BHMEDS-R3

Behavioral Health Medications

- Generic and Brand Medication Names
- Purpose
- Usual Dose and Frequency
- Potential Side Effects
- Emergency Conditions
- Cautions
- Substance Use Disorders Treatment Medications

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Mid-America (HHS Region 7)

ATTC Addiction Technology Transfer Center Network

Funded by Substance Abuse and Mental Health Services Administration

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This Publication is available for free download via the Mid-America ATTC Website at www.attcnetwork.org/midamerica.org.

All content in this Publication is also available in a FREE mobile app. The BHMEDS-R3 app is available in the Apple App Store and Google Play and gives healthcare and addiction professionals, patients, and families FREE, FAST, and SEARCHABLE access to credible information on medications used to treat persons with behavioral health conditions.

SAMHSA
Substance Abuse and Mental Health Services Administration

About this Publication

Originally developed as a companion piece to the Mid-America ATTC curriculum, *A Collaborative Response: Addressing the Needs of Consumers with Co-Occurring Substance Use and Mental Health Disorders (2000)*, this publication is now available as a downloadable PDF and replicates the content included in the new BHMEDS-R3 app now available in the Apple App Store and Google Play.

Back by popular demand, this 10th Edition publication is acclaimed for its accessibility as an educational reference for addiction professionals, patients, and families. Educators and addiction counselor training programs across the United States have asked that we continue to update and publish a downloadable publication to reflect the same credible and up-to-date information included in the BHMEDS-R3 app. We attempt to update the BHMEDS-R3 app content annually and publish an updated publication biannually.

INFORMATION IN THIS PUBLICATION

Medications are organized in 11 sections:

- Alcohol Use Disorder Treatment
- Antianxiety Medications
- Antidepressant Medications
- Antimanic/Mood Stabilizer Medications
- Antipsychotics/Neuroleptics
- Hypnotics (Sleep Aids)
- Medications Induced Symptoms Treatment
- Narcotic and Opioid Medications
- Opioid Use Disorders Treatment
- Stimulant Medications
- Tobacco

Each section includes the following topics for the different medication types:

Generic and Brand Name Medications: includes both approved FDA approved and "off label" medications.

Purpose: Describes typical uses of medications, including specific symptoms treated and positive treatment response expected.

Dose & Frequency: Discusses when and how medications are administered.

Side Effects: Discusses potential side effects, and methods for monitoring side effects.

Emergency Conditions: Includes risks associated with overdose, withdrawal or other medications' reactions.

Misuse Potential: Elaborates upon those medications with risk factors related to misuse and/or development of physical dependence.

Cautions: Describes general guidance on risks associated with taking medications

IMPORTANT NOTES ACROSS MEDICATION TYPES

Name brand medications have a limited patent. When the patent expires, the medication may be made as a generic. The generic name of a medication is the actual name of the medication and never changes. A generic medication may be made by many different manufacturers and can make several forms of a single medication with only slight variations in color, size, or shape.

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Alcohol Use Disorder Treatment

Alcohol Relapse Prevention Agents

GENERIC	BRAND
acamprosate*	Campral*
disulfiram*	Antabuse*
gabapentin	Neurontin
naltrexone extended-release injection*	Vivitrol*
naltrexone*	ReVia*
topiramate	Topamax

Alcohol Withdrawal Agents

GENERIC	BRAND
Anticonvulsant Medications (e.g., carbamazepine, divalproex sodium, gabapentin, phenobarbital, zonisamide)	Tegretol®, Depakote®, Neurontin®, Luminal®, Zonegran®
Benzodiazepine Medication (e.g., diazepam, chlordiazepoxide, and lorazepam)	Valium®, Librium®, Ativan®

*FDA approved for treatment of Alcohol Use Disorders AUDs.

Note: For more information on benzodiazepines and anticonvulsants see:

- Link here to Antimanic Medications
- Link here to Antianxiety Medications
- Link here to Hypnotics (Sleep Aids)

Purpose

Medications involved in alcohol use disorder treatment include those used for acute alcohol withdrawal as well as a growing number used for alcohol relapse prevention. In cases of acute alcohol intoxication, steps to manage the intoxication and subsequent withdrawal must be taken before medications for alcohol relapse prevention should be implemented.

Alcohol withdrawal:
Symptoms of alcohol withdrawal typically present within the first 12 hours of discontinuing the ingestion of alcohol, but can occur earlier in patients with severe physiologic dependence. Though usually only

treated for 1 to 5 days, signs and symptoms of alcohol withdrawal may persist for weeks or months. Signs and symptoms of alcohol withdrawal differ in severity but may include the following: nausea, vomiting, tremor, sweating, tachycardia, hypertension, anxiety, agitation, hallucinations, craving alcohol, and delirium tremens. A common tool used to assess the level of severity of alcohol withdrawal is the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989).

Benzodiazepines are the most commonly used medications for treating acute alcohol withdrawal. The benzodiazepines frequently utilized include diazepam, chlordiazepoxide, and lorazepam. Benzodiazepines work through binding to GABA receptors and potentiating GABA's inhibitory effects. The most common differences among benzodiazepines is in their route of administration, onset of action, duration of action, and half-life. Typically symptoms of alcohol withdrawal and associated agitation can be managed with benzodiazepines over the course of a week or less. When used for longer periods there are concerns of potential tolerance and dependence, necessitating that the benzodiazepine be gradually tapered off to avoid associated benzodiazepine withdrawal. Intravenous or intramuscular thiamine is also recommended for treatment to reduce the risk of neurological deficits (e.g. Wernicke-Korsacoff Syndrome) related to alcohol ingestion. It is not uncommon that deficiencies in Vitamin B12 and folic acid may develop and require treatment with supplementation.

Anticonvulsants such as carbamazepine, divalproex sodium, phenobarbital, and gabapentin have also been reported to offer some clinical benefit in managing symptoms of alcohol withdrawal. Carbamazepine is considered a first-line agent for alcohol withdrawal symptoms in Europe, along with benzodiazepines. (National Institute for Health and Care Excellence, October 10, 2017) The advantage in using these medications is that they can be prescribed for weeks and months versus only days. Propranolol, a beta-blocker, and clonidine, an alpha-2 agonist, are sometimes used in alcohol withdrawal treatment along with either benzodiazepines or anticonvulsants to decrease anxiety, heart rate, sweating, and blood pressure. Antipsychotics may be used if the person develops severe alcohol withdrawal related hallucinations.

Alcohol relapse prevention:
Naltrexone and acamprosate have evolved into treatment options of first choice for the treatment of moderate to severe alcohol use disorder (2018 APA Alcohol Use Disorder Guideline). Naltrexone was first developed as a selective μ-opioid receptor blocker and used in monitored treatment programs for opioid dependence. Many persons with opioid use disorder, however, stopped taking it and returned to opioid use or they preferred methadone maintenance therapy. In alcohol use disorder studies, patients taking naltrexone were less likely to return to drinking alcohol and to reduce overall drinking days. In addition, naltrexone has helped to decrease alcohol craving. In less structured aftercare settings naltrexone is not considered as effective. Baseline and subsequent liver function testing may be required in some patients.

A long-acting injectable form of naltrexone is also available and provides an additional unique delivery method. Use of this once monthly treatment, especially in those persons where adherence to medication is a concern, has led to a reduction in days drinking; and when drinking does occur, less alcohol is typically consumed. Naltrexone is non-psychoactive and as an opioid receptor blocker, it can interfere with the use of opioids for treatment of acute pain.

Acamprosate's proposed mechanism of action is through the potentiation of the GABA system and subsequent antagonism of glutamate. Acamprosate has been shown to reduce alcohol craving, reduce

return to drinking following achievement of abstinence, and prevent relapse. Outcome studies indicate that acamprosate is best initiated following alcohol detoxification and once abstinence from alcohol is achieved. It is considered nonpsychoactive, has minimal drug interactions, and does not produce tolerance or withdrawal symptoms even if alcohol is consumed during treatment. Acamprosate is not metabolized by the liver and is not considered hepatotoxic, though it is eliminated renally and kidney function should be assessed.

Acamprosate does not appear to be effective in persons who are less than moderately motivated to abstain from alcohol use. Because of low bioavailability (the degree and rate at which the medication is absorbed in the body), it is typically taken on a three times daily dosing schedule.

The oldest medication used in alcohol relapse prevention is disulfiram, though no longer considered a first-line agent. Disulfiram blocks the breakdown of alcohol by inhibiting aldehyde dehydrogenase, resulting in elevated levels of acetaldehyde in the body. This in turn leads to severe nausea and vomiting. The use of disulfiram is an aversive therapy and is most effective when used in persons motivated to take it regularly, or in those that receive it in a "monitored" fashion 3 to 5 times per week. It works by causing the person to rethink a move to impulsive drinking knowing that having taken disulfiram; they will likely experience significant nausea, vomiting, and the sensation of heat, headache, and flushing. Disulfiram should be avoided in patients with a known seizure disorder and those who experience withdrawal symptoms when they discontinue use of alcohol. Disulfiram has been associated with hepatoxicity, tachycardia, and QTc prolongation and should be monitored accordingly.

Topiramate and gabapentin are considered next-line alternatives in the event that naltrexone and acamprosate are not effective (The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder, January 2018). An additional treatment option includes zonisamide when these other options have failed. While considered viable treatment options, these agents are not FDA approved for alcohol relapse prevention.

Topiramate has been shown to decrease the number of drinking days per week, alcohol craving, the number of drinks per day, and the number of heavy drinking days per week (Johnson BA, et al. JAMA, 2007 and Knapp CM, et al. Journal of Clinical Psychopharmacology 2015.; Batki SL, Pennington DL, Lasher B, Neylan TC, Metzler T, Waldrop A, Delucchi K, Herbst E. Topiramate treatment of alcohol use disorder in veterans with PTSD: A randomized controlled pilot trial. Alcohol Clin Exp Res, 2014:38(8):2169-2177). Additional findings have suggested a reduction in the number of drinks on a drinking day and reductions in craving. Topiramate has been associated with the side effects of weight loss, sedation, and confusion. Patients taking topiramate should be educated about maintaining adequate hydration to minimize the potential of developing nephrolithiasis. Topiramate extended-release should be avoided within 6 hours prior to and 6 hours after drinking.

Gabapentin has been associated with increased days of abstinence from drinking and a reduction in the number of heavy drinking days and is considered to be moderately effective. (Ahmed S, Stanciu CN, Kotapati PV, Ahmed R, Bhivandkar S, Khan AM, Afridi A, Qureshi M, Esang M. Effectiveness of gabapentin in reducing cravings and withdrawal in alcohol use disorder: a meta-analytic review. The Primary Care Companion to CNS Disorders, 2019; 21(4).) Of note, gabapentin has not been associated with reducing the need for as needed benzodiazepine use in alcohol withdrawal. (Vadiei N, Smith TL, Kjome KL. Impact of gabapentin adjunct use with benzodiazepines for the treatment of alcohol withdrawal in a psychiatric hospital. Psychopharmacology Bulletin, 2019; 49(1):17-27.)Gabapentin has itself been associated with abuse and misuse, which should also be considered when making a

determination of whether or not to be used. Gabapentin has also been associated with improving negative affect and improving sleep in treating alcohol use disorder (Leung JG, et al. Annals of Pharmacotherapy, 2015 and Mason BJ, et al, Expert Opinion on Investigational Drugs, 2018). Gabapentin is renally eliminated and renal function should be assessed prior to and during use.

Zonisamide has also been shown to reduce percentage of days drinking per week, reduce the number of drinks per day, and also reduce the number of heavy drinking days per week (Knapp CM, et al. Journal of Clinical Psychopharmacology 2015). Patients allergic to sulfa-based medications should not take zonisamide.

Phenobarbital is another antiepileptic medication that has been studied for the treatment of alcohol withdrawal, though the results have been mixed.

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. Disulfiram (as any other medication) should never be given to people without their full knowledge or when they are intoxicated. It should not be given until the person has abstained from alcohol for at least 12 hours and avoided in those who experience alcohol withdrawal with discontinued use. Persons should also be instructed to avoid the use of alcohol containing products including perfumes, colognes, and mouthwashes. A daily, uninterrupted dose of disulfiram is recommended until the person, in consultation with their physician, has decided that they have made the necessary lifestyle changes to support and maintain recovery. Maintenance therapy may be required for months, years, or for the rest of their lives.

Naltrexone in its oral form is usually taken once a day during the week with the option to administer a larger dose on Saturdays. Additionally, alternative dosing regimens may be considered that includes the use of higher individual doses every other day or every three days. The injectable form of naltrexone is administered once a month with the injection occurring in the upper outer gluteal (buttock) region. Patients must be completely withdrawn and abstinent from opioids (including the use of tramadol) for 7 to 10 days, but up to 14 days if the patient had just previously been taking methadone or buprenorphine prior to initiating treatment with naltrexone.

Patients should continue to take naltrexone, until they, in consultation with their physician, have decided that they have reorganized their life to maintain recovery. Maintenance therapy may be required for months, years, or for the rest of their lives.

Because of acamprosate's low bioavailability and the potential to produce diarrhea when exposed to gut epithelium, it is recommended to be taken three times a day with each dose separated by at least four hours.

Side Effects

(*Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

***Potential side effects for acamprosate (Side effects on therapeutic doses of acamprosate are rare, other than mild transient gastrointestinal symptoms during the first week):**

- Agitation
- Coma
- Confusion
- Decreased urine output
- Depression
- Diarrhea
- Dizziness
- Headache
- Irritability
- Lethargy
- Muscle twitching
- Nausea
- Rapid weight gain
- Seizures
- Swelling of face, ankles or hands
- Weakness

***Potential side effects for naltrexone:**

- Anxiety
- Decreased appetite
- Dizziness
- Dysphoria
- Injection site reactions
- Nausea
- Sedation
- Vomiting

Potential side effects for gabapentin:

- Diarrhea
- Dizziness
- Dry mouth
- Somnolence
- Swelling of ankles and hands

***Potential side effects for topiramate:**

- Abnormal vision
- Appetite reduction
- Cognitive slowing

- Diarrhea
- Dizziness
- Fatigue
- Memory loss
- Nausea
- Nervousness
- Somnolence
- Speech problems
- Nephrolithiasis (kidney stones)
- Weight loss

***Potential side effects for disulfiram (rare at lower doses, mostly occur at higher doses > 500 mg day):**

- Dark urine
- Drowsiness
- Erectile dysfunction
- Eye pain
- Fatigue
- Indigestion
- Inflammation of optic nerve
- Jaundice
- Light-colored stool
- Liver inflammation
- Loss of vision
- Metallic taste
- Psychotic reactions
- Sedation
- Skin rashes, itching
- Tingling sensation in arms and legs

Emergency Conditions

An overdose of any alcohol use disorder treatment medication is always considered an emergency and medical treatment should be sought immediately.

