

# Oral Sedation: A Primer on Anxiolysis for the Adult Patient

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The use of sedatives has established efficacy and safety for managing anxiety regarding dental treatment. This article will provide essential information regarding the pharmacology and therapeutic principles that govern the appropriate use of orally administered sedatives to provide mild sedation (anxiolysis). Dosages and protocols are intended for this purpose, not for providing moderate or deeper sedation levels.

**Key Words:** Sedation; Anxiolysis; Oral sedation; Minimal sedation; Hypnotics; Sedatives.

**F**ear and anxiety regarding dentistry continue to persist despite the modern advances in local anesthetic agents.<sup>1-19</sup> The majority of individuals admit they are fearful to some extent but many avoid dental care altogether.<sup>13,19</sup> Using coping skills, most of the general public that have fears and anxieties are able to carry on with normal daily life. An individual with a “specific phobia” is defined as having a fear and anxiety that is so great it inhibits them from normal daily function.<sup>20</sup> These patients present the greatest challenge for the dentist.

When looking at fear and anxiety towards dentistry, the majority of the general public have a low level of fear, but they are able to receive dental treatment through various coping mechanisms. A small, but significant portion of the public, have fears so great that it impedes their ability to properly maintain oral health care.<sup>13,19</sup> These are the patients with a high level of fear who probably do not seek dental care on a regular basis. Between these 2 groups are those with moderate levels of fear and anxiety. This group may be able to tolerate minor dental treatment but have a higher level of anxiety for more involved treatment. For example, they may tolerate hygiene appointments, but may not be willing to accept other, more invasive treatments, such as a

crown preparation or a root canal treatment. Patients with a moderate to high level of fear and anxiety are more likely to miss, cancel, or avoid a dental appointment.<sup>2,7,10,13,19,21,22</sup> The majority of these fearful patients can be easily and safely treated with oral sedatives (see Table). Adults, in general, have few objections to taking medications by mouth. The oral route is widely accepted, easy, convenient, painless, and inexpensive. The use of sedatives to produce anxiolysis (minimal sedation) in healthy adults is typically safe and effective provided the appropriate dose is prescribed and adequate time is given to allow the drug to reach its peak effect.<sup>23</sup>

As with all techniques, oral sedation has its limitations, however. Oral sedation can help the majority of patients with mild to moderate levels of fear and anxiety but may be ineffective in patients with higher levels of anxiety. The practitioner must remember that a certain portion of the fearful public will not be successfully managed using oral sedation because empiric dosing is not an exact science. For these patients dosages must be titrated intravenously. Even with intravenous sedation, there are still those who will require deeper levels of sedation, deep sedation, or general anesthesia, if dental care is to be provided successfully.

Levels of sedation progress as a continuum and each level can be achieved regardless of the route of administration. Employing oral sedation does not guarantee that a patient will be in a state of anxiolysis, nor does it

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Drugs Commonly Used for Sedation<sup>40</sup>

Generic Name (Brand Name)	Dose Range (mg)*	Oral Formulations	Onset (min)†	Half-Life (h)†	Comments
Nonprescription drugs					
Diphenhydramine (Benadryl)	25–50	Syrup: 12.5 mg/5 mL and 25 mg/5 mL Tablets and capsules: 25 and 50 mg	15–60	2.4–9.3	Anticholinergic side effects can occur
Hydroxyzine (Atarax, Vistaril)	50–100	Syrup: 10 mg/5 mL Capsules: 10, 25, 50, and 100 mg Oral suspension: 25 mg/5 mL Tablets and capsules: 25, 50, and 100 mg	15–60	14	Anticholinergic side effects can occur
Promethazine (Phen- ergan)	25–50	Syrup: 6.25 mg/5 mL and 25 mg/5 mL Tablets: 12.5, 25, 50, and 100 mg	15–60	7–15	Anticholinergic side effects can occur
Prescription drugs: benzodiazepines					
Triazolam (Halcion)	0.125–0.5	Tablets: 0.125 and 0.25 mg	15–30	1.5–5	Very good for short to moder- ate length appointments (2– 4 hours)
Lorazepam (Ativan)	0.25–4	Oral solution: 2 mg/mL Tablets: 0.5, 1, and 2 mg	30–60	>8	Very good for longer appoint- ments (>3 hours)
Diazepam (Valium)	2–10	Oral solution: 5 mg/5 mL and 5 mg/mL Tablets: 2, 5, and 10 mg Extended release tablets: 15 mg	20–40	>24	Best administered the evening before a sedation appoint- ment given long half-life
Prescription drugs: nonbenzodiazepines					
Eszopiclone (Lunesta)	1–3	Tablets: 1, 2, and 3 mg	30	6	Metabolized by CYP450‡ 3A4 and 2E1
Ramelteon (Rozerem)	8	Tablets: 8 mg	30	1–2	Melatonin receptor agonist Not a controlled substance
Zolpidem (Ambien)	5–10	Tablets: 5 and 10 mg	30	1.5–4.5	Not contraindicated in preg- nancy
Zaleplon (Sonata)	5–20	Capsules: 5 and 10 mg	20	0.5–1	Good for short appointments (1–2 hours) Not contraindicated in preg- nancy

\* In general, therapy should be started at the low end of the dose range and increased if needed based on effect.

