Haenszel risk ratio (MH) is used for categorical data replacing the odds ratio (OR) [32].

6.20.14 What Do I Tell Patients and Families when Asked About Suicide and ADHD Medication?

Some patients may inquire about suicide risk when taking ADHD medications particularly in North America after Health Canada announcement in March 2015: "ADHD drugs may increase risk of suicidal thoughts and behaviours in some people; benefits still outweigh risks."

Health Canada reported increased risk of suicidal ideation when the ADHD medication was started, when the dose was changed, and when the medication was stopped. Mood symptoms may be induced by psychostimulants (irritability, dysphoria).

It was suggested that while patients and their families should be made aware of the increased risk of suicidal thoughts and behaviors among people who have ADHD, families should also be told that this strong warning on ADHD medications should not be a cause for panic and that:

- Patients taking ADHD medications, as well as their parents, families, and friends, should be monitored for suicidal thoughts and behaviors.

- Patients and families be encouraged to report any distressing thoughts or feelings immediately to their doctor. This applies at all stages of treatment and even after ADHD therapy has been stopped.
- ADHD medication should not be changed or stopped without medical advice.
- Healthcare professionals monitor patients more closely around the start of treatment, at dose change, and when medication is stopped.
- Suicide risk assessment for patients at moderate or high risk of suicide is essential and a clear management plan should be developed (CADDRA 2015).

6.20.15 Describe Some of the Pharmacological Treatments for Tics?

6.20.15.1 Alpha-Adrenergic Agonists

- Alpha-adrenergic agonists are first-line drug treatment for mild-to-moderate tics because of their efficacy and low possibility of adverse effects:
  - Clonidine and guanfacine are the two most common alpha-2 agonists:

    They both act via a presynaptic alpha-2 adrenoceptor mechanism, resulting in the release of norepinephrine.
    Studies have shown that both drugs have shown efficacy in reducing tics in individuals with or without ADHD.
    Guanfacine is often preferred due to its milder adverse effects (less drowsiness and sedation).
  - Common adverse effects include sedation, headache, hypotension, and upset stomach [33, 34].

6.20.15.2 Neuroleptics

Neuroleptics had been used in the treatment of moderate-to-severe tics.

Typical (First-Generation) Neuroleptics/Antipsychotics

- **Haloperidol** and **pimozide** are the only two drugs that have been approved by the US Food and Drug Administration for the treatment of TS in the USA:
  - They are *typical (first-generation) neuroleptics* and *antipsychotic* drugs that act via dopamine D2 receptor antagonism.
  - Adverse effects associated with typical neuroleptics include sedation, depression, weight gain, hepatotoxicity, and extrapyramidal symptoms, e.g., akathisia and acute dystonic reactions, parkinsonism, rigidity, abnormal movements, and tardive syndromes (e.g., tardive dyskinesia and tardive dystonia) (Serajee FJ 2015).

Atypical (Second-Generation) Neuroleptics/Antipsychotics

- These drugs may act via dopamine D2 receptor (as do *typical antipsychotics*), and also block serotonin receptors to differing degrees.
- Risperidone, aripiprazole, and quetiapine are some *atypical antipsychotics* that have been studied for the treatment of TS.
- Risperidone is the most studied atypical antipsychotic for the treatment of TS.
- Aripiprazole has a different action than other atypical antipsychotics. It is a partial agonist at dopamine D2 and D3 receptors and it is a partial agonist at serotonin 5-HT (1A) receptors.
- Adverse effects of atypical neuroleptics include sedation, metabolic effects (e.g., weight gain and glucose intolerance, dyslipidemia), cardiac adverse effects, and extrapyramidal side effects (Serajee FJ 2015).

6.20.16 Other Pharmacological Treatments

Other medication options that were used include *benzodiazepines* (e.g., clonazepam), atomoxetine, tetrabenazine, topiramate, baclofen, and onabotulinum toxin A injections (botulinum toxin can be used to target localized and potentially dangerous tics) and finally, in case of medication resistance, deep brain stimulation (DBS) can be considered [35].

6.20.16.1 Possible New Medications for ADHD (Investigational or Emerging)

1. Viloxazine
   Norepinephrine reuptake inhibitor (NRI) that demonstrated activity in ADHD. Some researchers concluded that in vivo, viloxazine increased extracellular 5-HT levels in the prefrontal cortex (PFC), a brain area implicated in ADHD. Viloxazine also exhibited moderate inhibitory effects on the norepinephrine transporter (NET) in vitro and in vivo and elicited moderate activity at noradrenergic and dopaminergic systems.
2. Centanafadine
   Centanafadine is a triple monoamine inhibitor of norepinephrine, dopamine, and serotonin transporter reuptake. Centanafadine demonstrates the highest activity for norepinephrine reuptake inhibition, 6 times less for dopamine reuptake inhibition, and 14 times less for serotonin reuptake inhibition.

   A recent phase II study supported the continued development of centanafadine-SR at doses up to 400 mg/day in treatment of ADHD.
3. Jornay PM
   Available in the USA. It is a methylphenidate product and is indicated for patients 6 years of age and older and is intended for dosing in the evening. The treatment utilizes a proprietary drug delivery platform which consists of two functional

film coatings: the first layer delays the initial drug release for up to 10 h and the second layer helps control the release rate of the active ingredient throughout the day.

4. Fasoracetam

Fasoracetam is a metabotropic glutamate receptor (mGluR) activator.

The glutamatergic neurotransmitter system may play an important role in attention-deficit hyperactivity disorder (ADHD). A recent 5-week, open-label, single-blind, placebo-controlled study designed to examine the safety, pharmacokinetics, and responsiveness of fasoracetam, in 30 adolescents, age 12–17 years with ADHD was completed. It concluded that this drug may improve ADHD symptoms.

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Chapter 7
Sedative Hypnotics

7.1 Describe Some of the Clinical Guidelines in the Evaluation and Pharmacological Management of Insomnia?

"Insomnia is primarily diagnosed by clinical evaluation through a thorough sleep history and detailed medical, substance, and psychiatric history. The sleep history should cover specific insomnia complaints, pre-sleep conditions, sleep-wake patterns, other sleep-related symptoms, and daytime consequences.

Instruments which are helpful in the evaluation and differential diagnosis of insomnia include self-administered questionnaires, at-home sleep logs, symptom checklists, psychological screening tests, and bed partner interviews. At minimum, the patient should complete: (1) A general medical/psychiatric questionnaire to identify comorbid disorders (2) The Epworth Sleepiness Scale or other sleepiness assessment to identify sleepy patients and comorbid disorders of sleepiness (3) A 2-week sleep log to identify general patterns of sleep-wake times and day-to-day variability.

Additional assessment instruments that may aid in the baseline evaluation and outcomes follow-up of patients with chronic insomnia include measures of subjective sleep quality, psychological assessment scales, daytime function, quality of life, and dysfunctional beliefs and attitudes.

Physical and mental status examination may provide important information regarding comorbid conditions and differential diagnosis.

Polysomnography and daytime multiple sleep latency testing (MSLT) are not indicated in the routine evaluation of chronic insomnia, including insomnia due to psychiatric or neuropsychiatric disorders.

Polysomnography is indicated when there is reasonable clinical suspicion of breathing (sleep apnea) or movement disorders, when initial diagnosis is uncertain, treatment fails (behavioral or pharmacologic), or precipitous arousals occur with violent or injurious behavior.