Misuse Potential

Medications used in the treatment of alcohol use disorder are not considered to have an addiction potential at the present time. However, because patients undergoing alcohol use disorder treatment may have a number of co-occurring conditions; attention should be given to the abuse potential of concurrent medications being administered but not directly given for alcohol use disorder.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and the dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (e.g. St. John's wort, echinacea, ginkgo, ginseng, and others).
- People taking disulfiram should be warned to avoid even small amounts of alcohol in other food products or "disguised forms" as this will cause a reaction (such as vanilla, sauces, vinegars, perfumes, cold and cough medicines, mouthwashes, aftershave lotions, liniments, etc.).
- People taking disulfiram should be warned that consuming even small amounts of alcohol will produce flushing, throbbing in head and neck, headache, difficulty breathing, nausea, vomiting, sweating, thirst, chest pain, rapid heart rate, blurred vision, dizziness, and confusion.
- People taking disulfiram should be warned that reactions have the potential to occur up to 2 weeks after the medication is stopped. Disulfiram should not be taken within 12 hours of the ingestion of alcohol.
- People taking disulfiram should carry an emergency card denoting that he/she is taking disulfiram.
- Avoid use of disulfiram in people meeting any one of the following conditions: intoxicated, taking metronidazole, oral medications in solutions that contain alcohol; has active psychosis; has an allergy to disulfiram or thiuram derivatives. Avoid use without the person’s full knowledge.
- People taking naltrexone should be warned that if they are dependent on opioids or prescribed opiates for pain, taking these medications may result in precipitating opioid withdrawal for up to three days and block the effect of any opioids taken for up to three days. People taking naltrexone should be warned that taking large amounts of opioids while on naltrexone in an effort to negate the effects of naltrexone could result in opioid intoxication or fatal overdose. Those requiring pain management with opioids may need higher doses, and experience more side effects, thus treating with non-opioid or rapid acting analgesics is recommended when possible.
- Avoid use of naltrexone in people meeting any one of the following conditions: taking opioid analgesics, currently dependent on opioids or in opioid withdrawal, with acute hepatitis or liver failure, allergy to naltrexone or components of the diluent (injection).
- Avoid use of acamprosate in people with severe renal impairment.
- Persons taking naltrexone and acamprosate should be monitored for depressed mood or suicidality.

Antianxiety Medications

Benzodiazepines

GENERIC	BRAND
alprazolam	Xanax®, Xanax XR®, Alprazolam Intensol®
chlordiazepoxide	Librium
clonazepam	Klonopin®, KlonopinWafers®
clorazepate	Tranxene®
diazepam	Valium®
lorazepam	Ativan®
oxazepam	Serax®

Beta-blockers

GENERIC	BRAND
propranolol	Inderal®, Inderal LA®, InnoPran XL®

Other

GENERIC	BRAND
buspirone	Buspar®
gabapentin*	Neurontin®*
hydroxyzine	Atarax®, Vistaril®
pregabalin*	Lyrica®*
tiagabine*	Gabitril®*

*Use of these medications for the treatment of anxiety disorders is “off label.”

Purpose

Antianxiety medications are used in many psychiatric conditions including anxiety spectrum disorders, mood disorders, psychotic conditions, and for sleep. They enhance a sense of calm and can be used alone or in combination with other psychiatric medications.

Selective *Serotonin* Reuptake Inhibitors (SSRIs) are among the safest drugs used to treat anxiety disorders. They are typically first line treatment for anxiety spectrum disorders, which include generalized anxiety disorder (GAD), social anxiety disorders (SAD), panic disorder, post-traumatic stress disorders (PTSD), and obsessive compulsive disorder (OCD). The safety, efficacy, and side effect profile

of this class of drugs are one reason they are so widely used. In spite of this, black box warnings exist on many SSRIs as they have been identified by the FDA to increase the risk of suicidal ideation (not attempted or completed suicides) in children, adolescents and young adults up to the age of 24.

Other commonly used medications for the treatment of anxiety disorders include serotonin norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, mood stabilizers, beta blockers and antipsychotics, although not all of these are FDA approved for this indication.

Positive treatment response to antidepressant medications (such as SSRIs and SNRIs) includes a gradual reduction in Anxiety, Panic, PTSD, or OCD symptoms over weeks to months. Often the SSRI or SNRI is initiated at a lower dose than in depression, but the end dose is often higher.

Benzodiazepines result in a calming effect by acting on gamma-aminobutyric acid (GABA) receptors in the brain. Positive treatment response to benzodiazepines occurs rapidly from 30 to 60 minutes to a few hours for most antianxiety medications. With long term use, the response may be short-lived and tolerance develops leading to the need for increased doses. Combined with alcohol, there is a synergistic effect adding to the level of sedation) one experiences. Physicians may use them for a short time as alcohol withdrawal medicines, or as sedatives in acute psychotic or manic episodes. If used in outpatient settings, careful monitoring for tolerance and misuse is needed. When taken on a scheduled basis, benzodiazepines are intended for short-term use because of their potential misuse and the development of tolerance and withdrawal. If used intermittently for the treatment of panic attacks, they may be used over a longer duration without the subsequent development of tolerance and withdrawal. Patients and providers must also be aware of the potential for a disinhibitory effect from benzodiazepines, where instead of a calming effect the patient may become increasingly active and aggressive. This risk of disinhibition is thought to be higher in children and those with developmental disabilities.

Beta-blockers act on the sympathetic nervous system and can help reduce the flight or fight response. They reduce heart rate, tremors, sweating and facial flushing. Propranolol is occasionally prescribed for performance anxiety and is not addictive.

Buspirone works through the serotonin system (specifically 5-HT1A) to induce calm. It is FDA approved for the management and short-term treatment of anxiety disorders. It lacks the dependence and tolerance issues associated with benzodiazepines, and the sexual side effects associated with SSRIs. It is deemed an effective treatment of GAD with associated depressive symptoms and is a consideration for anxiety in patients with substance use disorders (Stahl, 2011, p.77; Egger & Hebert, 2011).

Hydroxyzine is an antihistamine that uses the drowsiness side effect of the antihistamine group to calm and relax. Hydroxyzine works within an hour of being taken. Buspirone and hydroxyzine do not lead to physical dependence.

Low doses of risperidone, quetiapine, olanzapine or other atypical antipsychotics are sometimes used "off label" as non-addictive antianxiety medications. They are usually used when several other medications have failed (though use of atypical antipsychotics is expensive and not FDA approved for treatment of anxiety disorders). When used in these situations the goal is to reduce anxiety and help the person think more clearly.

Gabapentin, tiagabine, and pregabalin have all been used to treat anxiety (off-label, none of these three are FDA approved for the treatment of anxiety disorders) especially in those persons with a substance use disorder history and for whom antidepressants have been ineffective. Gabapentin and pregabalin are thought to work by blocking specific calcium channels and decreasing excitatory neurotransmitter release, while tiagabine potentiates GABA, the major inhibitory neurotransmitter in the central nervous system. These agents all possess mild sedative properties. Gabapentin and pregabalin have also been increasingly associated with drug abuse, particularly in patients with a history of opioid abuse. (Evoy KE, Covvey JR, Peckham AM, Ochs L, Hultgren KE. Reports of gabapentin and pregabalin abuse, misuse, dependence, and overdose: An analysis of the Food and Drug Administration Adverse Events Reporting System. Research in Social and Administrative Pharmacy, 2019; 15(8):953-958. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. Drugs, 2017; 77(4): 403-426.)

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. People are sometimes started on a low dose of medication, which may be raised gradually if symptoms persist (however, this is not always the case, as it depends on the illness and severity). Major factors considered in establishing the correct dose are individual body chemistry, weight, and ability to tolerate the medication. Use of standardized rating scales to monitor response over time can help to guide response and titration

People taking benzodiazepines for longer than 4 to 8 weeks may develop physical tolerance to the medication. Even when taken as directed, withdrawal symptoms may occur if regular use of benzodiazepines is abruptly stopped. Withdrawal from high doses of benzodiazepines may be a life-threatening situation. For these reasons benzodiazepines are often prescribed for brief periods of time-days or weeks-and sometimes only as needed for stressful situations or anxiety attacks. Discontinuation of benzodiazepines should be done under the direction of your provider, who will develop a tapering schedule to safely decrease your dose over a period of time. Except for treating alcohol or benzodiazepine withdrawal, or for acute sedation in manic or psychotic states, benzodiazepines are not recommended for most people with a past or current history of a substance use disorder (Lader, 2011).

Beta-blockers act on the sympathetic nervous system and are not considered addictive. They also are used to treat high blood pressure, thus side effects may include low blood pressure and heart rate as well as dizziness. Beta-blockers may enhance the effects of other psychotropic medications and are inexpensive. Propranolol is taken as needed for performance anxiety. It is also taken on a regularly scheduled basis for treatment of high blood pressure and other heart conditions.

Buspirone (not to be confused with bupropion) is used to treat Generalized Anxiety Disorder (GAD) and is considered safe for long-term therapy. Buspirone is not a benzodiazepine and does not interact with GABA receptors. The onset of effect with buspirone is delayed and may require 2 to 3 weeks of therapy before benefit is noticed. Persons with a history of anxiety treated with benzodiazepines often report less benefit with buspirone, in part because of the delayed onset to effect.

Hydroxyzine is an antihistamine used to treat anxiety on an as needed basis. Common side effects include dry mouth, blurry vision and sedation. Less common side effects are weight gain, constipation, and urinary retention in older men that may lead to more serious complications.

Antidepressants such as SSRI's, SNRI's and less commonly TCA's are also used as anti-anxiety medications. For more details please see the section on antidepressant medications.

Side Effects

Potential side effects vary by drug class.

(See side effects of SSRIs, SNRIs under Antidepressant Medications).

(* Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

*Potential side effects for Benzodiazepines:

- Blood cell irregularities
- Constipation
- Depression
- Drowsiness, sedation, or lightheadedness
- Dry mouth
- Fatigue
- Heart collapse (weakened heart muscles)
- Hyperexcitability or disinhibition
- Loss of coordination and balance
- Memory impairment
- Mental slowing or confusion
- Slowed heartbeat
- Slurred speech
- Stomach upset
- Suppressed breathing (restrained or inhibited)
- Weight gain

*Potential side effects for Buspirone:

- Dizziness
- Headache
- Nervousness Sedation
- Excitement, restlessness
- Nausea

*Potential side effects for Hydroxyzine:

- Blurry Vision
- Constipation
- Dry mouth
- Sedation
- Tremor

- Urinary Retention
- Weight Gain

***Potential side effects for Beta Blockers:**

- Bradycardia
- Bronchospasm
- Dizziness
- Exacerbation of peripheral vascular disease
- Fatigue
- Glucose changes
- Hypotension
- Sexual dysfunction
- Sleep disturbances
- Weight gain

***Potential side effects for Gabapentin:**

- Ataxia
- Dizziness
- Fatigue
- Peripheral edema
- Somnolence

***Potential side effects for Pregabalin:**

- Ataxia
- Dizziness
- Dry mouth
- Fatigue
- Headache
- Peripheral edema
- Somnolence
- Tremor
- Visual changes
- Weight gain

***Potential side effects for Tiagabine:**

- Decreased concentration
- Dizziness
- Nausea
- Nervousness
- Somnolence
- Tremor
- Weakness

Emergency Conditions

Benzodiazepines can cause respiratory depression (slower than normal breathing). When these medications are combined with other sedative medications (phenobarbital or opioids) or combined with alcohol, the sedation is much greater. Under these conditions respiratory depression, which can be a life-threatening medical emergency, can occur. Overdose on the older tricyclic antidepressant medications, which are often used for comorbid anxiety and depressive disorders, can cause life threatening arrhythmias and immediate referral to emergency care is indicated.

Withdrawal from regular use of any of the benzodiazepines and similar medications must be done slowly, via physician guided taper. Abrupt withdrawal from these medications can cause hypertension, tachycardia, hallucinations, delirium, disorientation, hyperactivity, and grand mal seizures. A protocol for decreasing or tapering off doses of benzodiazepines is needed.

Misuse Potential

In the United States, the misuse of benzodiazepines continues to be widespread. Some of the more commonly misused benzodiazepines are alprazolam, clonazepam, lorazepam and diazepam. In addition, individuals who use benzodiazepine and opioids in conjunction are at particularly high risk of overdose and death. (Substance Abuse and Mental Health Services Administration SAMHSA, 2014).

Between 11 and 15% of people in the U.S. take a form of antianxiety medication-including benzodiazepines-at least once each year. If antidepressants are included, this figure is doubled. Benzodiazepines may cause at least mild physical dependence in almost everyone who uses the medication for longer than six to eight weeks (for example, if the medicine is abruptly stopped, the person will experience anxiety, increased blood pressure, fast heartbeat, and insomnia). However, physical dependence on benzodiazepines is not synonymous with a benzodiazepine use disorder. Most people can be gradually tapered off of the medication.

In general, shorter acting benzodiazepines (alprazolam and lorazepam) have a higher risk of misuse when compared to longer acting agents (clonazepam and oxazepam).

Risk Factors Related to Developing Dependency on Antianxiety Medication:

Less than 1% of persons who do not have a current substance use disorder or a history of substance use disorder will develop a benzodiazepine use disorder. These people are at ***little or no risk***. They are more likely to skip doses, take lower doses than prescribed, or decrease their dose over time.

People with a prior history of substance use disorder who are in recovery are at increased risk of becoming dependent on antianxiety medications. These people are at ***moderate risk***.

Those with a history of misusing antianxiety medications or those with opioid use disorder are at ***higher risk*** of developing a benzodiazepine use disorder. Some studies indicate there is a moderately higher risk for persons with alcohol use disorder to develop a benzodiazepine use disorder.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (such as St. John's wort, echinacea, ginkgo, ginseng, etc.).
- People taking antianxiety medications should not increase their dose unless this has been checked with their physician and a change is ordered.
- People should not stop using these medications without talking to a physician.
- People taking antianxiety medication are particularly vulnerable to adverse medical consequences if they concurrently use alcohol and/or street drugs.
- People taking benzodiazepines should be cautioned against driving and operating heavy machinery due to the potential for excessive sedation and confusion.
- Using alcohol in combination with benzodiazepines may result in breathing failure and sudden death.
- Propranolol occasionally prescribed for performance anxiety, will lower your pulse (heart rate) and can lead to fatigue (tired feeling). Certain medications and medical conditions can be impacted by propranolol. Be sure to keep the doctor and pharmacists aware of all medications and medical conditions a client may have.

Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRI)

GENERIC	BRAND
citalopram	Celexa®
escitalopram	Lexapro®
fluoxetine	Prozac, Prozac Weekly®, Sarafem®
fluvoxamine	Luvox®
paroxetine	Paxil®, Paxil CR®
sertraline	Zoloft®

Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

GENERIC	BRAND
desvenlafaxine	Pristiq®
duloxetine	Cymbalta®
levomilnacipran	Fetzima®
venlafaxine	Effexor®, Effexor ER®

Serotonin Partial Agonist and Reutake Inhibitors (SPARI)

GENERIC	BRAND
vilazodone	Viibryd®

Norepinephrine and Dopamine Reuptake Inhibitors Antidepressants (NDRI)

GENERIC	BRAND
bupropion	Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, Zyban®, Aplenzin®

Serotonin Antagonist and Reuptake Inhibitors (SARI)

GENERIC	BRAND
nefazodone	Serzone®
trazodone	Desyrel®, Oleptro®

Noradrenergic and Specific Serotonin Antidepressants (NaSSA)

GENERIC	BRAND
mianserin	Bolvidion®
mirtazapine	Remeron®

Other antidepressants

GENERIC	BRAND
brexpiprazole	Rexulti®
vortioxetine	Trintellix®

Tricyclic and Tetracyclic Antidepressants

GENERIC	BRAND
amitriptyline	Elavil®
amoxapine	Asendin®
clomipramine	Anafranil®
desipramine	Nopramin®
doxepin	Sinequan®
imipramine	Tofranil®
maprotiline	Ludiomil®
nortriptyline	Aventyl, Pamelor®
protriptyline	Vivactil®
trimipramine	Surmontil®

Monoamine Oxidase Inhibitors (MAOI)

GENERIC	BRAND
isocarboxazid	Marplan®
phenelzine	Nardil®
selegiline transdermal patch	EMSAM®
tranylcypromine	Parnate®

Purpose

Antidepressant medications are used to treat a variety of mental health conditions including depression, the depression phase of bipolar illness, and anxiety disorders. Most antidepressants may start to provide benefit within three weeks, but to be considered an adequate trial, should be taken for 6 to 8 weeks.

SSRIs and SNRIs are considered first-line medications for anxiety disorders such as generalized anxiety disorder (GAD), panic disorder, post-traumatic (PTSD), and social anxiety disorder (SAD). SSRIs and SNRIs are also prescribed in higher doses to treat obsessive-compulsive disorders (Farach et al., 2012).

Positive early treatment responses to antidepressant medications include improved energy, concentration, and sleep. Later positive treatment responses include improved mood, attitude, and statements of "feeling better."

Treatment for a single episode of major depression should be continued for at least 1 year after symptoms resolve. Since major depression is a chronic recurrent illness for many people, long-term use of antidepressants is often indicated (much as one would take medication for high blood pressure or diabetes for a long period of time). Discontinuing antidepressant therapy before the depression is completely resolved may result in the person decompensating and possibly becoming medication resistant. Untreated depression has been associated with increased morbidity and mortality rates. Patients with depression should be screened for suicidal ideations prior to treatment, weekly in the first 4 to 6 weeks after treatment initiation, and then periodically thereafter. Use of standardized rating scales such as the Beck Depression Inventory (BDI) and Hamilton Anxiety Rating Scale (HAM-A) can also help to gauge response to treatment.

TYPES OF ANTIDEPRESSANTS

SSRIs (selective serotonin reuptake inhibitors) are the most frequently prescribed class of antidepressants because of their broad effectiveness and general safety profile. The primary mechanism of action of SSRIs relates to their ability to increase serotonin which results in a complex series of changes at a cellular and receptor level that is targeted to improve symptoms of both depression and anxiety. The extended-release formula of fluoxetine can be dosed once per week. A specific form of fluoxetine is also FDA approved for the treatment of Premenstrual Dysphoric Disorder (PMDD). Most SSRIs are available in generic formulations which are typically more affordable options for patients. SSRI antidepressants include the following: fluoxetine, sertraline, fluvoxamine, citalopram, escitalopram, and paroxetine. Vilazodone also exhibits selective serotonin reuptake properties, while also possessing partial agonist activity at the 5HT1A receptor.

SNRIs (serotonin norepinephrine reuptake inhibitors) such as duloxetine, levomilnacipran, venlafaxine, and desvenlafaxine work to inhibit the reuptake of both serotonin and norepinephrine, resulting in an increase in neurotransmitter levels of each respectively.

More recently developed antidepressant medications have not only focused on inhibiting the reuptake of serotonin, but also offer specific serotonin and other receptor targeted activity. Vortioxetine is also an antidepressant with proposed multiple serotonin-based mechanisms of action. Vortioxetine inhibits the reuptake of serotonin, while also serving as a specific antagonist at the 5HT3 receptor and an agonist at the 5HT1A receptor. Brexpiprazole serves as a partial agonist at 5HT1A and D2 receptors, while exhibiting antagonist properties on the 5HT2A receptor. Brexpiprazole is only approved as adjunctive therapy with antidepressant treatment and is also indicated in the treatment of schizophrenia.

Bupropion is a norepinephrine and dopamine reuptake inhibitor (NDRI) that increases norepinephrine and dopamine levels in the brain. In addition, bupropion can be "activating" (as opposed to sedating) and is typically not used in those with anxiety disorders. It is generally thought to be less likely to contribute to weight gain or sexual dysfunction when compared to other antidepressant medications. Bupropion should be avoided by people who are at risk for or who currently have a seizure disorder, eating disorders, or electrolyte imbalances, and/or abrupt discontinuation of alcohol or benzodiazepines since it can increase the possibility of having a seizure.

Trazodone, a serotonin 2 antagonist/reuptake inhibitor (SARI), is an antidepressant often prescribed as treatment for insomnia due to its antihistamine properties. Nefazodone is another SARI, though it is much less commonly used because of hepatotoxicity concerns. Mirtazapine, a noradrenaline and specific serotonergic agent (NASSA) is often used to treat depression in persons with a reduced appetite, weight loss, and insomnia, due to its potential to stimulate appetite and sleep.

The MAOIs, TCAs and tetracyclic antidepressants (named for their chemical structures) are older and less commonly used due safety concerns and less tolerable side effects. MAOIs are used for "atypical depression," which produce symptoms like oversleeping, overeating, and rejection sensitivity. Also, they may be used when a person does not respond to other antidepressants. MAOIs should not be stopped without medical supervision. MAOIs have many medication and food interactions that can last up to 14 days after a person has stopped taking them.

Used in conjunction with other antidepressants, eskatamine is a NMDA receptor antagonist approved for treatment resistant depression. Risk of excessive sedation requires individuals to be observed in a clinical setting for a minimum of 2 hours after administration and the medication can only be distributed by pharmacies certified in a Risk Evaluation and Mitigation Strategy (REMS). This has limited wide spread clinical use.

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. Several factors are considered before an antidepressant is prescribed: the type of medication, the person's individual medical history, body chemistry, weight, and age. Generally, people are started on a low dose, and the dosage is slowly raised until the optimal effects are reached without troublesome side effects.

Both mild sedation and mild agitation may occur with SSRI and SNRI use. One bothersome side effect from antidepressant use is sexual dysfunction which may present in the form of delayed ejaculation/orgasm, decreased libido, and erectile dysfunction. This is often an uncomfortable side effect for patients to discuss and is best addressed in private settings. A common side effect seen with bupropion is insomnia or sleeplessness. For the older tricyclic antidepressants (TCAs), side effects include: dry mouth, constipation, dizziness, and sedation.

Side Effects

(* Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

***Potential side effects for SSRI and SNRI antidepressants:**

- Anxiety, agitation or nervousness
- Change in appetite (lack of or increase)
- Confusion
- Diarrhea or loose stools
- Dizziness
- Dry mouth
- Headache
- Heart rhythm changes
- Heartburn
- Increased sweating
- Insomnia or sleepiness
- Lack or increase of appetite
- Nausea
- Platelet dysfunction
- Sexual dysfunction (delayed ejaculation, decreased libido, erectile dysfunction)
- Shakiness
- Stomach upset

- Taste disturbances (bupropion)
- Weight change (loss or gain)

***Potential side effects for SPARI Antidepressants:**

- Bleeding
- Bruising
- Diarrhea
- Dizziness
- Insomnia
- Low sodium
- Nausea
- Sexual dysfunction (less than SSRIs)
- Vomiting

***Potential side effects for NDRI Antidepressants:**

- Abdominal pain
- Agitation
- Anxiety
- Body aches
- Constipation
- Dizziness
- Dry mouth
- Headache
- Insomnia
- High blood pressure
- Rash
- Ringing in ears
- Sweating
- Tremor
- Weight loss

***Potential side effects for SARI Antidepressants:**

- Blurred vision
- Bradycardia
- Constipation
- Dry mouth
- Edema
- Headache
- Incoordination
- Nausea
- Priapism (painful erection, considered an emergency)
- Rash
- Sedation
- Seizures
- Tremor
- Vomiting

***Potential side effects of NaSSA Antidepressants:**

- Bizarre dreams
- Confusion
- Constipation
- Dizziness
- Dry mouth
- Flu like symptoms
- Hypotension
- Increased appetite
- Neutropenia
- Sedation
- Urinary function changes
- Weight gain

***Potential side effects for Tricyclic and Tetracyclic Antidepressants:**

- Allergic reactions
- Anxiety
- Blurred vision
- Changes in heartbeat and rhythm
- Constipation
- Difficulty with urination
- Dizziness when changing position
- Dry mouth
- Fatigue
- Headache
- Heart block -QT prolongation
- Hyperthermia
- Hypotension
- Increased sweating
- Kidney failure
- Liver Failure
- Low sodium
- Muscle twitches
- Neuroleptic Malignant Syndrome
- Paralytic Ileus
- Seizures
- Sexual dysfunction
- Stroke
- Weakness
- Weight gain

***Potential side effects for MAO Inhibitor Antidepressants:**

- Appetite decrease
- Constipation
- Diarrhea

- Dizziness when changing position
- Dry mouth
- Fluid retention (swollen ankles, feet, legs or hands)
- Headache
- Increased blood pressure
- Insomnia
- Liver toxicity
- Nausea
- Rapid heartbeat
- Sedation
- Seizures
- Sexual dysfunction
- Weight gain

Emergency Conditions

Serotonin syndrome results from elevated levels of serotonin, usually due to concomitant use of two or more antidepressants (MAOIs, SSRIs, SNRIs) or medications that affect serotonin (tramadol) that interfere with **serotonin levels** in the brain. Symptoms of serotonin syndrome are quite varied and can include the following: myoclonus, hyperreflexia, tremors, unsteady gait, headache, agitation, confusion, hallucinations, sweating, fever, shivering, tremors, muscle rigidity, uncontrollable posturing, seizures, coma, abdominal pain, nausea, vomiting, diarrhea, flushing, hypertension, enlarged pupils, salivation, rapid breathing, hyperthermia, and rapid heartbeat. The syndrome is potentially fatal and is treated symptomatically by removing the offending drugs and giving intravenous rehydration (Boyer, & Shannon, 2005; Wimbiscus, Kostenki, & Malone, 2010). Cyproheptadine has also been used (Ables &Nagubilli, 2010) due to its serotonin antagonistic effects. Any individual experiencing symptoms concerning for serotonin syndrome should immediately contact their prescriber or call 911.

Food and beverage interactions. MAOIs can cause dangerous interactions with foods and beverages that contain high levels of tyramine - an amino acid that regulates blood pressure. (Note: the chances of a tyramine interaction are reduced with transdermal selegiline). The following foods contain tyramine and should be avoided when taking MAOIs:

- aged cheeses and meats
- banana peel
- concentrated yeast extracts
- draft beer (including alcohol-free beer)
- fava beans
- broad bean pods
- smoked or aged meat, fish, or poultry
- sauerkraut, kimchee
- soybean products
- tyramine-containing nutritional supplements

Consuming these foods while taking MAOIs can cause a hypertensive crisis and is considered a medical emergency (Wimbiscus et al., 2010).

An overdose of any of the MAOIs, TCAs, tetracyclics, or other antidepressants is serious and potentially life threatening and must be reported to a physician immediately. Symptoms of TCA and tetracyclic overdose may include rapid heartbeat, dilated pupils, flushed face, agitation, loss of consciousness, seizures, irregular heart rhythm, respiratory depression, and potentially death.

The potential for a fatal outcome from an overdose with the SSRIs and SNRIs is much less. However, the possibility that a person has attempted suicide should be dealt with as an emergency situation that needs immediate attention.

Misuse Potential

Antidepressant medications have a low risk of misuse. However, withdrawal or discontinuation reactions have been reported with both the traditional (tricyclic and tetracyclic agents) and the novel (selective serotonin and serotonin- norepinephrine reuptake inhibitors) antidepressants, though the likelihood varies with individual medications. Withdrawal symptoms may present as “flu-like” and may include the following: insomnia, anxiety, dizziness, upset stomach and headache. Monoamine oxidase inhibitor (MAOI) withdrawal can cause these symptoms in addition to muscle twitches, aggression, hallucinations and delirium. Tapering off for antidepressants is generally recommended to avoid withdrawal symptoms, to monitor for symptom return or exacerbation. Fluoxetine is the one antidepressant that generally does not require a taper due to its long half-life and active metabolite. For management of the tricyclic antidepressant withdrawal, benztropine has been used with some success to offset cholinergic rebound (Warner, Bobo, Warner, Reid & Rachal, 2006).