† Administration of a drug with a fast onset and short half-life decreases the risk of adverse effects such as falls.

‡ CYP450 indicates cytochrome P450.

guarantee that the patient will not drift into deeper levels of sedation. For this reason, patients should be treated with the lowest effective dose of the sedative agent chosen to best suit their needs. When providing sedation, the airway is always of chief concern, regardless of the level provided. While it is unlikely that appropriate doses of the drugs commonly used for oral sedation produce significant respiratory depression, it is important not to get this confused with airway obstruction; obstruction and respiratory depression are not synonymous. For example, a patient's airway may become obstructed by depressing the mandible during treatment. Until this occurs, a sedated patient may breathe normally, but may

not initiate enough ventilatory effort to overcome this obstruction and hypoxemia can occur. This risk for obstruction is a consideration when using any central nervous system (CNS) depressant, regardless of its ability to actually depress medullary respiratory drive.

## HISTORY OF ORAL SEDATIVES

By definition, a sedative drug decreases activity, moderates excitement, and calms the recipient.<sup>24</sup> The evolution of sedative drugs started with the introduction of fermented beverages by the Sumerians circa 9000

BC.<sup>25</sup> Aside from nitrous oxide and ether, the modern age of sedative medications began in the 19th century with bromides and chloral hydrate. While the bromides were excellent drugs in their day, they were not often manufactured into pharmaceutically elegant products, allowing the incorporation of impurities. This worsened the already negative side effect profile of bromides which included frequent urination, sweating, visual disturbances, and electrolyte disturbances.<sup>26</sup>

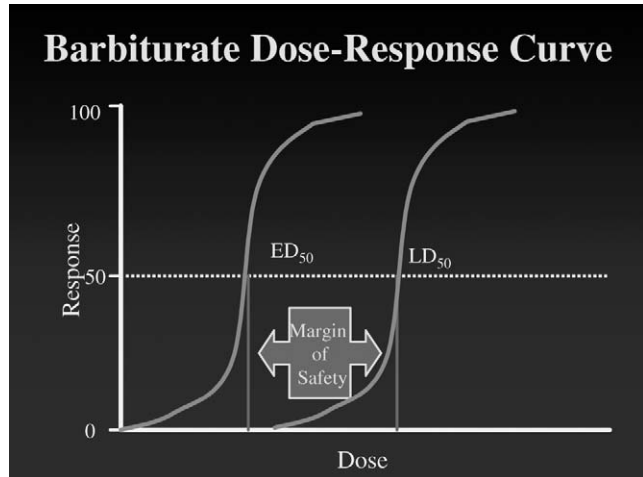
Chloral hydrate (Noctec) was synthesized in 1832 by the German chemist, Justus von Liebig, and represented the first class of sedative agents to show longevity on the mainstream pharmacopeia. Chloral hydrate is a generalized CNS depressant that acts rapidly, and if given alone, is capable of inducing deep sleep in approximately 30 minutes. It was soon discovered that chloral hydrate worked more quickly in combination with alcohol and, when slipped into whiskey, it was the “knockout drops” of the underworld, also called a “Mickey Finn.”

The most popular sleeping pills of the early 20th were the barbiturates, although the progenitor of the barbiturates was actually discovered in the mid-19th century. A Prussian chemist, Adolf von Baeyer, is credited with inventing and naming barbituric acid in the early 1860s. In 1903, a student of Baeyer’s, along with another German chemist, produced a new compound out of barbituric acid and a diethyl derivative. The new chemical, given the tradename Veronal (barbital), was an excellent sedative and sleep aid. Other researchers came up with more barbituric acid derivatives; the most widely used was phenobarbital. Many European and American pharmaceutical companies developed new barbiturates in the 1920s and 1930s. The Eli Lilly Company produced the widely used Amytal (amobarbital) and Seconal (secobarbital), and Abbott Laboratories invented Pentothal (thiopental) and Nembutal (Pentobarbital).