J. Sadek, *Clinician's Guide to Psychopharmacology*,
https://doi.org/10.1007/978-3-030-60766-1_7

Initial approaches to treatment should include at least one behavioral intervention such as *stimulus control therapy or relaxation therapy, or the combination of cognitive therapy, stimulus control therapy, sleep restriction therapy with or without relaxation therapy*—otherwise known as cognitive behavioral therapy for insomnia (CBT-I).

Although all patients with chronic insomnia should adhere to rules of good *sleep hygiene*, there is insufficient evidence to indicate that sleep hygiene alone is effective in the treatment of chronic insomnia.

7.1.1 Pharmacological Treatment

Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.

When pharmacotherapy is utilized, the choice of a specific pharmacological agent within a class, should be directed by: (1) symptom pattern; (2) treatment goals; (3) past treatment responses; (4) patient preference; (5) cost; (6) availability of other treatments; (7) comorbid conditions; (8) contraindications; (9) concurrent medication interactions; and (10) side effects.

For patients with primary insomnia (psychophysiologic, idiopathic or paradoxical ICSD-2 subtypes), when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is: Short-intermediate acting benzodiazepine receptor agonists (BZD or newer BzRAs): examples of these medications include temazepam, zolpidem, eszopiclone, and zaleplon.

Alternate short-intermediate acting BzRAs or ramelteon if the initial agent has been unsuccessful.

Sedating antidepressants can be used, especially when used in conjunction with treating comorbid depression/anxiety: examples of these include trazodone, amitriptyline, doxepin, and mirtazapine" [2].

7.2 Explain the Pharmacology of Nonbenzodiazepine Hypnotics?

They are highly selective for the GABA-chloride channel within the type I BDZ (BZ_1) receptors in the CNS. They have a strong sedative and hypnotic profile that predominates over the anticonvulsant and anxiolytic activity and, moreover, appears practically devoid of myorelaxant properties. There are several nonbenzodiazepine hypnotics approved by the Food and Drug Administration for the treatment of insomnia including zolpidem, zaleplon, zopiclone, and eszopiclone.

Zaleplon is an ultrashort-acting Z-drug that has the benefit of reducing sleep latency and can be taken after trying but failing to fall asleep. Zaleplon, though not appropriate for sleep maintenance therapy, may be taken for middle-of-the-night awakening.

Zopiclone is a cyclopyrrolone drug with a chemical structure unrelated to zolpidem, benzodiazepines, or other CNS depressants; it has similar pharmacodynamic and pharmacokinetic properties to zolpidem. It is available as a racemic mixture of two enantiomers, one of which is marketed in the USA, the (S)-enantiomer, eszopiclone. Zopiclone shows preferential agonist activity at the α_1 subunit of the $GABA_A$ receptor and its duration of action is the longest of the Z-drugs, comparable with some short-acting benzodiazepines. Hence, zopiclone is useful in both induction and maintenance of sleep. Eszopiclone differs from its racemic mixture in that it has greater efficacy at the α_2 and α_3 subunits. The addition of the R-enantiomer in racemic zopiclone may augment the efficacy at the α_1 subunit and potentially lead to increased sedation and residual effects.

Zopiclone is a cyclopyrrolone that differs from zolpidem by acting on the α1 and α2 subunits of GABA-A receptors and presenting a half-life of 5.3 h. Zopiclone with the longest duration of action has the greatest residual effect, like short-acting benzodiazepines. Zopiclone has been prescribed in the treatment of early chronic insomnia or sleep maintenance and is well tolerated by the elderly; the recommended dose is 3.75 to 7.5 mg.

Eszopiclone is cyclopyrrolone and may be used for sleep maintenance insomnia, with reported benefits of improving quality of life, reducing workplace absenteeism, and decreasing the severity of insomnia with doses between 1 and 3 mg at bedtime [4–11, 13].

Compare the dose range of nonbenzodiazepines:

	Daily dose range	T max (h)
Zolpidem IR	5–10 mg	1–2
Zolpidem ER	6.25–12.5 mg	1.5–2.5
Zopiclone	3.75–7.5 mg	1.5–2
Eszopiclone	1–3 mg	1–1.5
Zaleplon	5–20	0.7–1.4

7.3 Describe the Pharmacology of Zolpidem [12–14]?

Indication: Zolpidem is a nonbenzodiazepine receptor modulator primarily used in the FDA-approved short-term treatment of insomnia aimed at patients with difficulty starting sleep. It improves measures of sleep latency and sleep duration, and

reduces the number of awakenings in patients with transient insomnia. It also improves sleep quality in patients with chronic insomnia as well and can act as a minor muscle relaxant. Research also shows that it is rapid and effective in restoring brain function in patients who are in a vegetative state after brain injury as the drug has the potential to completely or partially reverse the abnormal metabolism of damaged brain cells. Usually, patients recover if the injury is in non-brain stem area.

Mechanism of action: Zolpidem, a nonbenzodiazepine hypnotic agent, works as a GABAa receptor chloride channel modulator/agonist that increases GABA inhibitory effects leading to sedation. It also has anticonvulsant, anxiolytic, and minor myorelaxant properties. The GABAa receptor also called as GABA-BZ is found in the sensorimotor cortical regions, globus pallidus, inferior colliculus, pons, ventral thalamic complex, olfactory bulb, cerebellum, and substantial in the brain. The drug upregulates these receptors allowing for the sedative effects leading to the preservation of deep sleep. Differing from benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem in vitro binds the BZ1 receptor preferentially with a high affinity ratio of the alpha1/alpha5 subunits. The selective binding of zolpidem on the BZ1 receptor may explain the relative absence of myorelaxant and anticonvulsant effects. Overall, zolpidem is not recommended for the general population as first-line treatment because of its high potential for abuse. Drugs like controlled-release melatonin and doxepin may be used as first line in addition to proper sleep hygiene and cognitive behavioral therapy.

7.3.1 Administration

Zolpidem is rapidly absorbed by the gastrointestinal tract and has a short half-life in healthy patients. It is administered in 5 mg and 10 mg tablets orally depending on the quality of sleep in which the patient is receiving. Zolpidem is then converted to an inactive metabolite and excreted by the kidneys. Tablets are not scored. Ingestion with or immediately after food intake may slow the effects of this drug.

Elderly patients must receive a 5 mg dosage as their concentrations were found to be higher than young adults during clinical trials. Dosage should be changed in patients with hepatic impairment as the half-life of zolpidem was found to be a multitude of times larger than patients with normal health. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7–8 h remaining before the planned time of awakening. Zolpidem clearance is lower in women.

Patients with end-stage renal failure undergoing dialysis do not need dosage adjustments, as they were not significantly different from patients with renal impairments. Their concentrations, however, should be closely watched daily.

Pediatric patients should not be given zolpidem as their effectiveness has not been found yet. The research found that hallucinations might occur in a small percentage of pediatric patients who received zolpidem.

Some adverse effects include anaphylaxis, changes in behavior, withdrawal, and central nervous system (CNS) depression.

In rare situations, patients have reported tongue, larynx, or glottis swelling in the form of angioedema. Also, patients have reported shortness of breath, airway closure, nausea, and vomiting. If patients report these, do not readminister patients with the drug. Patients who do experience closure in throat, glottis, or larynx should be sent to the emergency department.

Changes in behavior and abnormal thinking have been reported as well. Patients have been found to show aggressiveness and extroversion that is abnormal for the person's usual behavior.

Like patients who have alcohol or drug toxicities, patients have experienced auditory and visual hallucinations associated with strange behavior and agitation.

The patient was also found to experience a behavior called sleep driving, in which the patient drives while not fully awake after intake of sedative-hypnotic with no recollection of the event. Consumption of alcohol or any other CNS depressant was found to increase these events as they enhance sedation when combined. In these cases, the drug needs to be discontinued.

