I. MEDICATIONS AND OTHER THERAPEUTIC MEASURES

A. Definitions.

Sedatives/hypnotics are medications that are used to reduce anxiety or to induce sleep. Medications that relieve anxiety are also called “anxiolytics” or “tranquilizers.” The term “hypnotics” generally refers to sleeping medications. Regardless of their marketed indications, many of these medications have both anxiolytic and sedative effects.

B. Scope.

This chapter discusses general prescribing recommendations, but not specific drug dosing guidelines.

C. Anxiolytics.

1. Benzodiazepines.

   a. Benzodiazepines make up the largest class of anxiolytics. Many are available generically.

   b. Benzodiazepines are rapidly effective for anxiety, and are thus highly sought-after by patients with previous experience with them.

   c. There are a number of agents with both long and short half-lives.

   d. There are a number of safety considerations with benzodiazepines:

      i) Physiologic dependence, which can lead to potentially dangerous withdrawal symptoms, such as seizures.

      ii) Psychological dependence and habituation, leading to problems with abuse and diversion, and well as rebound anxiety upon discontinuation.

      iii) Sedation-related side effects, including memory impairment, confusion, and ataxia.

      iv) Concomitant use of alcohol potentiates all of the above concerns.
e. Despite these drawbacks, benzodiazepines are sometimes the most effective option for some of the more severe anxiety syndromes, such as panic attacks or post-traumatic stress disorder. Their primary benefit, however, is rapid onset, and some evidence suggests that SSRIs are equally, if not more, effective in the long-term.

2. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs).

a. SSRIs and SNRIs are primarily antidepressant agents, but they also have significant anxiolytic effects. There are several branded and generic options available.

b. While there are some safety considerations with these medications, and prescribers should become familiar with the agents they use, there is less problem with sedation, little danger in overdose, and virtually no risk of physiologic or psychological dependence.

c. SSRIs and SNRIs thus are often more appropriate choices for anxiety than benzodiazepines. They may also be used concomitantly with benzodiazepines, reducing the amount needed.

3. Other pharmacologic agents.

a. Antihistamines, such as diphenhydramine (Benadryl) and hydroxyzine (Vistaril), also have at least modest anxiolytic effects; these effects are more prominent at higher doses. They are rapid-acting, and present a viable option to benzodiazepines, especially in benzodiazepine-naïve patients. Patients who have experience with benzodiazepines will rarely be satisfied with these agents. Sedation is a common side effect—though this may not be totally undesirable.

b. Buspirone appears to be as effective as benzodiazepines for the treatment of general anxiety, but the onset of action can be several weeks. There is less risk of sedation, and virtually no risk of physiologic or psychological dependence. Given other short-term supportive care, buspirone is an attractive option to benzodiazepines, especially in benzodiazepine-naïve patients. However, it appears to be less satisfactory to patients who have experience with benzodiazepines.

c. Tricyclic antidepressants have at least some anxiolytic effect, though the onset is slow, and anticholinergic side effects are common; there are also other considerations, including cardiac conduction abnormalities and high mortality in overdose. While they may have an adjunctive role in difficult-to-manage patients, their use has largely been supplanted by SSRIs/SNRIs.

d. Beta adrenergic blockers are sometimes used on a PRN basis for performance anxiety. They are best used in small doses under well-defined circumstances. To avoid psychological dependence, it is advisable to consider concomitant behavioral
therapy, which is often quite effective in such instances. Orthostatic hypotension and bradycardia can be limiting side effects.

e. Monoamine oxidase inhibitors have exhibited utility in some anxiety disorders. Given their numerous and potentially serious dietary and drug interactions, they are best reserved for use in exceptional circumstances by experienced prescribers.

f. The second generation anticonvulsants gabapentin (Neurontin, generic) and pregabalin (Lyrica), have exhibited utility in some anxiety disorders. They are generally safe, and may be used in combination with other agents.

g. Older medications, such as barbiturates and “non-barbiturate barbiturates” like meprobamate, are still available, though they are rarely used, since they have most all of the same sedation, addiction, and habituation effects as benzodiazepines, often to a more severe degree, with a greater risk of death in accidental or purposeful overdose.

4. Cognitive-behavioral therapy (CBT) has been shown in several randomized controlled trials to be at least as efficacious as drugs for treatment of panic and other anxiety disorders; improvements are often maintained or increased in the 6-12 months after completion of treatment, without the deleterious effects of pharmacologic agents. These measures are best employed by practitioners with specialized training.