Though the barbiturates are effective sleep aids, they are not without risks. Barbiturates support addictive behavior, can have a variety of unpleasant side effects, and their effectiveness is greatly increased when taken concurrently with other CNS depressants. In fact, barbiturate sleeping pills can quickly cause death when taken with alcohol due to their significant cardiovascular and respiratory depressant effects. It is this narrow margin of safety that prompted the development of safer sedative/hypnotic medications (eg, benzodiazepines) during the next few decades. Due to their unacceptable safety profile, the use of barbiturates for sedation can no longer be recommended in most clinical situations.

## BENZODIAZEPINES

The benzodiazepines and their newer derivatives are the most widely used class of drugs for anxiolysis and se-

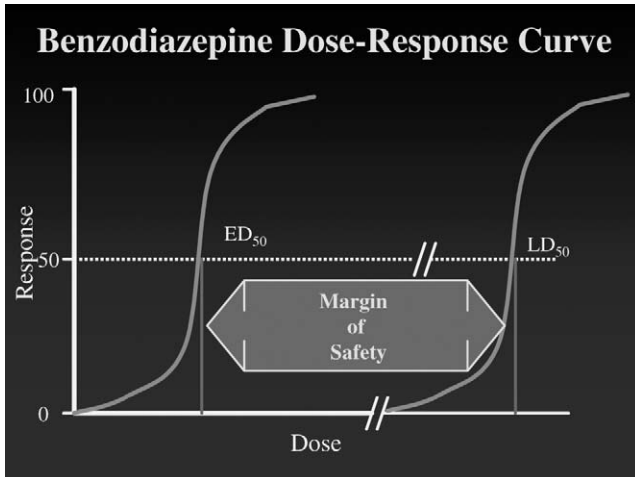


**Figure 1.** Dose-response curve for barbiturates.

dation. This is for good reason. Their efficacy is equivalent to or greater than any of the other classes of sedatives and their safety profile is enviable.

Virtually all effects of the benzodiazepines result from their specific actions on the central nervous system. They promote the binding and influence of the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) to the  $GABA_A$  subtype of GABA receptors in the brain.  $GABA_A$  receptors are actually multi-subunit complexes closely associated with gated chloride ion ( $Cl^-$ ) channels within the cell membrane of neurons. When GABA activates its receptor, the channel opens allowing greater influx of chloride ions and a more negative resting membrane potential. This renders the neuron less responsive to excitatory stimuli.

It is significant that benzodiazepines do not open the chloride channel. They bind to specific benzodiazepine (BZ) receptors on the  $GABA_A$  complex, separate from the actual receptor for GABA. Activation of the BZ receptor enhances the chloride ion channel’s response to GABA, but no effect is produced if GABA is not present. A benzodiazepine agonist can only potentiate the body’s endogenous neurotransmitter. This concept is a likely explanation for the relative safety of benzodiazepines compared to chloral hydrate, barbiturates, or propofol. These other agents also have distinct receptors on the  $GABA_A$  complex, but actually open the chloride channel independently of GABA. High doses of these agents may be lethal, but death following overdose of benzodiazepines alone is virtually unheard of. This wide margin of safety (high therapeutic index) for benzodiazepines is illustrated using dose-response curves (Figures 1 and 2). Unlike barbiturates, illustrated in Figure 1, the effective-dose curve and the lethal-dose curve for the benzodiazepines are separated by a very large margin. Even the high doses required for our “hypo-re-



**Figure 2.** Dose-response curve for benzodiazepines.

sponder” patients are unlikely to cross over to the lethal dose curve.

The safety and sedative efficacy of the numerous benzodiazepine formulations are virtually identical. Individual differences in the onset and duration of clinical effects are due to each drug’s unique pharmacokinetic profile. An understanding of these differences will enable the practitioner to select the right drug at the right dose for the right patient and for the right procedure.<sup>27</sup>

### Diazepam (Valium)

Diazepam is often considered the prototypical benzodiazepine and the “grandfather” of the drug class; it has been available for over 42 years and continues to be widely used. It is a highly lipophilic molecule resulting in fast onset of action (usually within 20–40 minutes), and peak plasma levels 1–2 hours after oral administration. It has 100% oral bioavailability and doses range from 2–10 mg for adults. The long elimination half-life of diazepam (20–80 hours) is due to a number of active metabolites (desmethyldiazepam and oxazepam) which may contribute to the daytime drowsiness and “hang-over” some may experience.<sup>28</sup> Diazepam undergoes hepatic metabolism by oxidative reduction and both the parent molecule and active metabolites are particularly influenced by aging, hepatic dysfunction, and drug-drug interactions.<sup>29</sup> Given these shortcomings, the use of diazepam for oral sedation has been largely supplanted by better benzodiazepine alternatives.