Patients who are depressed should also not take zolpidem as it worsens depression along with suicidal ideations and actions.

Contraindication: It is only contraindicated in patients with a known allergy to the drug or inactive ingredients in the formula. Also, before administering zolpidem, other causes of sleep deprivations must be evaluated, for example, any presenting physical or psychiatric histories.

Caution should be used in patients who are also taking drugs that affect drug metabolism via cytochrome P450. Consider giving a lower dosage of zolpidem as patients have shown to enhance sedative effects.

Patients taking imipramine and chlorpromazine should avoid using zolpidem. When combined, these medications cause decreased alertness and psychomotor performance.

7.3.2 Monitoring

The drug elimination half-life for 5 mg of zolpidem was found to be 2.6 h. Respectively, the elimination half-life for patients who are given 10 mg of zolpidem is 2.5 h with ranges between 1.4 and 3.8 h. Zolpidem undergoes a linear pattern of kinetics when the drug dose range is between 5 and 20 mg. The drug was also found to be mostly bound to protein and remained unchanged in concentration subsequently extracted through the renal system.

Patients experience anterograde amnesia after drug administration if plasma concentrations are high at the time of stimulus. This is attributed to either inattention or consolidations to memory process.

This drug has a high potential for overuse and daily dependence. Patients with a few weeks' drug use have a low behavioral dependency on zolpidem. Patients who used zolpidem in higher single doses or had a history of drug abuse should be monitored carefully when using zolpidem or any other hypnotic.

7.4 Benzodiazepines

7.4.1 Indications

Anticonvulsant: acute seizure management
Hypnosis: induction of anesthesia
Anxiolytic: pre-op anxiety, anxiety disorders
Amnesia/sedation: ICU, procedural
Muscle relaxant: back spasm

7.4.1.1 Mechanism of Action

Benzodiazepines are composed of a benzene ring and a diazepine ring. They interact with the receptor by binding between **alpha** and **gamma** subunits. With **allosteric** activation, the binding changes the conformation of the receptor to make it **more sensitive to the effect of GABA. See** Fig. 7.1.

Classification

- **2-Keto-**
  - chlordiazepoxide, clonazepam, clorazepate, diazepam, *flurazepam*

    Metabolized by oxidation, multiple active metabolites
- **3-Hydroxy-**
  - lorazepam, oxazepam, *temazepam*

    Conjugation with a glucuronide radical (can be used in elderly or liver disease) [3]
- **Triazolo-**
  - alprazolam, triazolam: oxidation

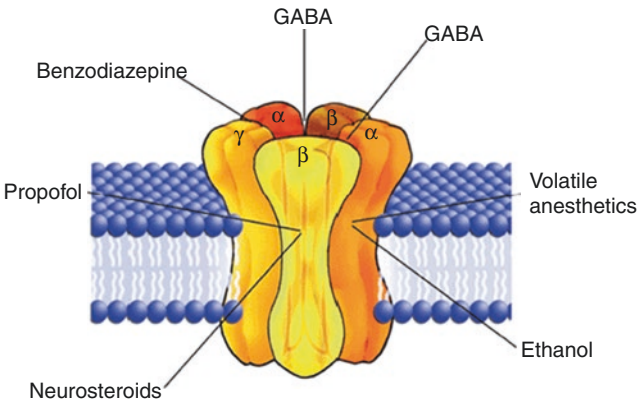

Fig. 7.1 Benzodiazepine binding receptors

Classification According to Potency

- **High-potency benzodiazepines, essentially alprazolam, clonazepam, and lorazepam, are used in panic disorder.**

7.4.2 Dosing

7.4.2.1 Adverse Effects

- **Excessive daytime drowsiness, dysphoria (dose related)**
- **Cognitive impairment (can persist in long-term users):**
  - **Impaired visuospatial ability and sustained attention tasks, memory particularly verbal memory**
- **Psychomotor impairment and a risk of falls and hip fractures**
- **Behavioral disinhibition:**
  - **Hostility, aggressiveness, rage reactions**
  - **Paradoxical excitement, irritability**
- **Depression, dysphoria**
- **Intoxication (even on therapeutic doses)**
- **Risk of traffic accidents to be increased by over 50%**
- **Respiratory problems**
- **Abuse and dependence**

Paradoxical Excitement
- **Has possible legal implications.**
- **This disinhibitory effect of the BZDs can produce increased anxiety, acute excitement, and hyperactivity.**
- **Aggressive impulses may be released with the emergence of hostility and rage and criminal acts such as assault and rape have been recorded.**

7.4.3 Long Half-Life vs. Short Half-Life

Long Half-Life
- **Pros**
  - **Less frequent dosing**
  - **No interdose rebound**
  - **Less severe withdrawal**
- **Cons: Accumulation**

Short Half-Life
- **Cons**
  - **More frequent dosing**

  - **Interdose rebound**
  - **More severe withdrawal**
- **Pros: Low accumulation**

7.4.4 Diazepam

Rapid onset but **long elimination** half-life (24–48 h)

- **Potent amnesic** effect
- Anticonvulsive activity
- Can be given orally, intramuscularly, and intravenously
- **IV administration is painful** and has a higher risk of causing thrombophlebitis

7.4.5 Midazolam Versed

- Newer water-soluble benzodiazepine (a lower incidence of discomfort during IV or IM injection)
- **Slower onset** vs. diazepam
- Major advantage is rapid hepatic clearance (**a short elimination** $T_{1/2}$, 1–4 h)
- More expensive and can only be administered **parenterally** (mostly) (Table 7.1) [1]

Table 7.1 Benzodiazepine pharmacokinetics

Benzodiazepine	Onset of action	Peak onset (h)	Half-life parent (h)	Half-life metabolite (h)	Comparative oral dose
Long acting					
Chlordiazepoxide (Librium®)	Int. (po)	2–4 (po)	5–30	3–100	10 mg
Diazepam (Valium®)	Rapid (po, IV)	1 (po)	20–50	3–100	5 mg
Flurazepam (Dalmane®)	Rapid	0.5–2	Inactive	47–100	30 mg
Intermediate acting					
Alprazolam (Xanax®)	Int.	0.7–1.6	6–20	–	0.5 mg
Clonazepam (Rivotril®)	Int.	1–4	18–39	–	0.25 mg
Lorazepam (Ativan®)	Int. (po) rapid (sl, IV)	1–1.5 (po)	10–20	–	1 mg
Oxazepam (Serax®)	Slow	2–3	3–21	–	15 mg
Temazepam (Restoril®)	Slow	0.75–1.5	10–20	–	30 mg
Short acting					
Midazolam (Versed®)	Most rapid IV	0.5–1 (IV)	1–4	–	–
Triazolam (Halcion®)	Int.	0.75–2	1.6–5.5	–	–

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Chapter 8
Drugs for Treatment of Cognitive Disorders

8.1 Acetylcholinesterase Inhibitors (AChEIs)

Studies report modest improvements or stabilization of dementia symptoms. Benefits were demonstrated in cognitive function, activities of daily living, behavioral function, and measures of global function but none of these treatment effects are large.

Currently, there is insufficient evidence for AChEIs in the outcome measures of delayed institutionalization, mortality, severe disease progression, and reduction of caregiver burden.

While some evidence suggests a role for AChEIs in the treatment of symptoms associated with severe Alzheimer's disease and in other types of dementias (vascular dementia and dementia with Lewy bodies), the clinical meaningfulness of randomized controlled trial outcome measures is controversial and donepezil is the only AChEI currently approved by Health Canada for severe Alzheimer's disease.