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and the dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (e.g. St. John's wort, echinacea, ginkgo, ginseng, and others).
- People taking antidepressant medications should not increase their dose unless this has been checked with their physician and a change is ordered.
- Withdrawal from SSRIs and other new antidepressants can cause flu-like symptoms. Discontinuing antidepressant therapy should be done gradually under a physician's care.
- People taking MAOI’s should avoid certain foods high in tyramine content to avoid a phenomenon known as tyramine induced hypertensive crisis.
- Several prescription and over-the-counter medications interact with MAOIs. It is largely for this reason that they are rarely used. Other medications should not be taken unless the treating physician approves them. Even over-the-counter cold medication can cause life-threatening side effects. A waiting period of at least two weeks is necessary after you stop taking MAOIs and start another antidepressant. There is also a 2 week washout period needed when switching from an SSRI to an MAOI, with the exception of fluoxetine, for which a 5 week washout is needed. Common nonprescription medicines, particularly certain cold remedies and diet pills, can also be dangerous when taken with an MAOI. The following list of medications have been shown to have contradictions or drug interactions with MAOIs some potentially life-threatening:

    - Amphetamines
    - Armodafinil
    - Brompheniramine
    - Bupropion
    - Chlorpheniramine
    - Clomipramine
    - Cyclobenzaprine
    - Desvenlafaxine
    - Dextromethorphan (contained in many cough-and-cold remedies)
    - Fentanyl
    - Local anesthetics containing vasoconstrictors

    - Linezolid
    - MAO inhibitors or MAOI-like properties
    - Meperidine
    - Methadone
    - Methamphetamine
    - Mirtazapine
    - Modafinil
    - Pentazocine
    - Phenylephrine
    - Phentermine
    - Pseudoephedrine
    - Procarbazine
    - Propoxyphene
    - Serotonin agonists (“triptans”)
    - Selective serotonin reuptake inhibitors (SSRIs)
    - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
    - Tramadol
    - St. John's wort
    - Venlafaxine

- Weight-reducing preparations that contain vasoconstrictors (such as, pseudoephedrine, phenylephrine, phenylpropanolamine, ephedrine, etc.).
- People using MAOIs should check all new medications with a physician or pharmacist before taking them.
- People taking antidepressant medications are particularly vulnerable to adverse medical consequences if they concurrently use alcohol and/or street drugs.
- If there is little to no change in symptoms after 6-8 weeks, talk to the doctor about raising the dose or changing the antidepressant.
- Treatment with antidepressants usually lasts a minimum of 12 months. Many patients are on long-term antidepressant therapy to avoid the frequency and severity of depressive episodes. Use in anxiety disorders is also typically long-term.
- Black Box warnings exist on many SSRIs as they have been deemed by the FDA to increase the risk of suicidal ideation in children, adolescents and young adults up to the age of 24 years.

Antimanic/Mood Stabilizer Medications

Lithium products

GENERIC	BRAND
lithium and associated salt forms: Lithium carbonate Lithium citrate	 Lithobid® Eskalith® Eskalith CR®

Anticonvulsant products

GENERIC	BRAND
carbamazepine	Tegretol®, Carbatrol®,Tegretol XR, Equetro®
lamotrigine	Lamictal®, Lamictal® ODT, Lamictal XR®
valproate (valproic acid / divalproex sodium)	Depakote®, Depakote Sprinkle®, Depakote ER®, Depakene®, Depacon®

Second Generation Antipsychotics (not all FDA approved for Bipolar Disorder)

GENERIC	BRAND
aripiprazole	Abilify®, Abilify Maintena®, Aristada Initio®, Aristada®
asenapine	Saphris®
brexpiprazole	Rexulti®
cariprazine	Vraylar®
clozapine	Clozaril®
Iloperidone	Fanapt®
lumataperone	Caplyta®
lurasidone	Latuda®
olanzapine	Zyprexa®, Zyprexa Zydis®, Zyprexa Relprevv®
olanzapine/fluoxetine	Symbyax®
paliperidone	Invega®, Invega Sustenna®, Invega Trinza®
quetiapine	Seroquel®, Seroquel XR®
risperidone	Risperdal®, Risperdal Consta®, Perseris®
ziprasidone	Geodon®

Purpose

Mood-stabilizing medications are used to treat both manic and depressive symptoms associated with bipolar illness. The term mood stabilizer has historically been a term used to include lithium carbonate or citrate and the antiepileptic medications, valproic acid / divalproex and carbamazepine. The term now is used to describe medications with mood stabilizing properties and has expanded to include a number of second generation antipsychotics and other antiepileptic medications. They are used in acute and maintenance phases to control manic symptoms that include mood elevation, irritability, impulsivity, rapid speech, and disorganized thoughts. Mood stabilizers are also used to address symptoms of depression, anxiety and associated psychiatric symptoms. Lithium has also been associated with reducing suicidality.

Primary bipolar illness is classified into three main distinct subtypes: Bipolar I, bipolar II or cyclothymia. The distinctions between each classification relates to the presence of mania, hypomania, and a depressive episode. The duration of symptom presentation is also considered.

Bipolar illness is classically characterized by cycling moods, from severe highs (mania) to severe lows (depression). Hypomania falls somewhere below mania and may allow for societal functioning, but considerably above what is "normal" for an individual's baseline temperament. The "highs" and "lows" vary in intensity, frequency, duration, and severity.

A diagnosis of Bipolar I requires at least one full manic episode. It could also include the occurrence of a hypomanic and a depressive episode. In Bipolar I disorder a treatment challenge is that the first presentation may be an acute depressive episode.

Bipolar II requires the presence of a hypomanic episode and a current or past major depressive episode. Bipolar II differs from bipolar I in that it does not include a full manic episode, but requires a depressive component and the lesser hypomanic symptoms for a diagnosis to be made. Some patients may have symptoms that are also consistent with the Mixed Features Specifier qualification in their diagnosis. This qualifier is often added when patients meet diagnostic criteria for mania, hypomania, or depression and also exhibit at least three symptoms of the opposite “pole” for a majority of days.

Cyclothymia has a longer course of presentation. It includes a subthreshold of hypomanic and depressive symptoms over two years that do not reach the level of diagnostic criteria or a Bipolar II diagnosis.

Bipolar cycles that occur at least four times a year are considered "rapid cycling." This condition is often found in people with higher rates of substance use.

Positive treatment responses to mood-stabilizing medications include a decrease in manic symptoms, overall mood stabilization, more organized thought processes, fluent and focused speech, enhanced sleep, cessation of risky behavior, cessation of suicidal ideation, a return to baseline function, and lessening of depressive symptoms.

During bipolar mania, it is also possible that persons may present with psychotic features. Psychotic symptoms may or may not be mood congruent. It is important to enhance the opportunity for a positive treatment response to initiate therapy early. By leveling mood swings with mood stabilizing medications, the risk of complications related to this diagnosis, including suicide, can be reduced.

The following medications are FDA approved for bipolar illness:

Acute Bipolar Mania: [with valproic acid/divalproex or lithium] quetiapine, quetiapine extended-release, aripiprazole, risperidone, asenapine, olanzapine; [monotherapy] valproic acid (divalproex), carbamazepine (Equetro® formulation only), lithium, aripiprazole, cariprazine, ziprasidone, risperidone, asenapine, quetiapine, quetiapine extended-release, chlorpromazine, and olanzapine.

Acute Mixed episodes: [with divalproex/valproic acid or lithium] quetiapine extended-release, aripiprazole, risperidone, asenapine, olanzapine; [monotherapy] valproic acid (divalproex), carbamazepine (Equetro® formulation only), aripiprazole, asenapine, cariprazine, ziprasidone, risperidone, asenapine, olanzapine.

Bipolar Maintenance: [with valproic acid/divalproex or lithium] quetiapine, quetiapine extended-release, aripiprazole, ziprasidone, risperidone long-acting injectable, lamotrigine; [monotherapy] aripiprazole, risperidone long-acting injectable, olanzapine, lamotrigine, lithium.

Acute Bipolar Depression: [with divalproex/valproic acid or lithium] lurasidone, olanzapine; [monotherapy] cariprazine, quetiapine, quetiapine extended-release, lurasidone, olanzapine/fluoxetine.

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. Most medications in this class are given from 1 to 4 times per day. Some extended-release formulations may be given every 12 to 24 hours. Dosage is determined by the active amount of medication found in the person's blood after taking the medication, and by their response to the medication. Close blood level monitoring is required until the person reaches their optimal dose.

Monitoring Medication Levels: Before beginning treatment with mood stabilizers, the provider may want to order baseline laboratory studies. These can include a complete blood cell count (CBC) and a comprehensive metabolic panel (CMP) to assess kidney function and serum electrolytes (sodium and potassium), liver function tests, thyroid function tests and a pregnancy test.

Certain mood stabilizers must be monitored periodically to establish therapeutic medication level or to identify possible toxicity. Therapeutic drug monitoring is often completed prior to the initiation of treatment, when a dose is adjusted or when toxicity is suspected. Therapeutic drug monitoring is used especially for lithium, carbamazepine, and valproic acid. The use of second generation antipsychotic medications also requires metabolic (glucose, lipids, weight) monitoring.

Lithium has a very narrow therapeutic index and as such, can easily become toxic to patients. Symptoms of lithium toxicity include nausea, vomiting, diarrhea, coarse tremor, dizziness, twitching, seizures, slurred speech, confusion, increased urination, coma, and at high levels death. Patients should seek immediate medical attention if these symptoms arise. Patients should not use diuretics (greatest risk is with thiazide diuretics) while taking lithium. Angiotensin converting enzyme inhibitors (ACEI) used in hypertension and non-steroidal anti-inflammatory (NSAID) medications may also increase lithium levels. The use of caffeine may decrease lithium levels by increasing its elimination through the kidneys.

Other side effects of lithium include acne, weight gain, goiter and excessive thirst (diabetes insipidus). Patients should be reminded to drink 8-12 glasses of water or other fluids each day, maintain a regular diet, and not change the amount of salt in their diet unless this has been prescribed by their physician. Dehydration or excessive water consumption can affect one's lithium level, which can either concentrate or dilute the blood level. Providers may also monitor kidney function more frequently in people taking lithium as it can have a detrimental effect on the kidneys.

Carbamazepine also requires blood monitoring at the beginning of treatment and when the dosage is changed. The most common side effects include nausea, dizziness, and sedation. It can also cause more serious blood dyscrasias and skin rash. It can also reduce the blood levels of other medications through hepatic enzyme induction. It should be noted that carbamazepine undergoes autoinduction and after one month blood levels may spontaneously decrease and may require additional dosage adjustment.

Valproic acid levels are typically acquired after the first 5 to 7 days of initiation of treatment and periodically when doses are changed. The most common side effects of valproic acid include weight gain, sedation, tremor, alopecia, and upset stomach. Providers may choose to monitor liver function and platelets more closely when using this medication. The use of valproic acid is contraindicated in those with liver impairment. The use of valproic acid has also been associated with the development of pancreatitis and elevated ammonia levels.

Side Effects

(Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

*Common side effects of mood stabilizing medications include sedation and weight gain. Other potential side effects of the mood stabilizing anticonvulsants and lithium include:

- Agranulocytosis
- Blurred vision
- Cardiac concerns [A]
- Coma [A]
- Dermatologic reactions (rash, Steven-Johnsons syndrome)
- Diarrhea
- Dizziness
- Drowsiness
- Hand tremor [A,B]
- Headache
- Hyponatremia [A,C]
- Increased thirst and urination [A]
- Inflammation of the pancreas
- Irregular heartbeats
- Kidney damage [A]
- Liver inflammation, hepatitis [B,C]
- Nausea or vomiting
- Problems with the blood, both red and white cells [B,C]

- Seizures
- Hypothyroidism [A]
- Weakness

A Associated with lithium most commonly.
B Associated with divalproex/valproic acid most commonly.
C Associated with carbamazepine most commonly.

Please see ANTIPSYCHOTICS for side effects related to antipsychotic medications.

Emergency Conditions

Lithium overdose is a life-threatening emergency. Signs of lithium toxicity may include nausea, vomiting, diarrhea, drowsiness, mental dullness, slurred speech, confusion, dizziness, muscle twitching, irregular heartbeat, blurred vision, coma, and potentially death. An overdose of any of the other mood stabilizers medications is always considered an emergency and treatment should be sought immediately.

Stevens-Johnson syndrome is a rare, serious disorder in which skin and mucous membranes react severely to a medication or infection. It can develop in those taking anticonvulsant medications. It typically starts with flu-like symptoms and progresses to painful red or purplish rash that spreads and blisters, eventually causing the top layer of the skin to die and shed. It is considered a medical emergency and requires hospitalization. Recovery can be extended, from weeks to months, depending on the severity of the condition. It has been especially noted with the use of lamotrigine, particularly when not introduced via gradual titration. Lamotrigine use with valproic acid also increases this risk. Any rash that develops while taking anticonvulsant medications should be promptly reported. Under these conditions respiratory depression, which can be a life-threatening medical emergency, can occur.

Misuse Potential

Misuse of mood-stabilizing medications is considered uncommon. In addition to lithium, several anticonvulsant medications are used in the treatment of mania and they are thought to have little to no potential for misuse. When combined with other CNS depressants however there can be an increased sense of drowsiness. Physical dependence has not been associated with lithium or anticonvulsants used as mood stabilizers to date. Patients that are on mood stabilizers may experience a rapid return of manic symptoms if it is stopped abruptly. Patients on anticonvulsants should not stop their medications without medical supervision as abrupt discontinuation of anticonvulsants may result in the occurrence seizures. Slow tapering off periods are recommended to slow or prevent the withdrawal effects described. The anticonvulsant lamotrigine, while approved for the maintenance treatment of bipolar disorder does not have an indication for acute depression or mania. Lamotrigine should be titrated slowly, especially when used with valproic acid and other enzyme inhibitors, or when used in younger patients to reduce the risk of developing Stevens-Johnson Syndrome. For patients with active seizures after sudden withdrawal of anticonvulsants, benzodiazepines like diazepam and lorazepam may be used to treat or suppress seizure activity.

Second generation antipsychotics are often used as mood stabilizers and are discussed separately in the antipsychotic section.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and the dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (e.g. St. John's wort, echinacea, ginkgo, ginseng, and others).
- People taking mood-stabilizing medications should not increase their dose unless this has been checked with their physician and a change is ordered.
- Persons taking mood-stabilizing medications are particularly vulnerable to adverse medical consequences if they concurrently use alcohol and/or street drugs.
- Sodium levels, and thyroid and kidney function must be monitored if a person takes lithium.
- Liver function and a CBC with differential (platelets) must be monitored if a person takes valproic acid.
- Sodium levels, liver function, and a CBC with differential must be monitored if a person takes carbamazepine.
- Valproic acid and carbamazepine have been associated with neural tube defects in infants exposed in utero during the first three months of pregnancy. Valproic acid should generally be avoided during pregnancy. The use of folic acid is also recommended for women of child-bearing potential who take antiepileptic medication.
- For medications that allow serum testing, blood tests for medication levels need to be checked frequently. Considerations for blood level testing including during dose titration, once stability is achieved, and adherence checks.
- Patients may attempt to dilute lithium levels by increasing their intake of water, however excessive over hydration may lead to an excessive loss of free water and result in lithium toxicity.
- Patients using caffeine or taking theophylline for asthma may increase the clearance of lithium, resulting in reduced lithium levels.
- The use of non-steroidal anti-inflammatory medications such as ibuprofen may increase lithium levels.
- The use of thiazide diuretics such as hydrochlorothiazide may increase lithium levels.
- The use of angiotensin converting enzyme inhibitors (ACE-I) such as enalapril may increase lithium levels.
- The use of some antiepileptic medications (e.g. carbamazepine, oxcarbazepine, phenytoin) can lower the effectiveness of birth control medications.