### Lorazepam (Ativan)

Lorazepam is considered an intermediate-acting benzodiazepine given its elimination half-life of approximately 10–20 hours. However, this system of classifi-

cation is actually misleading. Despite a half-life shorter than diazepam, the actual sedative effect is generally longer because it has lower lipid solubility which slows its redistribution from the brain.<sup>30</sup> Lorazepam undergoes phase II hepatic metabolism via glucuronide conjugation to inactive metabolites that are rapidly excreted via the kidney, rather than phase I hepatic metabolism which is affected by competition by the cytochrome  $P_{450}$  enzyme system often resulting in active metabolites. Lorazepam is therefore less affected by variables such as advanced age, hepatic dysfunction, or drug-drug interactions. It has an oral bioavailability of 83 to 100% with peak plasma levels occurring 1–2 hours after administration. The onset of action following oral administration occurs within 60 minutes.<sup>31</sup> Usual adult doses for dental sedation patients can range from as low as 0.5 mg to 4 mg depending on patient and procedural criteria.<sup>32–34</sup>

### Triazolam (Halcion)

Triazolam is widely used for the short-term treatment of insomnia. Its rapid onset, short duration of action, and lack of active metabolites makes it a near ideal anti-anxiety medication for dental patients.<sup>35</sup> It is short-acting with an onset of activity usually within 30 minutes, and with peak blood levels occurring after approximately 75 minutes. The oral bioavailability for triazolam is only 44% but can be increased to 53% with sublingual administration.<sup>35–37</sup>

The usual adult dose for oral sedation can range from 0.125 mg to 0.5 mg.<sup>27,38</sup> Triazolam has no active major metabolites. It is metabolized by oxidative reduction via the hepatic cytochrome  $P_{450}$  3A4 system and like diazepam, can be influenced by aging, hepatic dysfunction, and drug-drug interactions.<sup>39,40</sup>

### Midazolam (Versed)

Midazolam is rapidly absorbed when administered orally either as a premixed syrup or by diluting the intravenous formulation in a pH-balanced, palatable, liquid vehicle (eg, apple juice). It has an oral bioavailability of 35 to 44% with an onset of action within 15–30 minutes, and peak plasma levels achieved within 20–50 minutes.<sup>41</sup> Midazolam has largely replaced chloral hydrate as the medication of choice for pediatric sedation patients.<sup>35,43,44</sup> Although, anecdotally, there have been reports of using the intravenous preparation of midazolam orally for short procedures on adults with doses at 0.25 mg/kg with a cumulative maximum of 20 mg being common, there have not been any published case series at this time to validate its effectiveness. Comparing pharmacodynamic effects, an oral dose of 0.25 mg of triazolam was found to be equivalent to oral midazolam

in doses of 5 mg to 8 mg.<sup>45</sup> Midazolam offers no advantage over triazolam for adult patients, unless they cannot swallow tablets. The actual niche for oral midazolam is for pediatric sedation and is not the focus of this article.

## THE NONBENZODIAZEPINE GABA AGONISTS

Although the benzodiazepines have been touted as ideal sedative agents, the GABA<sub>A</sub> receptor complex has many subunits that make up the macromolecular structure.<sup>35</sup> The GABA<sub>A</sub> receptor is composed of 5 subunits, with the  $\alpha$ 1,  $\alpha$ 2,  $\alpha$ 3, and  $\alpha$ 5 receptors thought to function as BZ receptor sites and mediate the clinical effects of benzodiazepines, including sedative, muscle relaxant, antiseizure, amnesic, and anxiolytic effects. However, the nonselective interaction between benzodiazepines and all of the GABA subunits may contribute to adverse drug effects, such as residual daytime sedation, cognitive impairment, rebound insomnia, and the risk of abuse. As research continues to clarify these receptor subunits, novel agonists will be developed that act more selectively.

The so-called “nonbenzodiazepine” hypnotics are the product of this goal, but marketing strategies are currently well ahead of actual scientific confirmation. These agents are chemically distinct from benzodiazepines. This allows them to be classified separately and be divorced from negative perceptions associated with benzodiazepines. However, they are BZ receptor agonists and their effects and clinical profiles are indistinguishable from benzodiazepines. Furthermore, their effects can be reversed using the benzodiazepine antagonist, flumazenil. They generally are claimed to have some selectivity for the  $\alpha$ 1 subunit (BZ<sub>1</sub> receptor) described above which putatively reduces their potential for cognitive impairment and abuse.<sup>46</sup> Whether these claims actually bear fruit remains to be seen.