There is no evidence of beneficial effect in progression from mild cognitive impairment to dementia at 1, 2, and 3 years of AChEI use in mild cognitive impairment. There is moderate-quality evidence that people with mild, moderate or severe dementia due to Alzheimer's disease treated for periods of 12 or 24 weeks with donepezil experience small benefits in cognitive function, activities of daily living and clinician-rated global clinical state. There is some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total healthcare resource costs. Benefits on 23 mg/day were no greater than on 10 mg/day, and benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose, but the rates of withdrawal and of adverse events before end of treatment were higher the higher the dose [1]. Recent Cochrane review mentioned that [2].

J. Sadek, *Clinician's Guide to Psychopharmacology*,
https://doi.org/10.1007/978-3-030-60766-1_8

8.2 Relative Contraindications of Acetylcholinesterase Inhibitors (AChEIs)

Patients with serious cardiovascular disease were excluded from clinical trials. Avoid use in patients with cardiac conduction abnormalities (except right bundle branch block), such as sick sinus syndrome, bradycardia, atrioventricular block, or unexplained syncope. Use cautiously in active coronary artery disease and congestive heart failure.

- Increased gastric acid secretion may result from increased cholinergic activity. Use cautiously in patients at risk of ulceration, such as those with peptic ulcer disease or concurrent nonsteroidal anti-inflammatory drug use.
- Use cautiously in obstructive urinary disease, as AChEIs may worsen symptoms.
- Use cautiously in patients with a history of seizure or seizure disorder, as AChEI may increase seizure risk.
- Increased cholinergic activity due to AChEIs may worsen symptoms in significant bronchospastic disease.
- Dose adjustments or avoidance of use may be necessary in severe renal or hepatic disease.

8.3 Potential Drug Interactions

8.3.1 All AChEIs

Avoid concurrent cholinomimetic agents, such as succinylcholine, neuromuscular blocking agents, or cholinergic agonists, due to synergistic effects (i.e., may potentiate muscle relaxants used during anesthesia).

- Avoid concurrent use of agents with anticholinergic properties, such as oxybutynin, tricyclic antidepressants including cyclobenzaprine (Flexeril) and paroxetine, or certain nonprescription medications such as dimenhydrinate and diphenhydramine, due to antagonistic effects.
- Monitor closely if medications with similar adverse effects as AChEIs are administered concurrently.
- Review product monographs at hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php and regularly review current Health Canada advisories, warnings, and recalls at www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index_e.html.

8.3.2 Donepezil and Galantamine

Substrates of cytochrome P450.

- CYP2D6 and CYP3A4 inhibitors, such as paroxetine, erythromycin, ketoconazole, or quinidine, may increase the risk of toxicity of donepezil and galantamine.
- Cimetidine does not significantly affect metabolism of donepezil, but does increase the bioavailability of galantamine by approximately 16% 0.12.
- CYP2D6 and CYP3A4 inducers, such as carbamazepine, phenytoin, phenobarbital, dexamethasone, or rifampin, may decrease the therapeutic effect of donepezil and galantamine.

8.3.3 Rivastigmine

Primarily metabolized via hydrolysis; therefore, the risk of cytochrome P450 interactions is expected to be minimal.

Switching therapy There is insufficient evidence demonstrating differences in clinical efficacy between donepezil, galantamine, and rivastigmine [3]. However, tolerability can vary among patients [4]. Considerations in the selection of an alternate AChEI include adverse effect profile, dosing profile, adherence, drug interactions, and comorbidities. When switching to an alternate AChEI, taper the first agent over 1–2 weeks, while starting the second agent at the lowest possible dose using the same titration schedule as initiation of new therapy.

Discontinuing therapy: In patients with advanced Alzheimer's disease, practitioners and caregivers should routinely re-evaluate the value of continuing therapy. There is insufficient evidence to guide the difficult decision of continuation or discontinuation of AChEI therapy in advanced Alzheimer's disease. Discontinue treatment when the risks of therapy are assessed to outweigh the perceived benefits. Although further research is warranted, discontinuation of donepezil appears to be generally well tolerated [2]. It is important to ensure prompt assessment by a practitioner should symptoms acutely worsen upon discontinuation of an AChEI. To attenuate potential withdrawal symptoms, consider gradual tapering of AChEIs, as opposed to abrupt discontinuation.

8.3.4 Memantine N-Methyl-D-Aspartate Receptor Antagonist

Memantine (Ebixa®) is approved by Health Canada as monotherapy or as adjunctive therapy with AChEIs for the symptomatic treatment of patients with moderate-to-severe Alzheimer's disease. Memantine is not indicated for the treatment of MCI.

Studies suggest that 20 mg per day of memantine offers symptomatic benefit on cognition, behavior, mood, and functional measures of daily living in moderate-to-severe Alzheimer's disease at 6 months. In mild-to-moderate Alzheimer's disease, studies suggest a marginal benefit in cognitive outcomes and lack of effect on measures of behavior and activities of daily living. The

magnitude of clinical significance and clinically important benefits of memantine remains uncertain. The DOMINO study reported no statistically significant benefits on cognition, function, and behavior with the addition of memantine to donepezil as compared to donepezil monotherapy in moderate-to-severe Alzheimer's disease. Memantine may be an option for the symptomatic treatment of moderate-to-severe Alzheimer's disease in patients with intolerance to or contraindications to AChEI treatment.

8.3.5 Adverse Effects

Memantine is generally well tolerated and attrition rates from clinical trials are similar between the treatment and placebo groups. The most common adverse effects of memantine include dizziness, headache, somnolence, constipation, and hypertension.

8.3.6 Relative Contraindication

Renal disease or conditions causing alkalinization of urine, such as renal tubular acidosis, severe urinary tract infection, or drastic dietary changes, may reduce systemic elimination of memantine.

- Use cautiously in patients with a history of seizure disorder, as these patients were excluded from clinical trials and memantine may increase seizure risk.
- Use cautiously in patients with cardiovascular conditions, as cardiovascular adverse effects have been observed in clinical trials.
- Hepatic disease.
- Ophthalmic disease.

8.4 Potential Drug Interactions

Not significantly metabolized by cytochrome P450.

- Primarily renally excreted. Elimination of memantine may be reduced with concurrent use of drugs which alkalinize urine, such as sodium bicarbonate or carbonic anhydrase inhibitors.
- Exercise caution with concomitant use of agents which are renally excreted, such as cimetidine, ranitidine, hydrochlorothiazide, triamterene, quinidine, metformin, or nicotine. Plasma levels of both agents may be altered.
- Avoid concurrent use of agents with properties similar to N-methyl-D-aspartate antagonists, such as amantadine, ketamine, or dextromethorphan, due to increased risk of adverse effects (especially central nervous system effects).

- Therapeutic effects of levodopa, dopaminergic agonists, and anticholinergics may be enhanced and may necessitate dosage adjustment of these agents.
- Review product monographs at hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php and regularly review current Health Canada advisories, warnings, and recalls at www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index_e.html.

