

Maximum cumulative doses of sedation medications for in-office use

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Note: This is the second article in a series on this important modality.¹ The AGD acknowledges that dentists may need an additional permit to perform the procedure described in this article. Many states require dental practitioners to have additional or advanced training in order to perform enteral sedation. In some states, practitioners must have an IV/conscious sedation permit before they are allowed to titrate (dose) oral medication. The ADA does not believe that oral medication can be titrated (dosed) without an IV sedation license. The AGD has adopted and published a white paper on sedation issues, which appeared in the September-October 2006 issue of General Dentistry. The AGD encourages continuing education in sedation modalities for general dentists.

Oral conscious sedation (OCS) is an increasingly common practice in dentistry and is at the forefront of evolving state regulations. At the center of the OCS controversy is the oral titration of medications. Most medications available for OCS are used in an “off-label” manner and have no determined maximum recommended dosage for that purpose. This article proposes cumulative maximum dosing guidelines for in-office OCS, with an emphasis on triazolam.

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Studies estimate that up to 30% of the United States population is anxious or fearful of dental treatment.² In the U.S., 80% of dentists are general dentists; less than 10% are either oral surgeons or dental anesthesiologists.³ These statistics indicate that there simply are not enough anesthesia-trained dentists to treat all of the patients who desire to receive dental treatment under sedation. General dentists must have an effective, safe method to help this underserved portion of the population.

Both critics and supporters of oral sedation agree about the need and demand for these services.⁴ Some dental patients require additional perioperative measures to tolerate and cope with stressful dental procedures; oral sedation is one of many effective tools (others include distraction techniques, calming dialogue, positive reinforcement, and so forth). It also is agreed that benzodiazepines, specifically triazolam and lorazepam, are well-suited as dental sedatives for in-office use.^{5,6} Developing guidelines for the safe practice of oral conscious sedation (OCS) will decrease the likelihood of adverse events and will add to the body of evidence in support of this important modality.

In most states, dentists without formal

anesthesia training can provide anxiolysis to patients without an additional permit. *Anxiolysis* involves a patient in a drug-induced state whose cognitive function and coordination may be affected but whose cardiovascular and respiratory functions are not. Typically, this level of sedation is achieved via a single dose of a sedative medication, usually a benzodiazepine. Conservative dosing guidelines based on patient-specific factors have been proposed.¹

The ADA defines conscious sedation as:

“A minimally depressed level of consciousness that retains the patient’s ability to independently and continuously maintain an airway and respond appropriately to physical stimulation or verbal command and that is produced by a pharmacological or non-pharmacological method or a combination thereof.”⁷

A typical OCS regimen may include a small dose of a benzodiazepine one hour before a dental appointment, which can be followed by subsequent doses to achieve and maintain an adequate level of sedation.^{8,9} This procedure has been termed *oral titration* and is the source of concern

for both the ADA and state dental boards. Oral titration also prompted several professional organizations, under the aegis of the United States Pharmacopeia Convention, to co-sponsor a workshop; a consensus statement was published in 2006.⁴

In 2003, the ADA changed the language in their anesthesia guidelines to include that: “...titration for the purposes of sedation is unpredictable...Except in unusual circumstances, the maximum recommended dose of oral medication should not be exceeded.”⁷

No cumulative maximum dose of triazolam has been established for the purpose of OCS. This article proposes guidelines for the cumulative maximum dose of triazolam to prevent oversedation and overdose, especially among patients who may be hypo-responders and may require more medication than usually is administered.

Rationale

In a previous article, the authors proposed guidelines for the dosing of triazolam and lorazepam, based on patient-specific factors such as age, weight, and medical complexity.¹ The proposed dosing strategy involved administering a single dose of the medication for anxiolysis. Other patients may require OCS and although the sedative medications may be identical, the doses and dosing regimen may differ.

Incremental administration for OCS may involve redosing a medication as the effects of the sedative wane over time, especially during a long appointment. Clinically, this is accomplished by administering an oral sedative to induce conscious sedation.^{8,9} Based on the pharmacokinetics of the specific medication, additional doses may be administered as the clinical signs of sedation decrease. For longer appointments, it may be necessary to give repeated doses over several hours to maintain sedation and continue the dental treatment. Cumulative maximum guidelines increase procedural safety by

providing a dose ceiling or *bailout point*, allowing dentists to determine when to stop administering medication, provided that the patient satisfies the definition of conscious sedation at all times.