### Zolpidem (Ambien)

Unlike the benzodiazepines, zolpidem produces muscle relaxation and anticonvulsant effects only at doses much higher than the hypnotic dose.<sup>47</sup> Zolpidem has a rapid onset of action, usually within 30 minutes, has a short elimination half-life and no active metabolites. This reduces the possibility of residual next-day effects from prolonged or excessive sedation. CNS depression with latent impairment of cognitive and motor function, commonly seen with barbiturates or long-acting benzodiazepines, is not common with zolpidem. Zolpidem is not contraindicated in pregnancy or in patients with narrow angle glaucoma; both are advantages over the benzo-

diazepines. The usual adult dose is 10 mg, although 5 mg tablets are also available and may be recommended for elderly patients or patients on other CNS depressants.<sup>48</sup> Flumazenil (Anexate, Romazicon) will antagonize the sedative actions of zolpidem.<sup>49</sup> Zolpidem received Food and Drug Administration (FDA) approval in 1993 and a supplemental new drug application was filed by Biovail Pharmaceuticals in January 2002 for approval of an oral disintegrating dosage form of zolpidem. Sustained-release zolpidem (Ambien CR) was approved by the FDA on September 2, 2005 and although it has a specific role in the treatment of insomnia (“controlled-release” to address sleep latency), this new formulation would have no role for in-office oral sedation.<sup>50</sup>

### Zopiclone (Imovane)

Zopiclone is another nonbenzodiazepine that produces its hypnotic effects via selective stimulation of the  $\alpha$ 1 subunit of the GABA<sub>A</sub> macromolecular complex.<sup>51</sup> While this medication is not available in the United States, the active S-enantiomer of this molecule, eszopiclone (Lunesta), has been marketed as a hypnotic agent in its own right. Zopiclone also has a rapid onset of action, usually within 30 minutes, and a short half-life (3.5–5 hours) and no active metabolites. This makes its pharmacokinetic profile very similar to zolpidem. The average adult dose is 7.5–15 mg, and it is available as 5 mg and 7.5 mg tablets. Flumazenil will also antagonize the sedative actions of zopiclone.<sup>52</sup>

### Eszopiclone (Lunesta)

Eszopiclone is one of the most recent additions to the nonbenzodiazepine class of sedative agents. As such there are very few data on its use in the dental realm. Its pharmacokinetic profile is similar to that of the parent compound, zopiclone, since eszopiclone is simply the S-enantiomer of the parent compound zopiclone. As such, flumazenil would also antagonize the sedative actions of eszopiclone.<sup>52</sup> Eszopiclone was approved by the FDA in December 2004.<sup>53,54</sup>

### Zaleplon (Sonata, Starnoc)

Zaleplon (Sonata, Starnoc) is a short-acting, nonbenzodiazepine sedative-hypnotic that also possesses anti-convulsant, anxiolytic, hypnotic, and myorelaxant properties. Zaleplon was FDA-approved in 1999 and has a faster onset of action and a shorter terminal elimination half-life than zolpidem. Zaleplon is available in 5 mg and 10 mg capsules and the usual dosing range is from 5 mg to 20 mg.<sup>55</sup> In Japanese adults (and possibly other

Asian populations), the maximum concentration in the blood ( $C_{max}$ ) as well as the total amount of drug absorbed from a single dose of zaleplon were increased 37 and 64%, respectively. This is likely due to differences in body weight or may represent differences in enzyme activities resulting from differences in diet, environment, or other factors. More conservative dosing of zaleplon in this patient population would be prudent. Flumazenil can also antagonize the sedative actions of zaleplon.<sup>56</sup>

Indiplon is from the same drug class as zaleplon and was being coproduced by Pfizer and Neurocrine Biosciences Inc to compete with Ambien and Lunesta.<sup>57</sup> By early 2006, however, they had failed to win federal regulatory approval in the United States, yet literature citing this drug's efficacy from other countries continues to populate the medical literature.<sup>58</sup>

### Ramelteon (Rozerem)

Ramelteon is the first drug in the melatonin receptor agonist class of hypnotic therapies which has recently been FDA-approved for insomnia management and which works by a completely different mechanism than all the medications discussed thus far.<sup>59</sup> The melatonin  $MT_1$  and  $MT_2$  receptors are thought to be involved in the maintenance of circadian rhythm, which regulates the sleep-wake cycle.<sup>60</sup> Ramelteon has high selectivity and affinity for melatonin  $MT_1$  and  $MT_2$  receptors which is believed to contribute to its sedation-promoting properties. Since its approval for the treatment of insomnia in 2005, ramelteon has been found to be very useful in treating patients having difficulty with sleep onset. The utility of this medication in the dental realm is slowly gaining interest, as this is the only sedative medication described thus far that is not a federally controlled substance. The unique and targeted mechanism of action of this drug also limits its side effect profile; it is not associated with an abuse potential or "hangover" effect often found with other sedatives. Ramelteon has no measurable affinity for the GABA receptor complex, dopamine, or opiate receptors. Ramelteon is available as 8 mg tablets and has an average onset of action of approximately 30 minutes and an elimination half-life of 2.6–5 hours.<sup>61</sup> Ramelteon does not offer the benefit of anterograde amnesia found with benzodiazepines or other nonbenzodiazepine agents discussed thus far. Its action cannot be reversed by flumazenil.