Generic name (trade name) (dosage form, strengths)	**Donepezil** (Aricept) (tablet: 5 mg, 10 mg) (rapidly disintegrating tablet: 5 mg, 10 mg)
Dose	5–10 mg PO once daily in the morning **Dose titration:** initial dose 5 mg once daily for 4–6 weeks; if tolerated, may increase to a maximum of 10 mg once daily. Consider initial dose of 2.5 mg once daily for frail patients or patients who have experienced adverse effects due to other AChEIs
Common adverse effects	**GI**: nausea, vomiting, diarrhea (dose related), anorexia, weight loss, abdominal pain, dyspepsia, constipation **CNS**: dizziness, headache, fatigue, insomnia, somnolence, depression, agitation, confusion, hallucinations, nightmares **CV**: hypertension, bradycardia, syncope are less common [4] **Resp:** rhinitis **MSK**: muscle cramps (donepezil), weakness, tremor, back pain **Urogenital**: urinary incontinence, UTI
Therapeutic considerations	May be administered without regard to food • Only AChEI approved for severe dementia of the Alzheimer's type. It is also approved for the symptomatic treatment of mild-to-moderate Alzheimer's disease • Lowest risk of GI adverse effects • Maximum recommended dose in elderly women of low body weight is 5 mg daily • Use caution in doses exceeding 5 mg daily in elderly patients with chronic comorbid disease(s)

Generic name (trade name) (dosage form, strengths)	**Rivastigmine** (Exelon, G) (capsule: 1.5 mg, 3 mg, 4.5 mg, 6 mg) (oral solution: 2 mg/mL) (patch: 4.6 mg released per 24 h [as 9 mg/5 cm^2 patch], 9.5 mg released per 24 h [as 18 mg/10 cm^2 patch])
Dose	3–6 mg PO bid **Dose titration (oral)**: initial dose 1.5 mg bid for 2–4 weeks; if tolerated, may titrate dose by 1.5 mg bid after a minimum of 2 weeks at each dose level to a maximum of 6 mg bid **Dose titration (transdermal patch)**: initiate 4.6 mg patch once daily for at least 4 weeks; if tolerated, may increase to a maximum dose of one 9.5 mg patch once daily **Switching from oral to transdermal:** <3 mg bid PO: use 4.6 mg patch 3–6 mg bid PO: use 9.5 mg patch

Common adverse effects	**GI**: nausea, vomiting, diarrhea (dose related), anorexia, weight loss, abdominal pain, dyspepsia, constipation **CNS**: dizziness, headache, fatigue, insomnia, somnolence, depression, agitation, confusion, hallucinations, nightmares **CV**: hypertension, bradycardia, syncope **Resp:** rhinitis **MSK**: muscle cramps (donepezil), weakness, tremor, back pain **Urogenital**: urinary incontinence, UTI Rivastigmine patch **Skin**: application-site hypersensitivity, urticaria, blister, allergic contact dermatitis
Therapeutic considerations	AChEIs are approved for the symptomatic treatment of mild-to-moderate Alzheimer's disease Administer oral doses with food • Significantly fewer adverse effects of decreased appetite, nausea, vomiting, dizziness, and asthenia with transdermal patch as compared to oral doses of 6–12 mg day.8 • If treatment is interrupted for >3 days, restart treatment as per initial dose titration • For patients >85 years of age and <50 kg or patients with renal or mild-moderate hepatic impairment, initiate at 1.5 mg once daily and titrate slowly. Contraindicated in severe hepatic impairment • The transdermal patch has not been studied in renal or hepatic impairment. Titrate dose cautiously in renal impairment. In mild-to-moderate hepatic impairment, titrate dose cautiously. In severe hepatic impairment, use in contraindicated

Generic name (trade name) (dosage form, strengths)	**Galantamine** (Reminyl ER, G) (ER capsule: 8 mg, 16 mg, 24 mg)
Dose	16–24 mg PO once daily in the morning **Dose titration**: initial dose of 8 mg once daily for 4–6 weeks; if tolerated, increase to 16 mg once daily for at least 4 weeks; if tolerated, may further increase to a maximum of 24 mg once daily
Common adverse effects	**GI**: nausea, vomiting, diarrhea (dose related), anorexia, weight loss, abdominal pain, dyspepsia, constipation **CNS**: dizziness, headache, fatigue, insomnia, somnolence, depression, agitation, confusion, hallucinations, nightmares **CV**: hypertension, bradycardia, syncope **Resp:** rhinitis **MSK**: muscle cramps (donepezil), weakness, tremor, back pain **Urogenital**: urinary incontinence, UTI [5]
Therapeutic considerations	AChEIs are approved for the symptomatic treatment of mild-to-moderate Alzheimer's disease Administer with food • Some evidence to suggest that 16 mg per day dose appears to be the best tolerated, with similar efficacy to higher doses. 7 If treatment is interrupted for ≥3 days, restart treatment as per initial dose titration • Maximum 16 mg daily in moderate renal (CrCl >10 mL/min) or moderate liver impairment (Child-Pugh 7–9). Not recommended for severe renal (CrCl <9 mL/min) or severe liver (Child-Pugh 10–15) impairment

Generic name (trade name) (dosage form, strengths)	**Memantine** (Ebixa, G) (tablet: 10 mg)
Dose	10 mg PO bid **Dose titration**: initial dose 5 mg once daily in the morning for at least 1 week. If tolerated, titrate dose to 5 mg bid for at least 1 week, then 10 mg in the morning, and 5 mg in the afternoon for at least 1 week, followed by titration to a maximum dose of 10 mg bid
Common adverse effects	**GI**: diarrhea, constipation, nausea, vomiting **CNS**: dizziness, headache, confusion, somnolence, anxiety, hallucination **CV**: hypertension, angina, bradycardia, cardiac failure **Resp**: cough **MSK**: back pain **Urogenital**: incontinence, UTI **Ocular**: cataract, conjunctivitis
Therapeutic considerations	Use cautious dose titration in moderate renal impairment (CrCl 30–49 mL/min). Maximum 5 mg bid in severe renal impairment (CrCl 15–29 mL/min) • No dosage adjustment in mild-moderate hepatic impairment. Avoid use in severe hepatic impairment

AChEIs Acetylcholinesterase inhibitors, *bid* twice daily, *cm* centimeter, *CNS* central nervous system, *CrCl* creatinine clearance in millimeters per minute, *CV* cardiovascular, *ER* extended release, *G* generic brands available, *GI* gastrointestinal, *kg* kilogram, *mg* milligrams, *mL* milliliter, *MSK* musculoskeletal, *NMDA* N-methyl-D-aspartate, *PO* oral, *Resp* respiratory, *UTI* urinary tract infection [6–11]

8.5 Overview on the Treatment of Frontotemporal Dementia (FTD)

Acetylcholinesterase inhibitors (AcheIs)

Not effective N-methyl-D-aspartic acid (NMDA).

Memantine is not effective in FTD patients.

Selective serotonin reuptake inhibitors (SSRIs)

Does not improve cognition but may improve the compulsion, aggression and impulsivity associated with FTD.

Antipsychotics

Mixed results in challenging behaviors.

Dopaminergics

Dopaminergic blockers can occasionally control some behavior disturbances in FTD, but patients with apathy and lack of motivation may benefit from the use of selective dopamine agonists.

Disease Modifying Agents with Ongoing Research

Microtubule-stabilizing drugs

Progranulin expression activators

Anti-tau monoclonal antibodies (passive immunotherapeutics)

Tau antigens (active immunotherapeutics)
Tau acetylation inhibitors
Tau aggregation inhibitors [12]

8.6 The Consensus Statement from the British Association of Psychopharmacology

The British Association for Psychopharmacology coordinated a meeting of experts in 2017 to review and revise its previous 2011 guidelines for clinical practice with anti-dementia drugs.

Levels of evidence are rated using accepted standards which were then translated into grades of recommendation A–D, with A having the strongest evidence base (from randomized controlled trials) and D the weakest (case studies or expert opinion).

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are effective for cognition in mild to moderate Alzheimer's disease (A). Memantine for moderate to severe Alzheimer's disease (A) and combination therapy (cholinesterase inhibitors and memantine) may be beneficial (B).