Triazolam is best for incremental dosing among adult dental patients.⁵ Although other benzodiazodiazepines, including lorazepam (Ativan, Wyeth Pharmaceuticals, Madison, NJ; 800.882.3845), alprazolam (Xanax, Pfizer Inc., New York, NY; 800.223.0182), and diazepam (Valium, Roche Laboratories, Nutley, NJ; 800.526.6367) are effective for anxiolysis, these medications are not appropriate for incremental dosing because of their longer half-lives. Midazolam (Versed, Roche Laboratories) is a benzodiazepine with a short half-life that is used commonly in pediatric sedation. Its short half-life means it can be used as an adult incremental dosing protocol for OCS; however, because of its weight-based dosing, it is not indicated for adults over 40 kg (88 lb). Table 1 lists the pharmacokinetic characteristics of common benzodiazepine medications.

The FDA's maximum recommended doses for triazolam were created in reference to treating insomnia. Maximal dose guidelines have never been recommended for OCS of a dental patient. This can lead to confusion and frustration, as difficult dental cases may involve many hours of treatment and require additional doses to maintain patient comfort.

The AGD's white paper on enteral conscious sedation has proposed guidelines designed to help dentists in this regard.¹⁰ The proposed guidelines state that "any medication that is used in multiple dosing beyond the maximum recommended dose in aggregate should be capable of being reversed." Two other principles should be recognized when considering titration of oral medication. First, the interval between doses must allow the dentist to evaluate depressant effects of previously administered medication(s) on the central nervous system. Second, no additional sedative medication(s) should be administered after patient and dentist believe that the patient is acceptably sedated.

The pharmacologic theory of first-order kinetics describes how serum concentrations of a drug change proportionally with a change in dose. Figure 1 uses Greenblatt's earlier kinetic-dynamic mod-

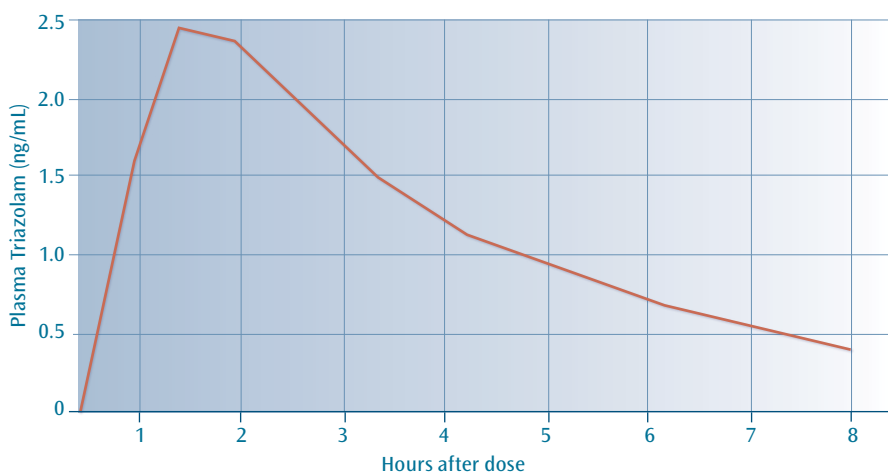


Fig. 1. Kinetic-dynamic modeling studies of what a single-dose 0.25 mg dose of triazolam given sublingually might look like graphically.⁸