## THE ANTIHISTAMINES

While antihistamines are primarily used to manage allergic type reactions, they also cause sedation as a side effect. The strong calming and sleep-inducing effects of

Atarax, Benadryl, and Phenergan in particular, led to these medications being marketed as sedative-hypnotics in addition to some of their other effects in preventing nausea, vomiting, and the adverse sequelae of allergic reactions. The actual sedative efficacy of these agents is generally less than that with benzodiazepines.

Hydroxyzine (Atarax, Vistaril) is an antihistamine ( $H_1$ -antagonist) sedative which has an onset of action within 15 to 30 minutes. The maximum effect is achieved after approximately 2 hours, and drug effect wanes after 3–4 hours. The incidence of side effects with hydroxyzine is low. Other than drowsiness, hydroxyzine has minimal effect on cardiovascular or respiratory function. Usual adult doses range from 50 mg to 100 mg.<sup>62</sup>

Diphenhydramine (Benadryl) is an  $H_1$ -antagonist of the ethanolamine class. Other members of this group include carbinoxamine, clemastine, dimenhydrinate (a salt of diphenhydramine), doxylamine, phenyltoloxamine, and others. Ethanolamine  $H_1$ -antagonists have significant antimuscarinic activity and produce marked sedation in most patients. Diphenhydramine is a popular antihistamine due to its relative safety after oral or parenteral administration. In addition to the usual allergic symptoms, the drug also treats irritant cough, although the airway drying effect may be counterproductive. Because of its anticholinergic properties, diphenhydramine is effective in the relief of nausea, vomiting, and vertigo associated with motion sickness.<sup>63</sup>

Diphenhydramine was originally approved by the FDA in 1946 as a prescription-only drug but was later changed to nonprescription, over-the-counter (OTC) status. Due to its ability to induce drowsiness, it is also promoted as an OTC hypnotic (Sominex). The onset of action following oral administration of diphenhydramine occurs in 15 to 30 minutes, with peak concentrations occurring in about 2 to 4 hours. Typical adult doses for sedation are 25 mg to 50 mg.<sup>64</sup>

Promethazine (Phenergan) has been available since 1951 and although it has long been utilized as a sedative agent, it is a phenothiazine as well as an antihistamine. It has considerable anticholinergic, sedative, antiemetic, and some local anesthetic properties. In November 2004 the FDA directed manufacturers of promethazine to include a Black Box warning contraindicating its use in children <2 years of age given the increased risk for fatal respiratory depression in these very young children. Typical adult doses for sedation are 25–50 mg.<sup>65</sup>

## THERAPEUTIC CONSIDERATIONS

The most common use of oral sedation in adults is for the reduction of anxiety preceding and during the dental appointment. For some, the use of oral sedation the

night before their appointment can ensure a more restful sleep leading to a more pleasant and relaxed patient for the dental appointment.<sup>66</sup>

Due to the varying recovery profiles of many different sedative agents available, the patient should be advised not to drive, make important decisions, or consume alcohol for a period of 24 hours after the appointment. This requires the patient to have an escort who must be a responsible adult. It would be ill-advised to allow a patient to leave the office unaccompanied.

On the day of the appointment, it would be prudent to administer the medication in the dental office where it is a controlled and monitored environment. Advantages of this protocol include the following:

1. The escort can be confirmed. Although a common scenario would be to have the patient take the sedative 1 hour at home prior to the start of the appointment, it may be beneficial to administer the medication at the dental office. Administering the medication in the office while supervised allows for the confirmation of the amount taken and can prevent the patient from self-medicating prior to arriving at the office and forgetting that an escort is needed, thereby driving unescorted to the dental office.
2. Written consent, if needed or required, can be obtained prior to administration of the sedative. Depending on the state or province, a practitioner may be required to obtain written informed consent that allows dental treatment while the patient is in an altered state of consciousness. If the patient were to take the oral sedative prior to arriving at the office, the informed consent must be acquired on a previous appointment.
3. Any change or confirmation of dental work that is or is not to be completed during the appointment can be confirmed prior to the administration of the sedative.

### Selecting the Medication

It is important for the clinician to choose the sedative agent that will best suit the patient based on the patient's age, weight, and medical history rather than solely based on the length of time required for the dental treatment. The choice of the drug also depends on the familiarity of the drug to the practitioner. The absolute contraindication of any medication is the lack of knowledge of the pharmacology of that drug.