Drugs should not be stopped just because dementia severity increases (A).

Until further evidence is available other drugs, including statins, anti-inflammatory drugs, vitamin E, nutritional supplements, and Ginkgo biloba, cannot be recommended either for the treatment or prevention of Alzheimer's disease (A).

Neither cholinesterase inhibitors nor memantine are effective in those with mild cognitive impairment (A). Cholinesterase inhibitors should be used for the treatment of people with Lewy body dementias (both Parkinson's disease dementia and dementia with Lewy bodies), and memantine may be helpful (A).

No drugs are clearly effective in vascular dementia, though cholinesterase inhibitors are beneficial in mixed dementia (B).

Early evidence suggests multifactorial interventions may have potential to prevent or delay the onset of dementia (B).

Many novel pharmacological approaches involving strategies to reduce amyloid and/or tau deposition in those with or at high risk of Alzheimer's disease are in progress [13].

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Chapter 9
Opioid Analegiscs and Drugs for Alcohol Use Disorder

9.1 Describe Pain Classification?

1. **Descriptive location** (head, neck, back, knee), or **duration** (acute, intermittent, chronic >3–6 months)
2. **Causative factors, disease-based diagnosis such as** trauma, inflammation, infection, nerve injury
3. **Intensity (VAS 0–10 scale), quality (MPQ) (>1970s)**
   Mild (1–4), moderate (5–6), severe (7–10); analgesics ladder
4. **Mechanism-based; evidence-based approaches (>1990s)**
   Nociceptive, inflammatory, neuropathic; specific conditions

9.2 What Are the Classes of Analgesics?

1. **Non-opioid analgesics**
   - NSAIDs, COX inhibitors (e.g., *ASA, ibuprofen, naproxen)*
   - Acetaminophen, COXIBs, selective COX2 inhibitors (e.g., *celecoxib)*
2. **Adjuvant analgesics**
   - Antidepressants, e.g., *amitriptyline (Elavil) 25–50 mg HS, duloxetine (Cymbalta) 60–90 mg daily*
   - Anticonvulsants, e.g., *gabapentin, pregabalin*
   - Topical, e.g., *lidocaine, capsaicin*

J. Sadek, *Clinician's Guide to Psychopharmacology*,
https://doi.org/10.1007/978-3-030-60766-1_9

3. **Opioid analgesics**

Examples: Morphine, codeine, oxycodone, methadone, hydromorphone, fentanyl
Mechanism of action
Mu-opioid receptor (μ-OR) agonists G-prots; decrease AC/cAMP/PKA; decrease Ca2+; increase K+; and increase PLC/PKC Opioid agonists bind to G-protein-coupled receptors to cause cellular hyperpolarization They work in the spinal cord; they decrease presynaptic Ca2+, and increase postsynaptic K+ and at supraspinal sites they activate descending pain modulatory pathways; contain NA, 5-HT; from brain stem [1]
Adverse effects
COMMON: sedation, nausea, vomiting, constipation (use laxatives)
LESS COMMON: immunosuppression, hormonal dysregulation, hyperalgesia, respiratory depression, fatality (>200 mg/day) Patients can develop tolerance to them and they are misused, abused, and diverted

9.3 Classification of Opioid by the Synthetic Process

Semisynthetic
- Diamorphine
- Dihydromorphine
- Buprenorphine
- Oxycodone

Synthetic
- Pethidine
- Fentanyl
- Methadone

Naturally occurring
- Morphine
- Codeine
- Thebaine and papaverine

Morphine
- Strong opioid, prototype of class, μ-OR agonist
- Limited oral bioavailability (30%, first-pass effect)
- Active M6G metabolite (caution in renal function)
- Immediate- and sustained-release forms (MorphineContin®)
- Can lead to dependence, tolerance, and addiction

Codeine
- Weak opioid
  - Better oral efficacy than morphine
  - Sustained-release forms (e.g., CodeinContin®)

  - Combined with acetaminophen (e.g., Tylenol #3)
  - Metabolized to morphine via CYP2D6 which
    (a) Shows genetic polymorphism (absent 8%)
    (b) Is inhibited by SSRIs and drug interactions
    (c) Also manifests as ultrametabolizers

- Can lead to dependence, tolerance, and addiction

Oxycodone
- Strong opioid
- Good oral efficacy, good BBB penetration
- Controlled-release forms (e.g., OxyContin®)

Can lead to death from respiratory depression if overtaken or mixed with other sedatives, including alcohol

Can lead to dependence, tolerance, and addiction

Methadone
- Good oral bioavailability
- Has large inter-individual variability
- μ-OR agonist, also NMDA-R antagonist (analgesic)
- Used in treatment of opioid addiction (oral stabilization)

Buprenorphine: Partial μ-OR Agonist, Ceiling Effect
- Combined with naloxone for treatment of opioid addiction (sublingual) (if used IV naloxone blocks actions) (Table 9.1).

Calculating Morphine mg Equivalent mmm

1. Determine the total daily amount of each opioid the patient takes.
2. Convert each to MMEs—multiply the dose for each opioid by the conversion factor.
3. Add them together.

Table 9.1 Opioid equivalent mg dose

Medication	Equivalent mg dose	Efficacy
Morphine	10	High
Codeine	30–60	Low
Oxycodone	4.5	Moderate
Hydrocodone	5 = 10	High
Methadone	10	High
Fentanyl	0.1	High
Sufentanil	0.02	High
Hydromorphone	1.5	High

Opioid (doses in mg/day)	Conversion factor
Codeine	0.15
Fentanyl transdermal (in mcg/h)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone 1–20 mg/day	4
21–40 mg/day	8
41–60 mg/day	10
≥61–80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Opioid Antagonists

- **Naloxone** (IV short t½), **naltrexone** (oral, long t½)
  - Used in opioid overdose, treatment of addiction

Other Opioids (Hybrid Drugs)

- **Tramadol**: inhibits NA/5-HT uptake; weak μ-OR agonist
  - Good oral bioavailability, limited dependence risk
  - Combination acetaminophen+tramadol

Tapentadol: newer drug, inhibits NA uptake, μ-OR agonist

9.4 What Is the Starting Dose of Each Opioid Drug?

Medication name	Starting dose
Morphine (immediate-release tablets, oral solution)	10 mg q 4 h (acute or chronic pain) 2–10 mg q 4 h (hospice) *Parental* 2.5 mg q 4 h
Controlled-release morphine (e.g., MS Contin, Kadian)	Not for initial dosing
Extended-release morphine (Avinza [USA], Embeda [with naltrexone, USA])	Avinza: 30 mg q 24 h, Embeda: 20 mg q 24 h
Hydromorphone (Dilaudid)	2 mg IV every 4–6 h as needed, or 2–4 mg orally every 4–6 h as needed
Controlled-release hydromorphone (Hydromorph Contin [Canada])	3 mg q 12 h
Oxycodone (e.g., Roxicodone [USA], Oxecta [USA], Oxy IR [Canada], also in Percocet, others)	5–15 mg q 4–6 h (acute or chronic pain) (product labeling), 5–10 mg q 8–12 h14 or 5 mg q 4–6 h (chronic noncancer pain)