Antipsychotics/Neuroleptics

First Generation Antipsychotics (FGA)

GENERIC	BRAND
chlorpromazine	Thorazine®
fluphenazine	Prolixin®, Prolixin Decanoate®
haloperidol	Haldol®, Haldol Decanoate®
loxapine	Loxitane®
mesoridazine	Serentil®
molindone	Moban®
perphenazine	Trilafon®
pimozide	Orap®
thioridazine	Mellaril®
thiothixene	Navane®
trifluoperazine	Stelazine®

Second Generation Antipsychotics (SGA)

GENERIC	BRAND
aripiprazole	Abilify®, Abilify Maintena®, Aristada Initio®, Aristada®
asenapine	Saphris®
brexpiprazole	Rexulti®
cariprazine	Vraylar®
clozapine	Clozaril®
Iloperidone	Fanapt®
lumataperone	Caplyta®
lurasidone	Latuda®
olanzapine	Zyprexa®, Zyprexa Zydis®, Zyprexa Relprevv®
olanzapine/fluoxetine	Symbyax®
paliperidone	Invega®, Invega Sustenna®, Invega Trinza®
quetiapine	Seroquel®, Seroquel XR
risperidone	Risperdal®, Risperdal Consta®, Perseris®
ziprasidone	Geodon®

Purpose

Both first and second generation antipsychotics (neuroleptics) are most frequently used for persons who experience psychotic symptoms as a result of having some form of schizophrenia, schizoaffective disorder, or symptoms of psychosis associated with other disorders. They may be used to treat brief psychotic episodes. Psychotic symptoms may include being out of touch with reality, hallucinations (visual, auditory, gustatory, and olfactory) and having delusions (paranoid, persecutory, derogatory, grandeur, etc. For example, thinking you are a famous person, thinking someone is out to hurt you, etc.). Antipsychotic medications can be effective in either minimizing or stopping these symptoms. In some cases, these medications can shorten the course of the episode or prevent it from happening again.

Positive treatment response to antipsychotic medications allows many with severe and disabling mental disorders to live and function in the community, often without limiting impairments in functioning. This positive response may include thoughts that are more rational, decreased psychosis, behavior that is more appropriate, and improvement in interpersonal relationships and work.

All of the older and newer antipsychotic medications are approved by the Food and Drug Administration (FDA) and are thus evidence-based treatments (EBT) for schizophrenia. The second generation antipsychotic medications generally demonstrate positive effects across a range of disorders. Many of these medications are also FDA approved treatments for bipolar disorder. Aripiprazole, brexipiprazole, and quetiapine are used adjunctively to treat depression. A growing number of the second generation antipsychotic medications have received FDA approval for treatment of bipolar illness. Aripiprazole, olanzapine, quetiapine, quetiapine extended-release, risperidone (long-acting injectable) and ziprasidone are FDA approved for use in bipolar maintenance therapy (Stahl, 2011, p. 698).

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. Early "acute" symptoms of psychosis may be treated with higher doses of oral medication, and then reduced after stabilization has occurred (Kreyenbuhl et al., 2009). Many antipsychotic medications are taken once a day, some at bedtime to take advantage of the drowsiness side effect of some antipsychotic medications. Several medications are taken in pill form or liquid form. Others are given by injection once or twice per month or quarterly to ensure that the medication is taken reliably. It is important to take medications on schedule. It is also important that people talk to their doctor so they know about potential side effects and steps they need to take to monitor their health.

Second generation antipsychotics are different from conventional antipsychotics in that they most typically block both serotonin (5-HT2) and dopamine receptors, where conventional agents only target dopamine blockade. Some second generation antipsychotics work differently and may serve as partial dopamine receptor agonists as well as partial 5HT1A agonists. Second generation antipsychotics exert benefit towards both positive and negative symptoms of schizophrenia. As noted in the previous section, many second generation antipsychotic medications also carry an FDA indication for the acute and maintenance phases of bipolar disorder. In addition, some have been FDA approved as an add-on treatment for depression, including quetiapine, aripiprazole, and brexpiprazole. Because of the dual

mechanism of action, second generation antipsychotics are also thought to result in lower rates of extrapyramidal symptoms (EPS).

The side effects of antipsychotic medications vary among individuals and may contribute to unpleasant side effects that negatively impact medication adherence. Some of the most common side effects include: sedation, hypotension (decreased or lowered blood pressure), anticholinergic effects (such as dry mouth, urinary hesitancy or retention, constipation and dry eyes), sexual dysfunction, and extrapyramidal symptoms (EPS) (see the Potential Side Effects section for more information about EPS). Many of these are more common in first-generation antipsychotics. Other potential side effects include hyperprolactinemia (an elevated level of prolactin in the blood that leads to the production of breast milk); cardiac arrhythmia (an irregular heartbeat or abnormal heart rhythm that can produce symptoms such as palpitations, dizziness, fainting, shortness of breath and chest discomforts); and agranulocytosis, which has been most commonly noted in the use of clozapine (Stahl, 2008, p.400-401).

Additionally, with second generation antipsychotics there are metabolic related concerns. These include the potential for weight gain, hyperglycemia (elevated blood sugar), and dyslipidemia (an abnormal amount of lipids [cholesterol and/or fat] in the blood). The greatest metabolic risks tend to fall with the use of clozapine and olanzapine, intermediate risk is seen with quetiapine and risperidone. Aripiprazole, lurasidone, and ziprasidone appear to present the lowest risk of metabolic syndrome. The most common mild side effects are either sedation or agitation, especially when starting the medications. The most worrisome side effects are weight gain and elevated blood sugar and lipids with some evidence that certain atypical antipsychotics may lead to the development of diabetes mellitus (Sernyak et al., 2002). Because diabetes is associated with obesity, it is unclear whether the diabetes is actually caused by certain atypical antipsychotic medications or obesity. These issues can be medically worrisome and lead to patients choosing to discontinue their medication. In addition, because effectiveness and side effects vary across medications and people, matching the right medication to the right person is imperative to appropriately address these issues.

Clozapine can very rarely cause serious abnormalities or irregularities in the blood cells (blood dyscrasias). As such, those taking clozapine must be entered into a national "Clozapine Registry". The registry is a systematic active post-marketing surveillance program mandated by the Food and Drug Administration (FDA). Program administrators are required to register patients, physicians and pharmacies, and collect and monitor absolute neutrophil blood counts (ANC). Approximately 1 to 2% of people who take clozapine develop a condition in which their white blood cell count drops drastically (agranulocytosis). As a result, they are at high risk for infections due to a compromised immune system, and this could be fatal. However, most cases of agranulocytosis can be treated successfully by stopping clozapine treatment. To maintain safety, absolute neutrophil counts must be checked each week for six months. If there are no low counts the patient can be monitored every two weeks for an additional six months. Afterwards, the patient may qualify for once every four week monitoring. The results must be sent to the person's pharmacy before he or she can pick up the next supply of medication.

Risperidone and olanzapine were the first second generation antipsychotics introduced into the market after clozapine with their primary mechanisms of action being related to 5HT2A and D2 receptor blockade. Risperidone may cause involuntary movements in the form of EPS that may include the presence of tremors, muscular rigidity, and muscle twitching. Risperidone can cause hyperprolactinemia (abnormally high levels of prolactin in the blood). Some studies have shown that as many as 60% of women and 40% of men have experienced this phenomenon.

Risperidone is available in tablet form, an orally disintegrating tablet, an oral solution, and as a long-acting injection. One form is available as a two-week injection (Risperdal Consta®) of microencapsulated medication that releases into the body at a constant level. An additional long-acting injectable form of risperidone is also available (Perseris®) that can be administered every 4 weeks. Side effects are similar to those for oral risperidone.

Olanzapine is highly sedating and has a higher tendency to cause weight gain and other metabolic changes (Leucht et al., 2013). Metabolic syndrome is a concern with the use of olanzapine. Providers may periodically monitor weight, body mass index (BMI) and waist circumference to evaluate risk in addition to the suggested metabolic lab monitoring. Olanzapine is available in tablets and orally disintegrating tablets, and also available as a long-acting injection (dosed every 2 to 4 weeks) as olanzapine pamoate. The long-acting injectable formulation requires close supervision post-dose for three hours to monitor for symptoms of delirium.

Quetiapine and quetiapine extended-release are used in the acute and maintenance phases of both schizophrenia and bipolar illness, bipolar depression, and as an adjunct in unipolar depression. Quetiapine exerts its therapeutic affects through the combined blockade of 5HT2A and D2 receptors, while the active metabolite, norquetiapine, also exhibits the property of inhibiting the reuptake of norepinephrine. It is highly sedating and can offer a benefit across a broad dosing range with lower doses in bipolar depression and adjunctive depressive disorder treatment, intermediate doses for bipolar mania, and higher doses for schizophrenia. It is also associated with a higher risk of weight gain and other metabolic changes.

Ziprasidone, lurasidone, and aripiprazole are second generation agents and clinical experience suggests a more favorable impact on metabolic factors including weight gain, diabetes, or lipid effects. Ziprasidone is available as an oral capsule and works by inhibiting 5HT2A and D2 receptors. Ziprasidone should be administered with food to enhance drug absorption. Ziprasidone has been linked to a serious heart condition called "torsades de pointes" and sudden cardiac death through its effect on QTc prolongation. This heart condition can lead to dysrhythmias (irregular heart rhythms) which need to be treated quickly to prevent serious complications. The likelihood of this heart condition is low, but should be evaluated by the doctor when beginning treatment with ziprasidone. Providers should order an EKG (electrocardiogram) in those with preexisting heart conditions and weigh the risk of use. A doctor or pharmacist should review the medications a patient is taking to check for medication interactions.

Lurasidone is a second generation antipsychotics and exerts its primary therapeutic effects through the antagonism of both 5HT2A and D2 receptors. Lurasidone is available in a tablet formulation and doses should be administered with food (350 calories) to promote absorption. More common side effects include somnolence, extrapyramidal symptoms, and stomach upset.

Aripiprazole is a second generation antipsychotic with antagonistic effects at 5HT2A receptors while serving as a partial D2 agonist as well as a partial 5HT1A agonist. Aripiprazole is available in an oral formulation, including a rapidly dissolving tablet, as well different formulations of a long-acting injectable that can be dosed on a 4, 6, or 8 week basis (Abilify Maintena®, Aristada®, Aristada Initio®). More commonly reported side effects include extrapyramidal symptoms (akathisia), sedation, and gastrointestinal upset.

Paliperidone and iloperidone are other second generation antipsychotics that work primarily through both 5HT2A and D2 receptor blockade. Both medications cause moderate sedation and weight gain.

Paliperidone can cause dose-dependent EPS (various movement disorders), hyperprolactinemia (an elevated level of prolactin in the blood), and dyslipidemia (an abnormal amount of lipids [cholesterol and/or fat] in the blood). Iloperidone is taken twice a day and can cause congestion, dry mouth, and tachycardia. Iloperidone may also cause dyslipidemia and orthostatic hypotension (a form of low blood pressure that happens when you stand up from sitting or lying down; it can make you feel dizzy or lightheaded, and maybe even faint).

Paliperidone tablets provide 24 hours of medication for the patient. Patients should be told that the paliperidone capsule will pass with their normal bowel function; this should not be a cause for alarm. Paliperidone long- acting injections (dosed every 4 weeks as Invega Sustenna® and every 3 months as Invega Trinza®) are also available for patients that have tolerated oral paliperidone or risperidone. These long-acting injection dosing formulations provide a treatment option for patients who do not like to take a daily oral medication or have poor adherence with oral medication.

Asenapine is a second generation antipsychotic with 5HT2A antagonistic properties along with partial agonist activity at D2 and 5HT1A receptors. It is available as an orally disintegrating tablet that the patient places on the tongue and the tablet will dissolve, but requires swallowing as there is little to no buccal absorption. Asenapine may cause some numbing of the mouth and throat, as well as somnolence, and extrapyramidal symptoms.

Brexpiprazole is a second generation antipsychotic that works by blocking 5HT2A receptors and serving as a partial agonist at D2 and 5HT1A receptors. Brexpiprazole is available in tablet form and is FDA approved for both schizophrenia and as add-on treatment for major depression. The most commonly reported side effects include weight gain and extrapyramidal symptoms.

Cariprazine is a second generation antipsychotic that is approved for the treatment of both schizophrenia and bipolar disorder. It serves as a partial agonist at both D2 and 5HT1A receptors and as an antagonist at 5HT2A receptors. More commonly reported side effects include gastrointestinal discomfort and the potential for extrapyramidal symptoms.

Lumataperone is a second generation antipsychotic that possesses antagonistic properties towards both 5HT2A and D2 receptors. It is available in capsule form with somnolence, sedation, and dry mouth being the most common side effects.

A number of first generation antipsychotics are also available in quick-acting, shorter duration of action injectable forms for acute agitation. An orally inhaled form of loxapine is also available for the treatment of acute agitation. In addition, ziprasidone, aripiprazole, and olanzapine are also available in short-acting injectable forms for acute agitation.

Side Effects

Extrapyramidal symptoms (EPS) are a constellation of symptoms that can be experienced by people taking antipsychotic medications. They are a collection of abnormal movements effecting voluntary muscles and coordination of the neck, spine, gait/walking, oral/facial, fingers, limbs, and eyes as well as associated vocalizations, breathing and swallowing. There are four main types of EPS: pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia. The onset of these side effects is

often seen within the first few weeks of treatment. The first three of the four main types of EPS listed above are typically reversible.

Tardive dyskinesia is a potentially irreversible side effect of antipsychotic medications. Symptoms include oral/facial movements, lip smacking, tongue thrusting, body jerks, spastic muscle contractions and/or stiffness and tics. Once recognized, it is imperative that treatment interventions be attempted as this condition may be reversible however if left unaddressed it may be irreversible. There are two FDA approved medications for the treatment of tardive dyskinesia, deutetrabenazine and valbenazine. Both agents offer VMAT2 inhibition as their primary mechanism of action and have been associated with significant reductions (improvements) in AIMS assessment scoring. (Huntington Study Group, JAMA, 2016 and Factor SA, et al. Journal of Clinical Psychiatry, 2017)

EPS can occur with both therapeutic and toxic doses of antipsychotics and may occur after any dosage change/cessation. They are more common in FGA, but are also seen in high potency SGA. Anticholinergic medications such as benztropine are used to manage the discomfort associated with EPS.