Since all patients will react differently to medications, it would be prudent to start with a shorter appointment and with treatment that is not too invasive in order to gauge the appropriateness of the chosen sedative agent. The amount administered should always be the lowest

effective dose. For the first appointment, the dentist should consider starting with the lowest dose that is known to be effective. Discussions with the patient the day after the initial sedation appointment will help to determine if the oral sedative used is appropriate in dose and type. What the physician deems as an adequate or inadequate dosage may actually differ from the patient's own experience of the appointment.<sup>67</sup> If the initial dose proves to be inadequate, the amount given can be increased during subsequent appointments. Although the weight of the patient can be useful in determining the initial dose, the level of fear and anxiety may be a more accurate determinant. At this time, however, there are few data that correlate the level of fear and the appropriate dose of an oral sedative.

The myriad of benzodiazepines and related agents have comparable efficacy and the one selected is most likely predicated on its pharmacokinetic properties. These will predict an onset and duration most appropriate for the treatment session. The following are a few examples.

For short dental procedures (<1 hour), the use of zaleplon has been shown to be effective. A study by Ganzberg et al has shown good efficacy with the use of zaleplon (Starnoc, Sonata) in patients for third molar extraction. This study demonstrated efficacy comparable to triazolam and a faster recovery from the sedation in the zaleplon arm of the study.<sup>68</sup> For very short dental appointments, zaleplon 10–20 mg given 1 hour prior to the procedure may provide adequate sedation.

For dental procedures of moderate length (1–2 hours), triazolam (Halcion), a short-acting benzodiazepine, in the dose of 0.125–0.5 mg, can be given 1 hour before the procedure. Triazolam is a popular choice among clinicians due to its anxiolytic, hypnotic, and amnesic effects, which are desirable in dental patients. It has a relatively short half-life with little residual hangover effects the next day.

For longer appointments (2–4 hours), a longer acting benzodiazepine such as lorazepam (Ativan) may be prescribed. Oral lorazepam in the dose of 1–4 mg may be given 1–2 hours prior to the dental procedure or 30–60 minutes prior for the sublingual preparation.

The antihistamines have also been used as sedatives for short to long dental procedures. Diphenhydramine (Benadryl) may be prescribed in the dose of 50 mg 1 hour prior to the dental procedure. Hydroxyzine (Atarax) with a longer half-life than diphenhydramine can be given in the dose of 50–100 mg 1 hour before the appointment. Yet another antihistamine with a similar half-life as hydroxyzine is promethazine (Phenergan), and it is typically given in a dose of 25–50 mg 1 hour prior to the procedure. Be aware that patients may experience anticholinergic side effects such as dry mouth; and

for patients with angle-closure glaucoma, these antihistamines should be avoided.<sup>69</sup>

### Geriatric Patients

The patient's age is important in the selection of an oral sedative drug and dosage. For geriatric patients, many physiological and psychological changes take place with age such as decreased cerebral blood flow, cardiac output, renal and hepatic blood flow, and pulmonary function. Furthermore, these individuals tend to suffer from at least one chronic condition such as heart disease, hypertension, arthritis, osteoporosis, and noninsulin-dependent (type 2) diabetes mellitus, all requiring long-term control with drug therapy and occasionally surgery. In addition, there are also pharmacodynamic and pharmacokinetic differences in elderly patients.

Pharmacokinetically, oral absorption, hepatic metabolism, and renal clearance all decrease with age. Pharmacodynamically, oral sedatives and other CNS depressants tend to have a greater effect in the elderly. This, together with polypharmacy in this patient population, contributes to the lower dosages and shorter acting medications that are typically required in order to avoid oversedation.<sup>70</sup>

A suggested short-acting benzodiazepine such as triazolam in a starting dosage of 0.125–0.25 mg given 1 hour before the dental appointment may be effective. For short appointments, another shorter acting (non-benzodiazepine) alternative is zaleplon in a starting dose of 10 mg, or zolpidem regular release in a dose of 5–10 mg 1 hour prior to the appointment may be used. Alternatively, for longer appointments, a longer acting benzodiazepine such as lorazepam may be prescribed. Oral lorazepam in the dose of 0.5–1 mg may be given 1–2 hours before or 30–60 minutes before the dental procedure for the sublingual preparation. Diazepam has a long half-life which is further extended in elderly patients; thus, its use in these individuals is not recommended.

The antihistamines are typically longer acting and have anticholinergic side effects that are less desirable in geriatric patients, those at risk for falls, and especially those with glaucoma or evidence of dementia.

### MEDICALLY COMPROMISED PATIENTS

Patients with underlying medical conditions will often benefit from oral sedation to minimize preoperative anxiety. Medical consultation is often recommended to understand the severity and stability as well as the treatment and control of any existing conditions prior to the administration of oral sedative drugs.