D. Hypnotics.

1. Benzodiazepines.
   a. Benzodiazepines have in recent decades been the largest and most frequently used class of sleeping medications. Many are available generically.
   b. Adverse reactions and safety considerations are discussed above under the Anxiolytics heading.
   c. In addition to those considerations, note that agents with long half-lives have a high risk of morning carryover sedation, while those with short half-lives may allow the patient to awaken during the night, requiring a second dose.
   d. Infrequent, PRN use of benzodiazepines for sleep is probably generally safe, though it is very common for patients to escalate usage to every night, developing habituation.

2. Non-benzodiazepine benzodiazepines.
   a. Also known as GABA-benzodiazepine receptor agonists, these are drugs that are not structurally related to benzodiazepines, but bind to the same receptors and/or some very closely-related receptors.
b. Examples include zaleplon (Sonata), zolpidem (Ambien, Ambien CR, generics), and eszopiclone (Lunesta).

c. These medications have the potential for all of the adverse effects and safety considerations described above for benzodiazepines, though to date they appear to occur somewhat less frequently.

3. Other agents.

a. Antihistamines, such as diphenhydramine (Benadryl) and hydroxyzine (Vistaril), have sedative effects. They may have carryover sedation into the next day, and, of course, are associated with antihistaminic side effects. They may be useful for intermittent, short-term use, but have not been shown to be helpful in long-term management of insomnia.

b. Tricyclic antidepressants, especially the tertiary amines, have sedative effects. The sedative effect appears at initiation of treatment, and may wane with continued use. Anticholinergic side effects are common, and there are also other considerations, such as cardiac conduction abnormalities and high mortality in overdose. They are most useful in insomnia with coexistent depression, but have not been shown to be effective in the management of chronic insomnia without depression.

c. Ramelteon (Rozerem) is a melatonin receptor agonist that has been approved for use in patients with insomnia characterized by difficulty with sleep onset. It appears safe, with no abuse potential, but has displayed unimpressive objective and subjective benefits on sleep efficacy.

d. Older medications, such as barbiturates and “non-barbiturate barbiturates” are still available, though they are rarely used, since they have most all of the same sedation, addiction, and habituation effects as benzodiazepines, often to a more severe degree, with a greater risk of death in accidental or purposeful overdose. One such agent still in relatively common use is chloral hydrate, which is sometimes employed for medical procedural sedation.

e. Various herbal and nutriceutical agents, such as valerian and melatonin, are marketed for insomnia. As with many such agents, preparations may vary widely, and there are few well-designed studies showing significant benefits on sleep efficacy. Melatonin may be an exception; it may have a modest hypnotic effect, and it appears safe in at least short-term use. It may be most useful in circadian rhythm disturbances, such as jet-lag. There are a wide range of preparations and recommended doses.

4. Cognitive-behavioral therapy (CBT) includes several nonpharmacologic interventions that have been shown to improve sleep efficacy.
Examples include relaxation therapy, biofeedback, stimulus control therapy, sleep restriction, and sleep hygiene measures.

With the exception of sleep hygiene counseling, many of these methods are most commonly employed by practitioners with specialized training.

While data show that long-term sleep improvements may be comparable to pharmacologic measures, without the drawbacks of medical therapy, there is not a clear consensus as to the relative efficacy of specific techniques. They are often used in combination, with or without hypnotic medications.

Sleep hygiene counseling is effective and easily given by primary care providers. Recommendations include the following:

1. Sleep only as much as needed to feel rested.
2. Keep a regular sleep schedule, both on work and non-work days; set an alarm clock to wake up at a fixed time each morning, including weekends.
3. Avoid forcing sleep; go to bed only when sleepy.
4. Get out of bed if unable to fall asleep within 10-15 minutes, and go to another room. Return to bed only when sleepy. Repeat this step as many times as necessary throughout the night.
5. Do not go to bed hungry, but do not eat a large meal within 2-3 hours of bedtime.
6. Deal with and “set aside” worries before getting into bed.
7. Do not watch television, read, or eat in bed. Use bed only for sleep and sex.
8. Naps are generally detrimental to evening sleep. For someone who has established brief naps as a long-time practice, and who feels more refreshed and functional after a brief nap, it may be advisable to continue them, though it should be recognized that this will reduce total evening sleep time.
9. Quit smoking.
10. Avoid caffeinated beverages after lunch.
11. Avoid alcohol within 3-4 hours of bedtime.
12. Exercise regularly, preferably a least 20 minutes per day, but not within 3-4 hours of bedtime.
E. Selected oral benzodiazepines and non-benzodiazepine benzodiazepines on the U.S. market, with approximate equivalencies to diazepam 10 mg. Adapted from Ashton, C. Heather; Benzodiazepines: How They Work And How To Withdraw.