Medication name	Starting dose
Controlled-release oxycodone (OxyContin [USA], OxyNeo [Canada])	10 mg q 12 h
Oxymorphone (Opana [USA])	10–20 mg q 4–6 h (acute pain) 5–10 mg q 4–12 h (chronic noncancer pain)
Extended-release oxymorphone (Opana ER [USA])	5 mg q 12 h
Hydrocodone (in Lortab [USA], Vicodin [USA], others)	5–10 mg q 4–6 h45 5–10 mg q 4–12 h (chronic noncancer pain)
Codeine	Oral 15–60 mg q 4 h (mild to moderately severe pain), 46 15–30 mg q 4–12 h (chronic noncancer pain) Parental 10 mg q 3–4 h
Controlled-release codeine (Codeine Contin [Canada])	50 mg q 12 h

9.5 How to Switch Opioids?

- **Switching from current opioid to morphine equivalent:**
- Morphine to morphine: multiply by 1
- Oxycodone to morphine: multiply by 1.5
- Hydromorphone to morphine: multiply by 5

- **Switching from morphine equivalent to the new opioid:**
- Morphine equivalent to morphine: multiply by 1
- Morphine equivalent to oxycodone: multiply by 0.667
- Morphine equivalent to hydromorphone: multiply by 0.2

- Transdermal fentanyl
- 60–134 mg morphine = 25 mcg/h
- 135–179 mg = 37 mcg/h
- 180–224 mg = 50 mcg/h
- 225–269 mg = 62 mcg/h
- 270–314 mg = 75 mcg/h
- 315–359 mg = 87 mcg/h
- 360–404 mg = 100 mcg/h

Nationalpaincentre.mcmaster.ca/opioid

9.6 List Some of the Recommendations of the 2017 Canadian Guidelines for Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain?

- They recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids when considering therapy for patients with chronic noncancer pain.
- For patients with chronic noncancer pain, without current or past substance-use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized non-opioid therapy, they suggest adding a trial of opioids rather than continued therapy without opioids.
- They recommend against the use of opioids for patients with chronic noncancer pain with an active substance-use disorder.
- For patients with chronic noncancer pain who are beginning long-term opioid therapy, they recommend restricting the prescribed dose to less than 90 mg morphine equivalents daily rather than no upper limit or a higher limit on dosing.
- For patients with chronic noncancer pain who are beginning opioid therapy, they suggest restricting the prescribed dose to less than 50 mg morphine equivalents daily.
- For patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering, they recommend a formal multidisciplinary program.
  http://nationalpaincentre.mcmaster.ca/documents/Opioid

9.7 Medications for Alcohol Use Disorder

9.7.1 FDA-Approved Medications [1, 2]

9.7.1.1 Acamprosate (FDA Approved)

Dose: 333 mg, take two tablets three times daily.
In moderate renal impairment, one tablet of 333 mg three times daily.
It is not metabolized so can be used in patients with hepatic disease.
Adverse effects: Diarrhea, asthenia, depression, anxiety, nausea, pain, anorexia, dizziness, dry mouth, sweating, paresthesia, pruritis, flatulence, poor sleep, and insomnia [3, 4].

9.7.1.2 Naltrexone (FDA Approved)

Dose: 50 mg daily and could increase to 100 mg daily.
Alternative dosing: 50 mg daily and 100 mg on Saturdays.

100 mg every other day.
150 mg every three days.

Injectable (Vivitrol): 380 mg once every 4 weeks.
Adverse effects: Nausea, vomiting, headache, diarrhea, anxiety, nervousness, fatigue, abdominal pain or cramps, joint or muscle pain, dizziness, insomnia, and poor energy [4].

9.7.1.3 Disulfiram (Antabuse) (FDA Approved) [5]

Dose: start with 250 mg daily and increase to 500 mg daily if not effective.
Adverse effects: Disulfiram alcohol interaction: palpitations, nausea, vomiting, flushing, headache.
Other adverse effects: Liver toxicity, hepatitis, polyneuritis, peripheral neuritis, drowsiness, impotence in men, metallic taste in mouth, fatigue, and allergic dermatitis.
The American Psychiatric Association recommends that this medication can be offered to patients who have insight and failed to respond to or did not tolerate Naltrexone and acamprosate.
An alternative is Topiramate or Gabapentin.

9.7.2 Non-FDA-Approved Drugs That Are Sometimes Used in Alcohol Use Disorder

9.7.2.1 Gabapentin (Antiepileptic) [6]

Dose: 300 mg daily day 1

300 mg twice per day on day 2 then 300 mg TID on day 3 to a maximum of 1800 mg daily.

Doses used in clinical trials of AUD are 600–1800 mg per day in three divided doses.
Adverse effects: Dizziness, somnolence, ataxia or gait disorder, and peripheral edema are the most common adverse effects.

9.7.2.2 Topiramate (TOPAMAX®) [7]

Dose: 25 mg per day or 25 mg twice daily and increase by 25 mg per week. Recommended maximum dose 100 mg twice daily to 150 mg twice daily.
Adverse effects: Paresthesia, dysgeusia, anorexia, difficulty with concentration/attention, nervousness, dizziness, and pruritis. Transient mental slowing and modest reductions in verbal fluency and working memory are generally dose related.

Topiramate Product Monograph Warnings and Precautions

Acute myopia and secondary angle closure glaucoma: Untreated elevated intraocular pressure can lead to permanent visual loss. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible.

Oligohidrosis and hyperthermia: Monitor decreased sweating and increased body temperature, especially in pediatric patients.

Metabolic acidosis: Baseline and periodic measurement of serum bicarbonate is recommended. Consider dose reduction or discontinuation of TOPAMAX® if clinically appropriate.

Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal behavior or ideation.

Cognitive/neuropsychiatric: TOPAMAX® may cause cognitive dysfunction. Patients should use caution when operating machinery including automobiles. Depression and mood problems may occur in epilepsy and migraine populations.

Fetal Toxicity: TOPAMAX® use during pregnancy can cause cleft lip and/or palate.

Withdrawal of AEDs: Withdrawal of TOPAMAX® should be done gradually.

Hyperammonemia and encephalopathy associated with or without concomitant valproic acid use: Patients with inborn errors of metabolism or reduced mitochondrial activity may have an increased risk of hyperammonemia. Measure ammonia if encephalopathic symptoms occur.

Kidney stones: Use with other carbonic anhydrase inhibitors, other drugs causing metabolic acidosis, or in patients on a ketogenic diet should be avoided.

Hypothermia has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use.

9.7.2.3 Baclofen [8]

GABA-B receptor agonist.

Dose: 30–180 mg in up to four divided doses.

Adverse effects: Drowsiness, dizziness, headache, confusion, muscle stiffness, excessive perspiration, itching/pruritis, abnormal muscle movements, numbness, and slurred speech.

9.7.2.4 Nalmefene [9]

mu- and delta-opioid receptor antagonist and a kappa-opioid receptor partial agonist.

Dose: 18 mg daily (5–80 mg used in clinical trials in single or divided doses).

Adverse effects: Nausea, dizziness, insomnia, headache, vomiting, fatigue, and somnolence.