Metabolic Symptoms - Symptoms of diabetes mellitus (associated with obesity)

Metabolic syndrome describes a group of risk factors that raise your risk for heart disease, diabetes and stroke. Five symptoms contribute to this constellation, and include a large waistline, high triglycerides, low HDL, high blood pressure, and high fasting blood sugar.

Other symptoms include:

- Excessive thirst and hunger
- Fatigue
- Frequent urination
- Headaches
- Slow healing cuts and/or blemishes
- Weight loss

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening condition that can occur with antipsychotic medications. The use of high-potency antipsychotics, a rapid increase in dose, and use of long-acting forms of medication can increase the risk of developing NMS. Treatment for NMS varies but is generally supportive care and removal of the offending antipsychotic medication.

Signs and symptoms of NMS include:

- Blood pressure changes (increase or decrease)
- Coma
- Death
- Diaphoresis
- Difficulty breathing
- Elevated CPK
- Fever

- Mental status changes
- Muscle rigidity
- Rapid heart rate
- Stupor
- Tremulousness

***Potential additional Side Effects of antipsychotic medications:**

(* Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

- Abdominal cramping
- Blurred vision
- Changes in sexual functioning
- Constipation
- Diminished enthusiasm
- Dizziness
- Drowsiness
- Dry mouth
- Hypotension
- Muscle rigidity
- Nasal congestion
- Nausea
- Restlessness
- Sensitivity to bright light
- Slowed heart rate
- Slurred speech
- Weight gain

Note: Any side effects that bother a person need to be reported and discussed with the prescribing physician. Anticholinergic/antiparkinsonian medications like benztropine, trihexyphenidyl, or diphenhydramine may be prescribed to control movement difficulties associated with the use of antipsychotic medications.

Emergency Conditions

Contact a physician and/or seek emergency medical assistance if the person experiences involuntary muscle movements, painful muscle spasms, difficulty urinating, eye pain, skin rash or any of the symptoms listed in the side effects section under EPS, tardive dyskinesia, and neuroleptic malignant syndrome. Also contact a physician if a person on clozapine has an abnormal blood count. An overdose is always considered an emergency and treatment should be sought immediately.

Misuse Potential

The potential for abuse for antipsychotics as a class is considered to be low. One novel antipsychotic that has had reports of misuse is quetiapine. There have been reports of individuals crushing and snorting the particles to self-medicate for anxiety and insomnia (Reeves & Brister, 2007). Physical dependence from continued use of these medications across the class is rare. A slow tapering off of some antipsychotics may be recommended to allow the body to readjust to the removal of the antihistaminic and other receptor blocking effects.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and the dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (e.g. St. John's wort, echinacea, ginkgo, ginseng, and others).
- People taking antipsychotic medications should not increase their dose unless this has been checked with their prescribing clinician and a change is ordered.
- “Black Box” warnings were issued on both first and second generation antipsychotics with regards to use in elderly patients with dementia (A black box warning is the sternest warning by the U.S. Food and Drug Administration [FDA] that a medication can carry and still remain on the market in the United States). An increased risk of death has been associated with their use to control dementia-related behaviors.
- Clozapine carries a “Black Box” warning for agranulocytosis, seizures and myocarditis as well as increased risk of mortality in the elderly.
- Ziprasidone and lurasidone should be administered with food to enhance drug absorption.

Hypnotics (Sleep Aids)

Barbiturates

GENERIC	BRAND
secobarbital	Seconal®

Benzodiazepines

GENERIC	BRAND
clonazepam	Klonopin®
diazepam	Valium®
estazolam*	ProSom®*
flurazepam*	Dalmane®*
lorazepam	Ativan®
oxazepam	Serax®
quazepam*	Doral®*
temazepam*	Restoril®*
triazolam*	Halcion®*

Non-benzodiazepines

GENERIC	BRAND
diphenhydramine	Benadryl®
eszopiclone*	Lunesta®*
melatonin	Melatonin
ramelteon*	Rozerem®*
zaleplon*	Sonata®*
zolpidem*	Ambien®*

Sedating Antidepressants (non-FDA approved for sleep)

GENERIC	BRAND
amitriptyline	Elavil®
doxepin	Sinequan®
mirtazapine	Remeron®
nefazodone	Serzone®
trazodone	Desyrel®

Sedating Antipsychotics (non-FDA approved for sleep)

GENERIC	BRAND
olanzapine	Zyprexa®,Zyprexa Zydis®
quetiapine	Seroquel®, Seroquel-XR®

*FDA approved for insomnia

Purpose

Hypnotics are used to help people with sleep disturbances get restful sleep. Lack of sleep is one of the greatest problems faced by those with psychiatric illness and substance use disorders, and may even exacerbate the symptoms. For example, mood changes, psychosis and irritability increase with insomnia, and likewise insomnia can often be a result of these conditions. Lack of sleep diminishes a person's ability to think clearly or process information. Sleep-wake cycles and the body's ability to heal itself also suffer when a person is sleep deprived. Older hypnotics, like barbiturates, cause the body to slow down and "pass out" or sleep. However, they also have a tendency to disturb sleep cycles. For this reason, and because of their potential for overdose, misuse and physical dependence, barbiturates are now rarely used.

Benzodiazepines are frequently used as a short-term treatment for insomnia. However, due to the risk of tolerance, physical dependence and subsequent withdrawal symptoms they are ideally used for periods no greater than four weeks. Gradual tapering is used to avoid symptoms of withdrawal which include anxiety, depression, nausea/vomiting, and rebound insomnia.

Non-benzodiazepines such as zolpidem and zaleplon affect one of the body's receptors for the natural calming agent, GABA. These medications are short acting and do not disturb sleep-staging cycles. Rebound insomnia is a side effect of both, however, if the medications are used for more than two weeks and then abruptly stopped. Ramelteon works with the melatonin pathways in the brain to help you fall asleep. It is non-habit forming and can be taken long term for chronic insomnia.

Sedating antidepressants work by using their sleep producing side effects (antihistaminergic) to induce sleep (e.g. trazodone). They are not addictive but have the capacity to produce all the side effects of their class of antidepressant. Sedating antipsychotics use their calming and sedation side effects (mostly antihistaminergic) to induce sleep but have the capacity to produce all the side effects of atypical - antipsychotics and they are an expensive alternative. Due to these reasons off label use of antipsychotics for the sole purpose of treating insomnia is not generally recommended. Anticonvulsants may be used for sedation when treating acute or prolonged withdrawal symptoms from alcohol.

Antihistamines such as diphenhydramine and hydroxyzine work through their naturally sedating properties, also histamine blockade, to induce sleep.

Paradoxically, those with substance use disorders (SUDs) can become rapidly tolerant and dependent on benzodiazepines and even on the non-benzodiazepines-zolpidem and zaleplon. Tolerance can lead to decreasing effectiveness, escalating doses, and an even worse sleep disorder when the agent is withdrawn. For this reason, most doctors treating SUDs use sedating antidepressants, anticonvulsants, or sedating antihistamines if the sleep problem continues past acute withdrawal symptoms.

Dose & Frequency

All medications have specific doses and frequencies. The physician will specify the exact amount of medication and when it should be taken. This information is provided on the prescription bottle. Some of these medications are used for limited periods. With some of these medications tolerance can develop and eventually the usual dose will no longer help the person sleep.

Side Effects

***Potential side effects of Sedative-Hypnotics:**

(* Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

- Breathing difficulty
- Dizziness
- Drowsiness
- Headache
- Lethargy
- Malaise
- Priapism
- Sedation (may wake-up tired)
- Somnolence
- Weakness

Emergency Conditions

- Overdose with any of these medications can be life threatening. Seek help immediately.
- Combinations of alcohol and barbiturates or alcohol and benzodiazepines can be deadly.

Misuse Potential

With hypnotics, there is the potential for development of tolerance and dependence on the medications with accompanying withdrawal. There are many drawbacks to long-term use of hypnotics such as damaged sleep staging and substance use disorders. Even zolpidem and zaleplon if taken for longer than 7 to 14 days, can have a discontinuation rebound insomnia effect. Non-habit-forming medications are available to treat insomnia.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and the dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (e.g. St. John's wort, echinacea, ginkgo, ginseng, and others).
- People taking hypnotic medications should not increase their dose unless this has been checked with their physician and a change is ordered.
- People taking hypnotic medications are particularly vulnerable to adverse medical consequences if they concurrently use alcohol and/or street drugs.
- There is potential for development of tolerance and dependence with accompanying withdrawal. Potential for abuse and misuse is high.

Medication Induced Symptoms Treatment

Antiparkinsonian Medications

GENERIC	BRAND
amantadine	Symmetrel®
benztropine	Cogentin®
diphenhydramine	Benadryl®
trihexyphenidyl	Artane®

Anti-Tardive Dyskinesia VMAT2 Inhibitors

GENERIC	BRAND
deutetrabenazine	Austedo®
valbenazine	Ingrezza®

Purpose

Symptoms associated with antipsychotic medication use can be very unpleasant and in some instances may contribute to a lack of medication adherence and negatively impact quality of life. Because of the action of antipsychotics, which cause dopamine blockade in various regions of the brain, patients can develop extrapyramidal symptoms (EPS). EPS can take the form of 1) drug induced parkinsonism; 2) akathisia; 3) dystonia; and 4) tardive dyskinesia. Depending upon the type of EPS that presents, providers may reduce the dose of the current medication, stop the medication completely, switch to a lower potency antipsychotic, or add a treatment to control the EPS side effect. Antiparkinsonian (anticholinergic) medications are typically used to control drug-induced parkinsonism associated with antipsychotic medications. They are called antiparkinsonian because the neurological side effects of antipsychotic medications are similar to the symptoms of Parkinson's disease (such as tremors, stiff or rigid muscles, poor balance, a distinctive unsteady walk, and diminished arm swing).

Although the medications most commonly used to address EPS consist of anticholinergic and antihistaminergic medications, benzodiazepines, beta-adrenergic antagonists (propranolol), beta-adrenergic agonists (clonidine), or dopamine agonists (amantadine) may also be used (Mueser, & Jeste, 2008).

Anticholinergics can be administered orally, however in more severe forms of EPS such as acute dystonia with oculogyric crises (eyes rolling back in the head accompanied by posturing) or diaphragmatic involvement (prolonged and unintentional muscular contractions of voluntary or involuntary muscles) which may impair a patient's breathing, an intramuscular injection of benztropine or diphenhydramine is required. Benztropine, trihexyphenidyl, and diphenhydramine are the most common anticholinergic medications given to control EPS (Kamin, Manwani, & Hughes, 2000).

Benzodiazepines, beta-adrenergic antagonists, and alpha2-adrenergic agonists are usually used for akathisia (restlessness, rocking, and fidgety feeling) (Kamin, Manwani, & Hughes, 2000).

The treatment of tardive dyskinesia (abnormal movements of the face, jaw, tongue, trunk, hands, and lower extremeties) often involves antipsychotic dose reduction, switching antipsychotics, or the addition of oral treatments. There are two current treatments for Tardive Dyskinesia which includes deutetrabenzine and valbenazine. The two agents are vesicular monoamine transporter type 2 (VMAT-2) inhibitors which work to reduce the amount of dopamine that gets released into the synaptic cleft. Both deutetrabenazine and valbenazine have been shown to result in significant improvement at reducing Abnormal Involuntary Movement Scale examination scores.(Fernandez HH, Stamler D, Davis MD. Long-term safety and efficacy of deutetrabenazine for the treatment of tardive dyskinesia. J Neurol Neurosurg Psychiatry, 2019; 0:1317-1323. Factor SA, Remington G, Comella CL, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. J Clin Psychiatry, 2017; 78:1344-1350. Additional treatment options for tardive dyskinesia include clonazepam, tetrabenazine, and ginkgo biloba.

Clinicians should periodically assess patients for involuntary movements associated with antipsychotic medication use. Patients should report any new symptoms associated with antipsychotic medication as soon as they occur. Acute extrapyramidal side effects tend to resolve rapidly when noted and promptly addressed.

It is important to note that the antiparkinsonian medications listed in this section are only those used in the management of the side effects of antipsychotic medications. There are other medications used to treat primary Parkinson's disease that are not discussed in this section because those medications are currently not used for the management of side effects related to antipsychotics. If you would like more information on Parkinson's disease, talk with your doctor or pharmacist.

Dose & Frequency

All medications have specific doses and frequencies. The physician will specify the exact amount of medication and when it should be taken. This information is on the prescription bottle. These medications have very specific doses and taking too much can be harmful. A doctor must be consulted in order to safely change the dose in response to side effects of the antipsychotic medications.

Side Effects

(*Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

- Angle closure glaucoma
- Blurred vision
- Bowel obstruction/dilation of colon
- Confusion
- Constipation
- Dizziness
- Dry mouth
- Hallucinations
- Heart failure
- Irritability
- Light-headedness

- Stomach upset
- Vomiting
- Tiredness
- Urinary dysfunction

Emergency Conditions

Report immediately any overdose or changes in heart rate and/or rhythm to the doctor.

Misuse Potential

There is not clear evidence on whether these medications could be misused by persons with severe mental illness who require neuroleptics. However, the results of a study from Australia developed by Buhrich et al. (2000) suggest that some of these medications could be misused. Many of the people who misuse antiparkinsonians in this study used these medications "to get high, to increase pleasure, to decrease depression, to increase energy and to relax" (Buhrich et al., 2000, p. 929). This survey study also found that the misuse of other drugs accompanied the misuse of antiparkinsonian medications.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (such as St. John's wort, echinacea, ginkgo, ginseng, etc.).
- People taking antiparkinsonian/anticholinergic medications should not increase their dose unless this has been checked with their prescriber and a change is ordered.
- The use of VMAT-2 inhibitors is cautioned in patients with pre-existing congenital long QT syndrome or who may have other risk factors for QT prolongation.
- Deutetrabenazine should be administered with food to enhance drug absorption.

Narcotic and Opioid Medications

Natural opioids:

Opium, morphine and codeine products

Pure, semi or totally synthetic derivatives:

Hydrocodone, methadone, oxycodone and others

GENERIC	BRAND
buprenorphine	BelbucaV®, Buprenex®, Subutex®(sublingual formulation)
buprenorphine + naloxone	Bunavail, Suboxone,®, Zubsolv®
buprenorphine long acting Injection	Sublocade®
butorphanol	Stadol®
codeine	Several codeine containing combination products
fentanyl	Actiq®, Duragesic®, Ionsys®, Sublimaze®, Subsys®, Lazanda®
hydromorphone	Dilaudid®, Dilaudid-HP®
levorphanol	Levo-Dromoran®
meperidine	Demerol®
methadone	Dolophine®, Methadose®, Methadose Sugar-Free®,
morphine	Duramorph®, Kadian®, MS Contin®, MS IR®, Oramorph SR®, Roxanol®
oxycodone	Roxicodone®, Oxycontin®
oxymorphone	Opana®, Opana ER®
tramadol	Ultram®

The following products use a combination of an opioid or narcotic along with aspirin, acetaminophen, or other pain reliever to treat mild to moderate pain.