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Half-life (hours) [active metabolite]</th>
<th>Equivalent dosages (mg)</th>
<th>Primary Market Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>6-12</td>
<td>0.5</td>
<td>anxiolytic</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>5-30 [36-200]</td>
<td>25</td>
<td>anxiolytic</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>18-50</td>
<td>0.5</td>
<td>anxiolytic, anticonvulsant</td>
</tr>
<tr>
<td>Clorazepate (Tranxene)</td>
<td>[36-200]</td>
<td>15</td>
<td>anxiolytic</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>20-100 [36-200]</td>
<td>10</td>
<td>anxiolytic</td>
</tr>
<tr>
<td>Estazolam (ProSom)</td>
<td>10-24</td>
<td>1-2</td>
<td>hypnotic</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>[40-250]</td>
<td>15-30</td>
<td>hypnotic</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>10-20</td>
<td>1</td>
<td>anxiolytic</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>4-15</td>
<td>20</td>
<td>anxiolytic</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>8-22</td>
<td>20</td>
<td>hypnotic</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>2</td>
<td>0.5</td>
<td>hypnotic</td>
</tr>
<tr>
<td><strong>Non-benzodiazepine benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>2</td>
<td>20</td>
<td>hypnotic</td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>2</td>
<td>20</td>
<td>hypnotic</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>6-9</td>
<td>3</td>
<td>hypnotic</td>
</tr>
</tbody>
</table>

II. POLICIES AND PROCEDURES

A. For new patients seeking sedatives/hypnotics, or established patients newly seeking such medicines, observe the following rules and workflow:

1. Assess the etiology of the patient’s symptoms or request for sedatives/hypnotics.

2. Assess the appropriateness of further diagnostic or therapeutic measures, or specialty referral. Treat any comorbid medical problems identified that could be adversely affecting anxiety or sleep.

3. Initiate and maximize nonpharmacologic measures to address the patient’s symptoms.

4. If the patient’s problem appears to merit pharmacologic treatment, initiate the safer, non-habituating options outlined above.

a. Patients may sometimes be resistant to such medications, stating they haven’t worked in the past, or that they have had various side effects or “allergies” to them. Point out that there are several agents to choose from, and that most often one can be found that is helpful and tolerable. Also explain that many side effects are self-limited, or are actually manifestations of anxiety or sleep deprivation themselves.

b. The physician is under no obligation to initiate sedatives/hypnotics, or to continue a prescription from another physician. If the patient continues to press for such
medications, it is often helpful to explain that, while every appropriate treatment will be employed to help with the patient’s symptoms, if the patient’s primary goal is to obtain these medications, he/she is not likely to be satisfied in this medical practice.

c. If the patient continues to be demanding or disruptive, tell the patient that it appears a physician/patient relationship cannot be established or continued, and submit the case to the Clinical Management Team. If necessary to maintain safety or decorum, call security.

5. For younger or benzodiazepine-naïve patients, be very reluctant to initiate benzodiazepines and similar habituating medications.

a. Exhaust all other options, and consider psychiatric referral before initiating long-term benzodiazepines.

b. For a well-defined, short-term indication, benzodiazepine use may be cautiously considered. Explain to the patient that it is intended only for short-term use, warn about habituation potential and side effects, and explain that if there should appear to be an ongoing need for such medications, better alternatives will be sought out.

6. If it is determined that sedative/hypnotic prescribing is appropriate, observe the following procedures:

a. Discuss departmental policies with the patient, and have the patient complete a CONTROLLED SUBSTANCES AGREEMENT, including the appropriate RISKS AND SIDE EFFECTS FORM.

b. Question the patient about a history of previous substance abuse. In the absence of such history, have the patient complete the OPIOID RISK TOOL. If there appears to be a high risk of opioid abuse, it is logical to assume there is a high risk of abuse of sedatives/hypnotics. While there may be occasions when sedative/hypnotic prescribing is appropriate in such patients, these circumstances are difficult to manage, and this is generally outside the scope of the typical primary care practice. Psychiatric referral should be made instead.

c. Given that depression is often concomitant with anxiety and insomnia, assess for depression with the BECK DEPRESSION INVENTORY, and treat accordingly.

d. Other major psychiatric diagnoses, such as schizophrenia and bipolar disorder, can make anxiety management very difficult. Many of these cases will be beyond the scope of a primary care office, and should prompt referral to appropriate psychological or psychiatric consultants.
e. Explain that it is unrealistic to expect complete resolution of all symptoms of anxiety or insomnia, though symptoms can usually be managed, and quality of life can be improved.

f. Use the lowest dose of the mildest medicine necessary, for the shortest period of time possible.

g. Continue and/or further explore alternative pharmacologic and nonpharmacologic treatment modalities.

h. Initially plan frequent follow-up visits, reassessing the patient’s level of symptoms, side effects, and the effectiveness of the prescribed measures.

i. Monitor for compliance, appropriate drug usage, and inappropriate behavior such as diversion. Urine drug screens should be obtained at the discretion of the physician.

j. Once the patient’s condition is stabilized at a satisfactory level, follow-up visits may be reduced to every three months.