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Appendix 1

Dosing of select psychotropic drugs (adults)

Drug	Start (mg/day)	Maintenance (mg/day)	Max (mg/day)	Common adverse effects
Conventional antipsychotics				
Haloperidol (high)	2–5	4–12	20	High EPSE, ↑prolactin
Flupenthixol (high)	3	3–6	18	High EPSE, ↑prolactin
Fluphenazine (high)	5–10	1–5	20	High EPSE, ↑prolactin
Loxapine (medium)	10–20	20–100	250	Medium EPSE, sedation
Methotrimeprazine (low)	25–75	50–200	Caution with >1000	Sedation, anticholinergic, orthostatic ↓BP
Atypical antipsychotics				
Olanzapine	5–10	10	20	Metabolic, sedation
Quetiapine	25–50	300–600	800	Metabolic, sedation
Risperidone	0.5–2	2–8	12	Metabolic, EPSE
Aripiprazole	10–15	15–30	30	Anxiety, GI, restlessness
Ziprasidone	40–80	40–200	200	GI, EPSE, ↑QTc
Asenapine	5	5–20	20	Dizziness, EPSE, ↑weight
Paliperidone	3–6	3–12	12	EPSE, ↑HR, GI
Lurasidone	20 in dep-40 schiz	40–120	120	Sedation, GI, EPSE
Clozapine	12.5–25	100–900	900	Neutropenia, GI, neuro, CV, Sz

J. Sadek, *Clinician's Guide to Psychopharmacology*,
https://doi.org/10.1007/978-3-030-60766-1

Drug	Start (mg/day)	Maintenance (mg/day)	Max (mg/day)	Common adverse effects
Depot antipsychotics				
Flupenthixol	Test dose 5 mg	20–40 q 2–3 weeks	80	Typical
Fluphenazine	Test dose 10 mg	12.5–25 mg q 2–4 weeks (decanoate)	100	Typical
Zuclopenthixol	Test dose 20 mg	150–400 every 2–4 weeks	400	Typical
Paliperidone/sustenna	150 mg day 1, then 100 mg on day 8	100/150/200 monthly	200 mg monthly	No need for oral
Risperidone	Initiate oral first	25–50 q 2 weeks	50 mg q2 weeks	Atypical
Aripiprazole	Initiate oral first for 14 days	300–400 mg monthly	400 mg monthly	Atypical
Antidepressants				AE
Escitalopram (SSRI)	5–10	10–20	20	GI, sexual, ↑or ↓weight, rash, ↑or ↓ sleep Seizure at high doses, other SE
Citalopram (SSRI)	10–20	20–40	40	
Fluoxetine (SSRI)	10–20	20	80	
Sertraline (SSRI)	25–50	50–200	200	
Paroxetine (SSRI)	10–20	20–40	60	
Fluvoxamine (SSRI)	50	100–300	300	
Mirtazapine (NaSSA)	15	15–30	45	↑sleep ↑ weight, GI
Venlafaxine (SNRI)	37.5–75	75–150	300?	↑BP, headache, ↑sweat
Desvenlafaxine (SNRI)	50	50–100	100	GI, dizzy, ↑sweat, ↓appetite
Duloxetine (SNRI)	30–60	60	120	GI, drowsiness, ↑sweat, ↓appetite
Vortioxetine (inhibits reuptake of serotonin (5-HT); agonistic activity at the 5-HT_{1A} receptor and antagonist activity at the 5-HT_3 receptor)	5–10	5–20	20	GI, dizziness, dry mouth, lower sexual SE
Wellbutrin/bupropion (NDRI)	100	100–300	450	Insomnia, GI, ↓weight
Common mood stabilizer				
Lithium for bipolar mania or depression or mixed	300–600	300–900 Serum level 0.8–1.2)	1800	Renal, GI, neuro, endocrine, dermatological

Drug	Start (mg/day)	Maintenance (mg/day)	Max (mg/day)	Common adverse effects
Divalproex sodium for bipolar mania or mixed	25 mg/kg/day	Level 350–700	60 mg/kg/day	Alopecia, PCO, GI, cognitive
Lamotrigine for bipolar depression	Week 1: 25 mg/day Week 2: 50 mg/day Week 3: 75 mg/day	100–200	400	Stevens-Johnson syndrome, GI, ↑ weight

Dosing for adults

Appendix 2: Pharmacology and Therapeutics Web Resources

1. General resources

   - Kellogg's page of subscribed drug resources:
   - http://www.library.dal.ca/Kellogg/Drug/
   - *Books*
   - Basic and Clinical Pharmacology (Lange)*
   - http://www.accessmedicine.com/resourceTOC.aspx?resourceID=16
   - Therapeutic Choices (CPhA)* as e-Therapeutics - e
   - http://www.library.dal.ca/Kellogg/E-Therapeutics/
   - *Electronic resources*
   - Cochrane Library*
   - http://www.thecochranelibrary.com
   - BMJ Point of Care*
   - https://www.pointofcare.bmj.com/default
   - Lexi-Comp* - e (good for drug interactions)
   - http://online.lexi.com/crlsql/servlet/crlonline?siteid=943

2. Specific resources

   - *Drug interactions*
   - http://www.drug-interactions.com
   - *Evaluation of new drugs*
   - The Medical Letter—available in print only.
   - *Drugs in pregnancy and lactation*
   - http://aleph1.novanet.ns.ca/F/?func=itemglobal&doc_library=NOV01&doc_number=001682697&year=&volume=&sub_library=DLNET
   - Teratogen Information Service* www.otispregnancy.org
   - MotherRisk* *http://www.motherisk.org/women/drugs.jsp*

J. Sadek, *Clinician's Guide to Psychopharmacology*,
https://doi.org/10.1007/978-3-030-60766-1

3. Herbal and herbal-drug interaction sources

- *Books*
- Barnes, J., Anderson, LA., Phillipson, JD. Herbal Medicines 3rd ed. 2007. Pharmaceutical Press. http://aleph1.novanet.ns.ca/F/?func=itemglobal&doc_library=NOV01&doc_number=001662965&year=&volume=&sub_library=DLNET
- *Free online sites**
- Med line Plus www.nlm.nih.gov/medlineplus/druginformation.html
- Memorial Sloan-Kettering Cancer Center. www.mskcc.org/aboutherbs
- College of Pharmacy Drug Information Resource.
- http://dir.pharmacy.dal.ca/alternative_herbal.php listing of useful natural health product resources. Includes database searching information specific for natural health products
- *Databases available by subscription**
- 5
- Natural Medicines Comprehensive Database
- http://www.library.dal.ca/dmsearch/dmsearch.php?q=1&t=0&r=2&type=databases&field=bool&keyword=natural+medicines+comprehensive+database
- Micromedex—available on campus only
- http://www.library.dal.ca/dmsearch/dmsearch.php?keyword=micromedex&q=1&t=0&r=2&type=databases&field=bool
- Lexi-Com Natural Products Database—encompassed in the library's subscription to Lexi-Comp online, URL as above. See here for description of product:
- http://www.library.dal.ca/dmsearch/dmsearch.php?keyword=lexi+comp+with+ahfs&q=1&t=0&r=2&type=databases&field=bool
- *Licensed Canadian Natural Health Products**
- Natural Health Products Directorate website www.hc-sc.gc.ca/dhpmps/prod-natur/index-eng.php

The Renal Pharmacy Group (UK)

- http://www.renalpharmacy.org.uk/
- This website is of general use—includes a bibliography of renal textbooks, a glossary of renal terms, and links to other websites, although it does not appear to have been updated for a couple of years.

South West Medicines Information Centre (UK)

- http://www.swmit.nhs.uk/renal.htm
- This MI center specializes in answering queries about drugs in renal failure. It has a small number of standard answers on specific drugs, useful background questions to ask, and a list of key references.

Merck Praxis MD

- http://merck.praxis.md/
- This offshoot of the Merck Medicus website lists a number of Best Practice of Medicine Reports, including an excellent one on Drug Dosing Guidelines in

Renal Failure. This is written by a reputable nephrologist who is the co-author of the Drug Prescribing in Renal Failure textbook. It describes the pharmacokinetics of dosing.

Drug Interactions

- https://www.drugs.com/drug_interactions.html
- www.themedicalletter.com
- www.druginteractioninfo.org
- www.pharmvar.org
- www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm
- http://medicine.iupui.edu/CLINPHARM/DDIS