Anexsia 5/500
Capital with Codeine
E-Lor® or Wygesic®
Empirin or Phenaphen with Codeine #3
Empirin or Phenaphen with Codeine #4
Endocet
Fioricet with Codeine
Fiorinal with Codeine
Lorcet Plus®
Lortab®
Maxidone®
Percocet®
Percodan®
Roxicet®
Roxicet oral solution® (contains alcohol)
Roxiprin®
Talacen®
Tylenol with Codeine syrup® (contains alcohol)
Tylox®
Vicodin®
Vicodin ES®
Zydone®

Purpose

Opiate medications are commonly used to control moderate to severe acute pain. They are typically used for a short time because they cause physiological tolerance (takes more to get the same analgesic effect) and physical dependence (cause withdrawal symptoms if abruptly stopped) as amount and duration of doses increase. Longer-term use is indicated to alleviate the chronic pain associated with cancer and certain other conditions, and research has shown that abuse of these medications rarely occurs in such patients. Severe and chronic pain has long been under treated in the United States due to fears that anyone prescribed opiates will become addicted. Opioids are appropriately prescribed to manage chronic cancer pain-especially fentanyl, oxycodone and methadone.

Opioid agonists, partial agonists, and antagonists are also used to treat addiction to opioid substances. Acute opioid-related disorders that require medical management include opioid intoxication, opioid overdose, and opioid withdrawal (see Opioid Use Disorder Treatment for more information on opioid use disorders treatment).

Methadone is a medication used in opioid use disorder. Many people who have been addicted to heroin and other opioids have returned to a productive life because of methadone treatment (heroin is a drug of abuse). Methadone is also frequently used to provide relief for specific types of pain, especially in

pain clinics. The management of chronic pain in persons with a history of opioid use disorders is one of the most challenging tasks in medicine.

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. Many narcotic or opioid medications are taken two or more times a day. Some medications are taken in pill or liquid form. A few are taken in a nasal spray or as topical patches on the skin. Injectable narcotics are not listed here because they are not often used outside a hospital setting.

Side Effects

*Potential side effects of Narcotic-and-Opioid-Analgesics:

(* Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

- Cognitive impairment
- Constipation
- Flushing and sweating
- Headache
- Hypotension
- Itching
- Pupil constriction
- Respiratory depression (slowed breathing rate)
- Stomach upset
- Tolerance
- Visual disturbances

Emergency Conditions

- Convulsions and/or cardiac arrest with high dosages.
- Overdose may increase pulse rate, result in convulsions followed by coma or death.
- Overdose may depress the breathing centers in the brain leading to inability to breathe.
- An opiate overdose can be life threatening and is always considered an emergency and treatment should be sought immediately.

Misuse Potential

Opioids are among the three most commonly abused prescription drugs in the U.S. (the others being central nervous system depressants and stimulants).

With narcotic and opioid medications, there is a potential for the development of tolerance and the need to escalate doses to produce the desired effect that results in the drive for continued use. As a result, opioids cause dependence as well as the possibility of abuse and severe withdrawal reactions. Resultant toxicity can lead to death as a result of respiratory suppression. There are many non-addictive pain medications available for pain management that can be used after acute pain is reduced.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (such as St. John's wort, echinacea, ginkgo, ginseng, etc.).
- People taking narcotic and opioid analgesics should not increase their dose unless this has been checked with their physician and a change is ordered.
- Because of the risk of respiratory depression, opioid narcotics should not be used in combination with alcohol, antihistamines, barbiturates, benzodiazepines, or general anesthetics.
- Persons taking an opioid medication are particularly vulnerable to adverse medical consequences if they concurrently use alcohol and/or street drugs, because alcohol and street drugs can increase the sedation effects of the opioids.
- Potential for development of tolerance and dependence exists.

Opioid Use Disorder Treatment

GENERIC	BRAND
buprenorphine and naloxone*	Bunavail®*Suboxone®*,; Zubsolv®;
buprenorphine extended release	Sublocade®
buprenorphine*	Buprenex®*, Butrans®*, Subutex®*
clonidine	Catapres®, Kapvay®
lofexidine	Lucemyrna®*
methadone*	Dolophine®*, Methadose®*, Methadose Diskets®*, Methadose Intensol®*
naloxone	Narcan®
naltrexone extended-release injection*	Vivitrol®*
naltrexone*	ReVia®*

*FDA approved for treatment of Opioid Use Disorder OUD.

Purpose

Medications are a key component in the stabilization of persons with Opioid Use Disorders (OUDs). Appropriate use of these medications has shown marked ability to decrease illness, crime, and deaths in this population. All patients identified as having an opioid use disorder should have access to naloxone and receive education on overdose prevention and treatment. Naloxone is available as an intranasal spray and an intramuscular injection.

Opioid withdrawal symptoms may include physical symptoms, such as diarrhea, cramping, and pain as well as psychogenic manifestations that can present as may include anxiety and restlessness. (Wesson DR, Ling W. J Psychoactive Drugs, 2003; 35:253-259) Mild opioid withdrawal symptoms such as anxiety and increased heart rate can be treated with clonidine, a medication typically used for the treatment of high blood pressure. Clonidine and tizanadine may be used ("off label," as it is not FDA approved for treatment of OUDs) in combination with sedatives such as benzodiazepines to attenuate autonomic withdrawal symptoms. An additional treatment option exists for opioid withdrawal in the form of lofexidine. Lofexidine has a similar mechanism of action as clonidine, but is FDA approved for the management of opioid withdrawal symptoms. Studies have demonstrated significant reductions in withdrawal symptoms over the course of seven-day treatment. (Gorodetzky CW, Drug and Alcohol Dependence, 2017; 176:79-88.) The physical presence of pain can be treated with a non-steroidal anti-inflammatory and diarrhea or nausea/vomiting symptoms may be managed with loperamide, ondansetron, or prochlorperazine in addition to rehydration strategies. Anxiety and disruptions in sleep may also be treated with benzodiazepines such as temazepam and diazepam (Longo DL, The New England Journal of Medicine, 2016; 375:357-368). Of note, benzodiazepines should be used with caution when treating those identified with opioid use disorder as the combination of opioids and benzodiazepines significantly increases the risk of overdose and death.

Methadone maintenance treatment is extensively researched. See TIP 45: Detoxification and Substance Abuse Treatment (CSAT, 2006) and TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs (CSAT, 2005). Methadone is a synthetic, long-acting opioid-agonist at the mu receptor used in the treatment of opioid use disorders. Methadone is typically titrated over several weeks. When used in proper doses, methadone stops the cravings but does not create euphoria or sedation. Many people with opioid use disorders have returned to a productive life because of methadone treatment programs. Methadone is also utilized clinically to provide relief for specific types of pain. When used in the treatment of opioid use disorder, methadone can only be initiated and maintained in specific clinic settings designated as opioid treatment programs or more commonly, methadone clinics.

Buprenorphine is an antagonist at the kappa opioid receptor and a partial μ-agonist. Buprenorphine provides another treatment option for opioid use disorder. Unlike methadone, buprenorphine can be prescribed for opioid use disorder from any office-based setting by prescribers who have received additional training and applied for a special waiver through the DEA. Prescribers have a cap on the number of patients they can prescribe buprenorphine to at one time

Buprenorphine sublingual tablets or buccal film can be used for both opioid withdrawal and as long-term treatment. Buprenorphine works at the opioid receptor to reverse the neurobiological changes

associated with chronic opioid exposure. It does not provide the user with the euphoria or rush typically associated with use of other opioids or narcotics. Because it works differently than opioids, it is necessary for people to have a short period of abstinence from opioids before initiating treatment. Generally, patients need to be in mild withdrawal and start at a low dose which is gradually increased until withdrawal symptoms and cravings are eliminated. Starting the medication too quickly or at too high of a dose can actually worsen opioid withdrawal symptoms.

The combination product of buprenorphine and naloxone may also be used in the management of opioid dependence. This product is available in different formulations that include a buccal film, a sublingual film, and a sublingual tablet. The presence of naloxone helps to serve as a deterrent to misuse of buprenorphine. Naloxone only gets into the body when injected or inhaled so combining it with buprenorphine neutralizes the effect one would get from snorting or injecting the combined product.

Buprenorphine should be used with caution in those with liver impairment as buprenorphine undergoes extensive hepatic metabolism. However, this is not considered a contraindication.

Naltrexone exhibits its effects by serving as a mu-opioid receptor antagonist. Naltrexone is available as an oral tablet and also an extended-release long-acting injectable that maintains its pharmacological action for approximately 4 weeks. Naltrexone completely blocks the pleasurable reinforcement that comes from opioids by blocking mu-opioid receptors and is also used for alcohol relapse prevention.

Dose & Frequency

- All medications have specific doses and frequencies. The physician will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle.
- Naltrexone in its oral form is usually taken once a day but can be taken at a higher dose on Mondays, Wednesdays, and Fridays. It is usually started at full dose. The injectable form of naltrexone is taken once a month.
- Buprenorphine combined with naloxone is given as a sublingual tablet (it is absorbed under the tongue). It is not absorbed if swallowed or chewed. If injected intravenously, buprenorphine will cause opioid withdrawal. Buprenorphine can be given by prescription and does not require daily attendance at a clinic. This is an advantage for persons who do not live near a methadone clinic. People should continue to take naltrexone, or buprenorphine until they, in consultation with their physician, have decided that they have reorganized their life to maintain recovery. Maintenance therapy may be required for months, years, or for the rest of their lives.

Side Effects

*Potential side effect for opioid treatment medications, see also Narcotic and Opioid Analgesics.

(*Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

- Abdominal cramps
- Body aches lasting 5-7 days
- Constipation
- Diarrhea
- Dizziness
- Eosinophilic pneumonia
- Fatigue
- Headache
- Hypotension (orthostatic hypotension)
- Insomnia
- Liver injury
- Nausea
- Nervousness
- Opioid withdrawal
- Runny eyes and nose
- Severe anxiety
- Vomiting

Emergency Conditions

- An overdose of any opioid use disorder medication is always considered an emergency and treatment should be sought immediately.
- **Taking large amounts of opioids to overcome medications that have opioid antagonist activity could result in overdose. Overdose on medications can lead to liver injury or can be fatal.**

Misuse Potential

A number of medications used in the treatment of opioid use disorders do carry a risk for misuse and diversion. Use of these medications requires careful monitoring that must be balanced with ensuring access to care without stigma. Clearly spelling out treatment expectations and adjusting frequency of visits based on patient specific factors is essential.
Additional agents such as naloxone and naltrexone are not thought to carry an abuse potential because of their opiate receptor antagonistic properties. When naloxone is administered in combination with buprenorphine, it is intended to mitigate buprenorphine's abuse potential.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and the dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (e.g. St. John's wort, echinacea, ginkgo, ginseng, and others).
- People taking opioid medications should not increase or decrease their dose unless this has been checked with their physician and a change is ordered.
- People taking opioid medications are particularly vulnerable to adverse medical consequences if they concurrently use alcohol and/or street drugs.
- People taking naltrexone should be warned that if they are dependent on opioids, taking these medications will cause opioid withdrawal for up to three days and block the effect of any opioids taken for up to three days.

Stimulant Medications

Stimulants

GENERIC	BRAND
amphetamine	Adzenys XR ODT®, Adzenys ER®, Dynavel XR®, Evekeo®,
armodafinil	Nuvigil®
d-amphetamine*	Dexedrine®*, Dexedrine Spansule®, Dextro Stat®*, ProCentra®, Zenzedi®
dexmethylphenidate	Focalin®, Focalin XR®
l & d mixedamphetaminemixed amphetamine salts*	Adderall®*, Adderall XR®*, Mydayis®
lisdexamfetamine*	Vyvanse®*
methamphetamine	Desoxyn®
methylphenidate*	Adhanasia XR®, Aptensio XR®, Concerta®*, Contempla XR-ODT®, Daytrana®*, Jornay PM®, Metadate ER®*, Metadate CD®*, Methylin®, Methylin ER®*, Quillivant ER®, Quillivant XR®*, Relexxi®, Ritalin®*, Ritalin SR®*, Ritalin LA®*,
modafinil	Provigil®

Non-stimulants for ADHD

GENERIC	BRAND
atomoxetine*	Strattera®*
bupropion	Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®
clonidine	Catapres®, Catapres TTS®, Kapvay®
guanfacine*	Tenex®*, Intuniv®*

*FDA approved for treatment of ADHD

Purpose

Stimulant medications are used most often to treat attention deficit/hyperactivity disorder (ADHD), which is typically diagnosed in childhood but also occurs in adults. They are also used in narcolepsy, off-label for treatment resistant depression, and to treat lethargy/psychomotor retardation associated with some medical conditions. Symptoms consistent with ADHD include short attention span, excessive activity (hyperactivity), and impulsivity. The underlying manifestation of ADHD is that it severely impacts and interferes with a person's daily functioning.

Positive treatment responses to stimulant medications include increased attention, focus and/or ability to stay on task, less hyperactivity, and moderation of impulsive behavior.

Non-stimulant medications for ADHD differ somewhat. Atomoxetine blocks the reuptake of norepinephrine, which helps reduce the symptoms of ADHD. Guanfacine, an alpha-2 agonist, and bupropion, a reuptake inhibitor of dopamine and norepinephrine, are both non-stimulants that have been used successfully to treat symptoms of ADHD. The advantage of these medications is that they are non-addictive, and do not cause a "high" even in larger doses. Atomoxetine and guanfacine are FDA approved. While studies have shown bupropion to be effective, it is not FDA approved.

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. With stimulants, there may be periods when the medication is not to be taken. The most common side effects of the stimulants are nervousness, sleeplessness, and loss of appetite. Some of these medications are expensive, but others are generic and quite inexpensive.