B. For patients who are already established in the practice, and who are already taking sedatives/hypnotics, observe the following rules and workflow:

1. Recognize that there is constant physician turnover in the residency’s medical practice, and thus it will be common to take over the care of patients who are using sedatives/hypnotics. The physician assuming such care should review the patient’s history and physical exam, and determine if continued prescribing of such medications is appropriate, rather than just automatically refilling these prescriptions.

2. If there are any doubts about the appropriateness of sedatives/hypnotics, further diagnostic evaluation should be undertaken.

3. If it is evident that there are safer pharmacologic or nonpharmacologic measures that should be considered, institute them.

4. The above notwithstanding, keep in mind the potentially dangerous consequences of sedative/hypnotic withdrawal, primarily seizures. In many cases, it is wise to continue the patient’s current medications while pursuing alternative treatments and diagnoses.

5. If it is determined that ongoing sedative/hypnotic prescribing is not warranted, the patient should be informed, and a tapering reduction of these medications should be initiated. Benzodiazepines can typically be tapered by 25% per week without physically dangerous sequelae.

6. It should be recognized that there are some circumstances where continuing sedatives/hypnotics may be the most reasonable course of action, even if the physician personally might not have chosen to initiate them. An example would be an patient
with many years of benzodiazepine use, on a stable dose, functioning at a comfortable level, without any untoward side effects; attempting withdrawal of benzodiazepines for such a patient would likely be met with rebound symptoms, dissatisfaction on the part of the patient, and frustration on the part of the physician. Under these conditions, it may be best to continue a stable dose, avoiding dosage escalation, and consider other agents, such as SSRIs/SNRIs, to minimize the need for benzodiazepines.

7. Once it is determined that ongoing sedative/hypnotic prescribing is warranted, proceed with prescribing policies as discussed under II.A.7 above.

C. Discontinuation or interruption of benzodiazepines and related medications.

While the practice’s CONTROLLED SUBSTANCES AGREEMENT explains that controlled substances are not refilled after hours or over the phone, there will be times the on-call physician will be contacted by patients who state they are out of their medications, raising the specter of the consequences of benzodiazepine withdrawal.

1. A general policy should be to make the patient come to the Emergency Department to be evaluated if he/she feels like she needs a refill before the patient’s primary physician can been seen in the office.

2. If the on-call physician is personally familiar with the patient, and feels an Emergency Department visit is not necessary, this recommendation may be waived.

3. If the patient’s medication and dosage are known, the patient should be prescribed enough medication to last until the office is open again.

4. If the physician is sure a patient is chronically using benzodiazepines, but there is uncertainty about the specific medication or dosage, a reasonable course of action is to prescribe enough clonazepam (Klonopin) 0.5 mg BID to last until the office is open again. The patient may not experience the same effects as the established medication would provide, but dangerous physical withdrawal symptoms will be unlikely.

D. Special considerations for insomnia and hypnotic use.

1. Consider medical problems that can impair sleep, and treat accordingly. Examples include:
   a. Acquired immunodeficiency syndrome.
   b. Asthma.
   c. Chronic fatigue syndrome.
   d. Chronic obstructive pulmonary disease.
   e. Congestive heart failure.
   f. Ischemic heart disease.
   g. Medication side effects.
   h. Peptic ulcer disease and reflux esophagitis.
i. Restless legs syndrome.
j. Rheumatic/arthritic disorders.
k. Sleep apnea.
l. Transient, self-limited illness.

2. One should be reluctant to initiate benzodiazepines and related sleeping medications for patients who are not already established on such drugs. Focus on alternative therapies discussed above.

3. When seeing patients who have been chronically using hypnotics every night for sleep, it is probably unrealistic to try to get them off of them. Continue a stable dose, and consider adjunctive measures rather than dosage escalation if sleeping problems should worsen in the future.

4. Realize that, while rebound insomnia is likely if a chronic hypnotic user abruptly stops the medication, dangerous physical withdrawal is unlikely, in contrast to a patient who is habituated to multiple daily doses of benzodiazepines for anxiety.

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