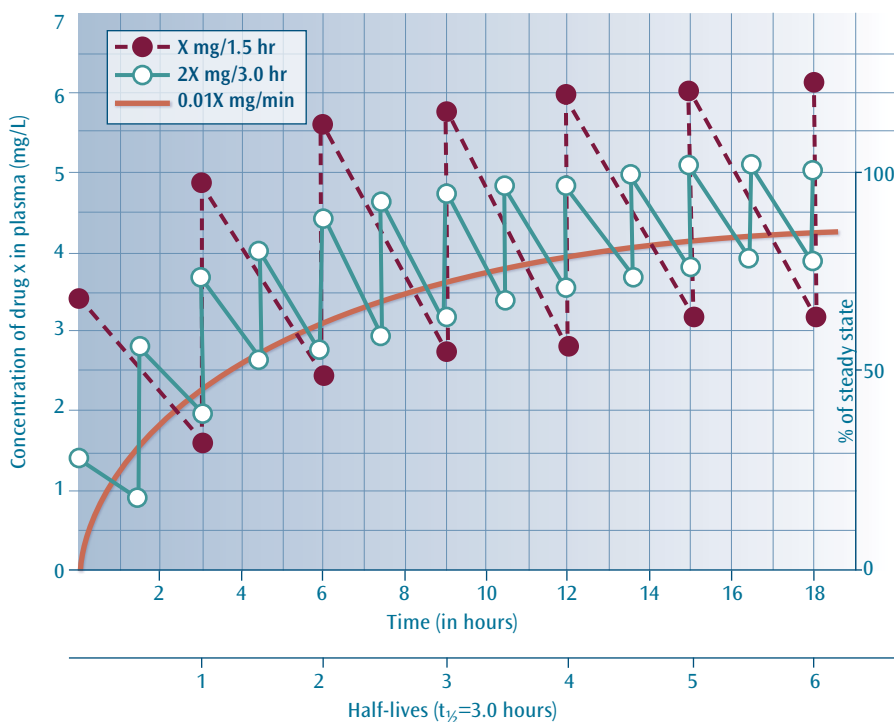


Fig. 2. The white dots represent how steady-state is reached when a medication with a half-life ($t_{1/2}$) of 3 hours is administered every 90 minutes. The same value would be reached by giving twice as much drug half as often (the black dots in the figure). The average of all of the peaks and troughs in the graph is depicted by the solid line, which represents a constant intravenous infusion of the drug. All three dosing modalities would reach the same steady-state.¹²

eling studies to illustrate a single 0.25 mg dose of triazolam given sublingually.¹¹

As the dentist increases the amount of drug administered—and the amount of drug in the body increases as a result—the amount eliminated increases as

well. Repeated oral administration of a medication (such as triazolam) will result in that medication reaching a constant blood-level after it is administered over the course of three to five half-lives. This principle is known as *steady-state*, in which

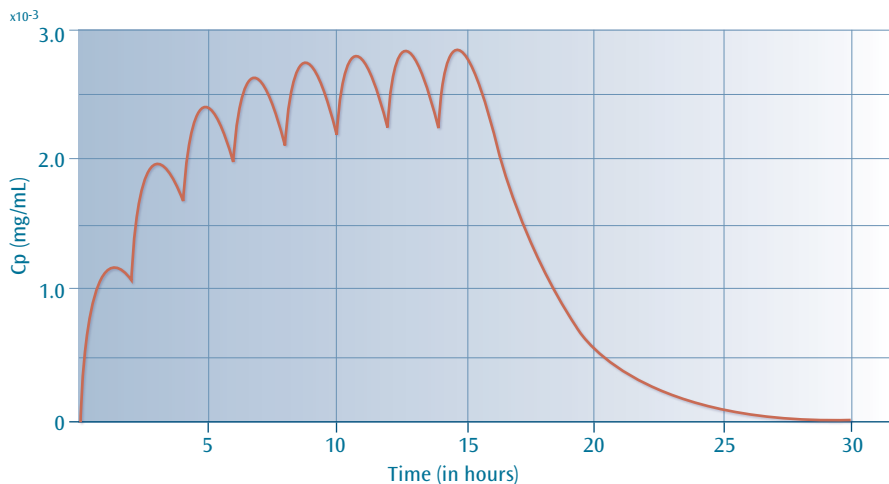


Fig. 3. Kinetic-dynamic modeling of repeated sublingual 0.25 mg doses of triazolam, administered every two hours. Adapted for sublingual triazolam using the Cp versus time (oral) applet.³⁰

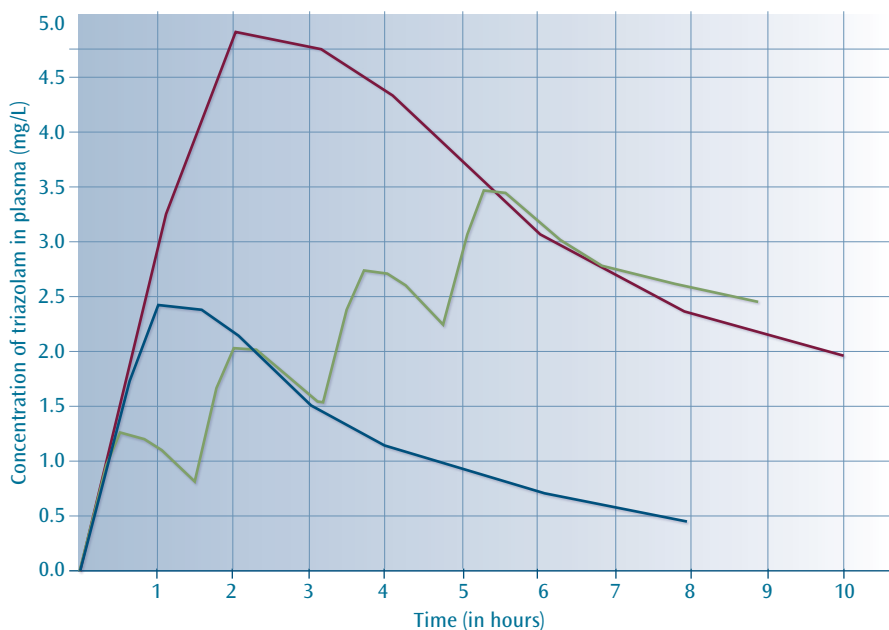


Fig. 4. Kinetic-dynamic modeling studies compare a single 0.5 mg dose (the maximum required dose for insomnia) of triazolam (red line) with a single 0.25 mg dose (blue line) and multiple 0.125 mg doses (green line), all given sublingually.¹¹

