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Anxiolytics: the Benzodiazepines

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Learning Objectives:
After studying this article, the reader should be able to:

1. Know the major indications for the use of the benzodiazepines.

2. Know some alternative medications that are effective for anxiety.

3. Recognize the major adverse effects of the benzodiazepines.

There are a number of medications that are effective in various types of anxiety disorders. For example, anxiety has already been mentioned as a possible use in earlier articles on the antidepressants. Both the selective serotonin re-uptake inhibitors (SSRIs) and the tricyclics have shown efficacy in generalized anxiety disorder and panic disorder. The SSRIs have also shown some effectiveness for obsessive-compulsive disorder (OCD), which is currently classified with anxiety-related conditions. However, there are other medications that are best known for their effects on anxiety. Some of them will be saved for later. This article will focus on the benzodiazepines, a group of chemicals that we believe act as agonists (potentiators) at the gamma-aminobutyric acid type A (GABAA) receptor complex in the central nervous system. Benzodiazepines are named for their chemical structure – a benzene ring fused to a seven-sided diazepine ring. All of these compounds, which have a clinically significant effect, also have a second benzene ring.

These medications are generally well absorbed orally, but aside from a few of them, such as lorazepam (AtivanTM) and midazolam (VersedTM), are not reliably absorbed intramuscularly. They generally work in about 30 minutes, and most reach peak serum concentrations in about one to six hours. The older ones are extensively metabolized in the liver and some, such as diazepam (ValiumTM) and chlordiazepoxide (LibriumTM), have long-acting metabolites, which also exert anxiolytic effects.

These medicines are used for generalized anxiety disorder, adjustment disorder with anxiety (which some believe to be the best indication for this family of medications), panic disorder and social phobia. They are also used for insomnia, with some of them, such as estazolam (ProsomTM), flurazepam (DalmaneTM), temazepam (RestorilTM) and triazolam (HalcionTM), being used primarily for this indication. They have been used as an adjunct treatment of mania in bipolar I disorder and for agitation in many disorders, including schizophrenia. They are also effective in treating antipsychotic-induced akathisia, a type of restlessness. One of the benzodiazepines, alprazolam (XanaxTM) has some antidepressant effects, and clonazepam (KlonopinTM) can be helpful to those who have higher levels of anxiety as part of their OCD.

There are a number of other uses for medicines in this class, including the treatment of epilepsy and muscle spasms. They are also used as a pre-treatment for some quasi-surgical procedures and to help patients withdraw from cross-tolerant substances, such as alcohol and barbiturates.

The benzodiazepines, like all other medicines, have possible side effects, including drowsiness, which occurs in about 10 percent of patients treated with these medicines. Some patients, particularly the elderly, experience dizziness and ataxia (staggering). Taken by themselves, these medicines are not very dangerous in overdose, but if other CNS depressants are taken concurrently, which is frequently the case, the resulting respiratory depression may lead to death. Hepatic disease can lead to toxic levels of these medicines. Cognitive inefficiency may occur, even without noticeable sedation, and patients with brain damage may become so disinhibited that they are belligerent – the so-called “paradoxical rage reaction.” All in all, however, these medicines are remarkably well tolerated by most patients. Their greatest drawback by far is that all will cause

tolerance and eventual dependence, with a withdrawal syndrome that is just as life threatening as that of alcohol or the barbiturates. Withdrawal seizures are also possible. These medicines should never be stopped abruptly once the patient has been taking them for longer than a few weeks – three weeks or more is a good rule of thumb, although specific benzodiazepine and dose do make a difference. Benzodiazepines mix poorly with clozapine (ClozarilTM), nefazodone (SerzoneTM), fluvoxamine (LuvoxTM), and cisapride (PropulsidTM) and should not be taken with grapefruit juice.

A benzodiazepine receptor antagonist, flumazenil (MaziconTM, RomaziconTM) can reverse the effects of this class of medicines, but this is usually done only in hospital settings such as the emergency room.

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