### Cardiovascular Disease

Anxiety and pain increase heart rate and blood pressure, leading to an increased oxygen demand of the myocardium. With coronary artery disease, this increased oxygen requirement may not be met and episodes of angina and dysrhythmias can result. The use of sedation as well as excellent pain control both during and after the appointment are of increasing importance. These patients often benefit from oral sedation due to the decreased stress of the appointment especially during long or traumatic appointments. Excessive sedation can cause significant respiratory depression leading to hypoxia and subsequent myocardial ischemia. The use of supplemental oxygen should be considered even with mild sedation. Adequate pain control through profound local anesthesia as well as postoperative pain control with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are important for patients with cardiovascular disease. All of these considerations are also applicable to patients with hypertension.

### Renal and Hepatic Disease

The benzodiazepines are generally safer than other anti-anxiety agents and short-term administration is effective. Because of the potential for drug or metabolite accumulation, chronic use of these agents is discouraged. For single doses used in oral sedation, no dose adjustment of the benzodiazepines is required. Chloral hydrate, however, is renally cleared and its use should be avoided in these patients.<sup>71</sup>

### Respiratory Disease

Minimal oral sedation in the usual doses is safe and beneficial for patients with asthma or chronic obstructive pulmonary disease (COPD). Stress can be a trigger for bronchospasm in patients with asthma as well as in patients with chronic bronchitis. The anticholinergic effects of the antihistamines may not only be desirable in these patients but may be of great benefit. The other oral sedatives such as the benzodiazepines can also be readily used.

### Epilepsy

Minimal oral sedation may also be of benefit to this group of patients. The benzodiazepines have anticonvulsant activity and are often the drugs of choice for these patients. With unintentional oversedation, supplemental oxygen should be given to avoid hypoxia that can trigger a seizure. Some antiepileptic drugs (eg, phenytoin, carbamazepine, phenobarbital, valproic acid) are

hepatic enzyme inducers that may increase the clearance of oral sedative drugs, thereby shortening their duration of action.

### Diabetes Mellitus

Oral sedation can be used in patients with type 1 or type 2 diabetes mellitus. It is important to remind patients to maintain their caloric intake and their regular meals both before and after the appointment. If they sleep through a meal or do not eat their regular full meal due to the sedation, then the doses of their insulin or their oral hypoglycemic medication may need to be adjusted. Appointments for patients with diabetes should be kept short to prevent long periods of fasting. Keep in mind that signs and symptoms of hypoglycemia such as altered mental state and fatigue can be easily confused with an exaggerated response to CNS depressants.

### Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) affects 2-4% of middle-aged adults.<sup>72</sup> It is defined as apnea events lasting 10 seconds or longer that occur 5 times or more per hour during sleep.<sup>73</sup> OSA can lead to hypoxemia, hypercarbia, polycythemia, systemic and pulmonary hypertension, and right ventricle failure. During rapid eye movement (REM) sleep, muscles that usually stent the airway open are relaxed. This results in significant narrowing of the airway. Patients with OSA are extremely sensitive to CNS depressants and are at risk for upper airway obstruction even with minimal doses of these drugs.<sup>74</sup> Treatment of patients with OSA using oral sedatives should be approached with caution as a loss of the airway can readily occur in this patient population. The use of supplemental oxygen is encouraged.

### CONCLUSION

This overview is intended as an introduction to minimal oral sedation (anxiolysis) in the dental office and is not meant to replace continuing education taught by those with advanced training in this area. Using oral sedation techniques will allow patients to visit the dentist in a stress-reduced state, where their fear and anxiety would otherwise impede their ability to seek and maintain proper oral health care. To date, this modality has been proven to be not only safe but very effective. Proper medication selection and patient management, however, are paramount to maintaining this safe practice.

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**CONTINUING EDUCATION QUESTIONS**

1. Lorazepam has a shorter half life than diazepam and produces a shorter duration of sedation.
  - A. First part true; second part false
  - B. First part false; second part true
  - C. Both parts true
  - D. Both parts false
  
2. Flumazenil can be used to reverse the action of all of the following sedatives EXCEPT:
  - A. Triazolam
  - B. Diazepam
  - C. Zolpidem
  - D. Hydroxyzine
  
3. Which of the following is the principal feature that distinguishes so-called nonbenzodiazepines such as zolpidem (Ambien) from benzodiazepines?
  - A. Molecular structure
  - B. Metabolism and half-life
  - C. Mechanism of action
  - D. Sedative efficacy
  
4. The only oral sedative agent in the following list that is NOT a controlled substance is:
  - A. Diazepam
  - B. Zaleplon
  - C. Ramelteon
  - D. Zopiclone