Side Effects

***Potential side effects of Psychostimulant Medications:**
(* Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

- Abdominal pain
- Anxiety/agitation
- Anorexia
- Blurred vision
- Change in heart rhythm
- Constipation
- Delayed growth
- Dry mouth
- Dilated pupils
- Elevated blood pressure
- Euphoria
- Excitability
- Headache

- Increased heart rate
- Insomnia
- Irritability
- Loss of appetite
- Mood swings
- Rare priapism
- Rash
- Seizures
- Sexual dysfunction
- Tremor
- Weight loss

Non-stimulants for ADHD

***Potential side effects of the non-psychostimulant Atomoxetine:**

- Anxiety, agitation
- Appetite decrease
- Constipation
- Dry mouth
- Dysmenorrhea
- Erectile dysfunction
- Fatigue
- Hepatotoxicity
- Hot flashes
- Hypertension
- Insomnia
- Nausea
- Priapism
- Rash
- Sweating
- Urinary hesitation and/or urinary retention and/or dysuria

***Potential side effects of Bupropion:**

- Appetite decrease
- Constipation
- Dizziness
- Dry mouth
- Hypertension
- Insomnia
- Rash
- Seizures
- Sweating
- Weight loss

***Potential side effects of Guanfacine:**

- Abdominal pain
- Constipation
- Dizziness
- Dry mouth
- Hypotension
- Sleepiness

Emergency Conditions

Psychiatric symptoms including paranoid delusions, thought disorders, and hallucinations have been reported when stimulants are used for long periods or taken at high dosages. Overdose with stimulants is a medical emergency. Seek help immediately.

Misuse Potential

Stimulant medications are among the most commonly misused psychiatric medications and have the potential for misuse by those taking them for treatment. Recreational or non-medically indicated uses have been reported for performance enhancement and/or weight loss. People with ADHD or narcolepsy, however, rarely misuse or become dependent on stimulant medications.

Many doctors use non-stimulants to treat ADHD in adults with co-occurring substance use disorders. Using stimulant medications to treat ADHD in children has been shown to reduce the potential development of substance use disorders.

Cautions

- Physicians, nurses, pharmacists and other healthcare professionals providing care should be told about all medications being taken and the dosage, including over-the-counter preparations, vitamins, minerals, and herbal supplements (e.g. St. John's wort, echinacea, ginkgo, ginseng, and others).
- People taking stimulant medications should not increase their dose unless this has been checked with their physician and a change is ordered.
- People taking stimulant medications are particularly vulnerable to adverse medical consequences if they concurrently use alcohol and/or street drugs.
- With stimulants, there is the potential for development of tolerance and dependence on the medications with accompanying withdrawal. The potential for abuse and misuse is high, as is true with all Schedule II drugs.
- Patients who have severe heart disease or cardiac abnormalities, pheochromocytoma, narrow angle glaucoma or liver disease should not use atomoxetine.

Tobacco

Nicotine Replacement Therapies (NRT)*

GENERIC	BRAND
nicotine inhaler	Nicotrol Inhaler®
nicotine nasal spray	Nicotrol NS®
nicotine patch/ transdermal nicotine	Nicoderm CQ®, Nicotine Step 1®, Nicotine Step 2®, Nicotine Step 3®
nicotine polacrilex gum	Nicorette®, Nicorelief®, Thrive®
nicotine polacrilex lozenges	GoodSense Nicotine®, Nicorelief®, Nicorette®, Nicorette Mini®, Thrive®

Pharmacotherapies for Smoking Cessation

GENERIC	BRAND
bupropion SR*	Zyban®*
clonidine	Catapres®
nortriptyline	Pamelor®
varenicline*	Chantix®*

*FDA approved for Smoking Cessation.

Purpose

Complete long-term abstinence from all nicotine containing products is the goal of tobacco cessation therapies. Medications and products for tobacco cessation assist clients with tobacco use disorder to achieve abstinence by alleviating or reducing common nicotine withdrawal symptoms (e.g. irritability, anxiety, insomnia, hunger, weight gain) and cravings, though nicotine replacement strategies do not necessarily mimic all reported pleasures and benefits from smoking. Numerous scientific studies have shown that it is easier for individuals to quit tobacco when supported by health professionals and adequate behavioral support is offered. For this reason, recommended treatment strategies incorporate both behavioral counseling and pharmacotherapy to increase quit rates for smokers. Nonetheless, pharmacotherapy is contraindicated for some specific populations (i.e., pregnant women, smoke-less tobacco users, light smokers, and adolescents). Recommended tobacco treatment strategies are available as cited in the 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment (Journal of the American College of Cardiology, 2018) and should be offered to patients willing to consider treatment options, even in the absence of immediate motivation to quit.

Nicotine Replacement Therapies (NRT) such as transdermal nicotine patch, nicotine polacrilex gum and lozenge, nicotine nasal spray, and nicotine inhaler are FDA-approved. The nasal spray and oral inhaler dosage forms are available only with a prescription, while the others are available as prescription and over-the-counter. These therapies reduce withdrawal symptoms and cravings by replacing nicotine normally obtained through chewing tobacco or smoking cigarettes. Numerous clinical trials involving NRT have demonstrated the effectiveness of these products for smoking cessation.

Bupropion, as an antidepressant, can help with withdrawal anxiety and depression. Sustained-release bupropion (bupropion SR) is one of two non-nicotine pharmaceutical aids that are FDA-approved for smoking cessation. This agent is thought to affect dopamine and norepinephrine levels, and blocks nicotinic receptors, thereby decreasing cravings for cigarettes and symptoms of nicotine withdrawal. The use of bupropion roughly doubles cessation rates relative to placebo, and the combination of bupropion with the nicotine patch has shown higher quit rates than using the patch alone.

Varenicline is an FDA-approved smoking cessation medication that targets alpha4 and beta2 nicotinic receptors as a partial agonist and prevents nicotine based dopamine stimulation in the mesolimbic region of the brain. It reduces the smoker's craving for nicotine by binding to nicotine receptors in the brain and thereby reducing withdrawal symptoms as well as resulting in a less satisfying smoking experience. Smokers using varenicline have better rates of smoking cessation compared to those who use bupropion. Varenicline offers an option for those who cannot tolerate the adverse effects associated with NRT and bupropion, and represents an alternative for clients with contraindications to such therapies.

Nortriptyline, a tricyclic antidepressant, and clonidine, an antihypertensive agent, are also considered potential treatment options. However, because of tolerability concerns they are relegated to second-line treatment considerations.

Dose & Frequency

All medications have specific doses and a prescribed frequency of administration. The physician or other prescriber will specify the exact amount of medication and when it should be taken; this information is provided on the prescription bottle. Some Nicotine Replacement Therapy (NRT) medications can be obtained without a prescription, including nicotine patch, nicotine gum, and nicotine lozenges. Specific information on how to use NRT products correctly, recommended dosing schedules, symptoms of overdose, and proper storage/disposal of the products are included on the product label or inside the package.

The nicotine patch is available in three strengths and a "step-down" approach is used: 21 mg for 6 weeks, then 14 mg for 2 weeks, then 7 mg for 2 weeks. For those who smoke less than one pack a day, consider starting at 14 mg dose. A new patch needs to be reapplied each day, at roughly the same time each day. The patch should be applied to a non-hairy, clean and dry area on the upper body or upper outer arm. The patch location should be rotated each day to reduce the potential of skin irritation. Use of the patch is associated with higher medication adherence rates and offers consistent delivery of nicotine over the course of a day. However, the combination of a patch and a more rapidly absorbed form of nicotine replacement therapy is considered to improve the chances of successful treatment.

The nicotine polacrilex gum and lozenge are offered in 2 milligrams (mg) and 4 mg strengths. Individuals who smoke fewer than 25 cigarettes per day should initiate therapy with the 2 mg strength, and heavier smokers should initiate with the 4 mg strength. During the initial 6 weeks of therapy, one piece of gum should be chewed every 1 to 2 hours while awake; up to at least nine pieces of gum daily. The gum should be used for up to 12 weeks and no more than 24 pieces should be chewed a day. A "chew and park" technique is necessary for nicotine to absorb correctly and food or beverages should be avoided 15 minutes before or after using the nicotine gum.

Unlike other forms of NRT, which are dosed based on the number of cigarettes smoked per day; the recommended dosage of the nicotine lozenge is based on the "time to first cigarette" of the day. Some studies suggest that the best indicator of nicotine dependence is having a strong desire or need to smoke soon after waking. Clients who smoke their first cigarette of the day within 30 minutes of waking are likely to be more highly dependent on nicotine and require higher dosages than those who delay smoking for more than 30 minutes after waking. During the initial 6 weeks of therapy, clients should use one lozenge every 1 to 2 hours while awake; at least nine lozenges daily. Clients can use additional lozenges (up to 5 lozenges in 6 hours or a maximum of 20 lozenges per day) if cravings occur between the scheduled doses. The lozenges should be used for up to 12 weeks with no more than 20 lozenges used a day. Lozenges should be allowed to dissolve in the mouth and food or beverages should be avoided 15 minutes before or after using the nicotine lozenge.

Bupropion SR should be started 7 days before a targeted smoking cessation date. Generally, for the first 3 days of treatment, individuals take 150 mg, then 150 mg twice a day for 7 to 12 weeks, and for some individuals, longer treatment may be required to increase the likelihood of long-term tobacco cessation.

The approved course of varenicline treatment is 12 weeks; however, an additional 12 weeks of treatment may increase the likelihood of long-term smoking cessation for some individuals. For the first 3 days of treatment, individuals take 0.5 mg once a day, followed by 0.5 mg twice a day for the next four days, and then 1 mg twice a day for the remainder of the treatment period.

For certain groups of smokers, it may be appropriate to continue NRT treatment or pharmacotherapies for periods longer than is usually recommended. In general, the more intense the treatment for tobacco cessation (e.g., combined use of NRT and pharmacotherapies), the higher the likelihood of successful cessation. Specific combinations of first line medications shown to be effective include the nicotine patch and bupropion SR, the nicotine patch and the inhaler, and long-term nicotine patch (greater than 14 weeks) and ad libitum NRT use. Varenicline is not recommended for use in combination with NRT because of its nicotine antagonist properties.

While NRT replaces the nicotine that the patient had while smoking, bupropion and varenicline are medications that aid in quitting. The underlying desire to quit must be present or bupropion and varenicline will have little to no effect on the patient that is trying to quit.

Side Effects

(* Side effect listings are provided in alphabetical order, not order of prevalence. Side effect lists are not intended to be all-inclusive.)

Potential side effects for NRT and pharmacotherapies for smoking cessation*

- Nicotine gum: mouth soreness, hiccups, indigestion, jaw muscle aches. Most of these are mild and subside with continued use of the gum.
- Nicotine lozenges: nausea, hiccups, throat irritation, heartburn. Use of the 4 mg dose has been associated with increased rates of headaches and coughing.
- Nicotine nasal spray and inhaler: headache, burning sensation of the nose (nasal spray), nausea, diarrhea, mouth irritation (inhaler), cough (inhaler), rhinitis (inhaler)

- Nicotine patch: skin reactions (i.e., itching, burning, redness or rash at patch site) are usually mild and often resolved by rotating patch site. Other side effects include insomnia, nausea, and/or vivid dreams.
- Bupropion SR: upset stomach, insomnia, and headache. Use with caution if there is a history of seizures or predisposing factors for seizures such as heavy alcohol use, or an eating disorder as use has been associated with seizure activity.
- Varenicline: nausea, headache, trouble sleeping, seizures, abnormal/vivid/strange dreams, increase in suicidal thoughts in some patients. DO NOT TAKE with alcohol.

See FDA package insert for each product for a more complete list of side effects and black box warnings. It is strongly recommended to read FDA insert thoroughly before beginning treatment.

Emergency Conditions

- An overdose of any substance use disorder treatment medication is always considered an emergency and treatment should be sought immediately.
- Symptoms of a nicotine overdose may include nausea, vomiting, diarrhea, stomach pain, cold sweats, headache, dizziness, problems with hearing or vision, confusion, an irregular heartbeat, chest pain, seizures, and death.

Misuse Potential

The abuse potential for medications used in tobacco use disorders primarily sits with the different nicotine replacement treatment options. As nicotine replacement therapy is simply a controlled means to administer nicotine in a manner other than cigarettes and chewing tobacco, the potential exists to self-administer doses of nicotine in a higher than intended purpose for gradually tapering off of nicotine all together. In addition, some tricyclic antidepressant medications of the tricyclic family that have been studied in nicotine abuse do carry an anticholinergic property as well as increasing noradrenaline, which may result in a brief euphoria. Antidepressants however are not considered controlled substances. Also, reports of bupropion abuse have been reported because of the increase in dopamine and noradrenaline release that can occur. Often bupropion may be crushed and snorted or injected to produce the desired high.

Cautions

- For all women of childbearing age who may be or think they may be pregnant, or who have recently given birth and plan to breastfeed should consult with their healthcare providers to discuss the safety of these and other medications before starting, continuing, or discontinuing medication treatment.
- Smoking can have an effect on the way the body processes other prescribed medications. Aromatic hydrocarbons found in tar in cigarettes stimulates enzymes in the liver (notably CYP450 1A2), and fluctuations in an individual's smoking pattern can result in higher or lower doses of medications needed to reach therapeutic levels.
- Although studies have now documented the lack of association between the nicotine patch and acute cardiovascular events, even with individuals who continued to smoke while on the patch, all NRT products should be used with caution for individuals who had a recent (within 2 weeks) myocardial infarction (MI), those with severe arrhythmias, or those with unstable angina pectoris.

- NRT products should be properly disposed of to insure safety of children and pets. Nicotine on hands can get into nose or eyes, causing stinging and redness. Wash hands with soap and water after handling the patch.
- Because seizures have been reported in 0.1% of patients, bupropion is contraindicated in individuals who have a history of seizure disorder, have a current or prior diagnosis of anorexia or bulimia, are currently using another form of bupropion, heavy drinkers or are currently using or have used a Monoamine Oxidase (MAO) Inhibitor within the past two weeks. Other factors that might increase the odds of seizure and are classified as warnings for this medication include a history of head trauma, central nervous system tumor, the presence of severe hepatic cirrhosis, and concomitant use of medications that lower the seizure threshold. Bupropion can be used safely in combination with NRT and may be beneficial for use in clients with underlying depression.
- Although varenicline is well tolerated in most individuals, there have been reports of exacerbations of existing psychiatric illness in clients who took varenicline. Labeling on varenicline indicates that depressed mood, agitation, changes in behavior, suicidal ideation, and suicide have been reported in clients attempting to quit smoking while using varenicline. Patients who have a change in personality, increase in anger or thoughts of suicide should be immediately referred back to their doctor.
- Because varenicline is eliminated almost entirely unchanged in the urine, it should be used with caution in clients with severe renal dysfunction.
- Alcohol use should be avoided when taking varenicline.