the amount of drug that is accumulated equals the amount that is eliminated.

If the unique pharmacokinetic constants of a drug are known, the concentration of the medication at steady-state can be calculated before giving even a single dose to a patient. The steady-state concentration of a medication in the blood ($C_{p_{ss}}$) can be calculated from a pharmacokinetic formula made up of constants that are particular to each drug: $C_{p_{ss}}$

$= F \times D / K \times V_d \times \tau$ (Fig. 2).¹² Since this approach is impractical in everyday practice, the authors suggest relying on “usual recommended doses” and trying not to exceed the maximum recommended dose as described above.

Benzodiazepines such as triazolam have predictable dose-response curves given calculable constants derived from these first-order pharmacokinetics.¹³⁻¹⁶ In the case of triazolam, which has a

sublingual bioavailability (F) of 53%, the steady-state of a 0.25 mg dose (D) that is administered at two-hour dosing intervals (τ) can be determined by calculating the pharmacokinetic constant (k). This constant is equivalent to the natural logarithm of 2 (that is, 0.693) divided by the half-life ($t_{1/2}$) of the drug (2.0 hours), or 0.35 hours⁻¹. In this example, where the patient’s weight is 70 kg, the volume of distribution (V_d) for triazolam is 1.1 L/kg; as a result, the steady state concentration of triazolam in the blood of a patient weighing 70 kg would equal $F \times D = 0.53 \times 0.25 / C_{p_{ss}} = F \times D / K \times V_d \times \tau = 0.35 \times (1.1 \times 70) \times 2 = 2.5 \mu\text{g/L}$. This equation is represented graphically in Figure 3.

After repeated sublingual administration, the plasma concentration of triazolam levels as steady-state is approached; at that point, the rate of drug accumulation is equal to the rate of elimination. The plasma concentration does not continue to increase in a linear fashion, which would increase blood levels and eventually lead to an overdose; this principle accounts for the intrinsic safety mechanism of benzodiazepines like triazolam. Clinically, it is much safer to give two smaller doses of triazolam (based on patient response) rather than one large dose at the outset. After two smaller doses are administered, the resulting blood levels actually are lower than the blood level following the larger single dose (Fig. 4).

A recent study by Jackson *et al* studied the pharmacokinetics and pharmacodynamics of multidose triazolam.¹⁶ The subjects received a total of 1.0 mg triazolam in three divided doses at fixed time points (0.25 mg at the outset, 0.5 mg at 60 minutes, and 0.25 mg at 90 minutes). These doses were not determined by patient-related factors (such as age or weight) and did not follow an assessment of persistent dental anxiety. Bispectral index monitoring and direct observer assessment revealed that four subjects had levels of sedation deeper than conscious sedation; however, it did not impair the patients’ ability to maintain airway patency independently.¹⁶ The study protocol followed by Jackson *et al* differs from the dosing strategy proposed in this article for two reasons: first, additional dosing of oral sedatives should only follow a time period sufficient enough to assess the drug effects; second, the determination

Table 1. Pharmacokinetics of some common benzodiazepines.^{1,11,17,18,24,34,35}

	T _{max} (hr)	T _{1/2 elim} (hr)	Pharmacologic antagonist	Minimum time between a additional doses (hr)
Midazolam	0.5	2.5 (1.8–6.4)	Flumazenil	0.5*
Triazolam	1.25	2.5 (1.7–4)	Flumazenil	1.5
Lorazepam	1.2	15.7 (14–16)	Flumazenil	N/A**
Alprazolam	1.5	11.2 (6.3–26.9)	Flumazenil	N/A**
Diazepam	1.5	24 (15–98)	Flumazenil	N/A**

* Although it is appropriate for OCS redosing protocols, midazolam's utility is reserved for pediatrics. Because of its weight-based dosing, it is not indicated for adults over 40 kg (88 lb).

**Given their long half-lives and the potential for accumulation and possible oversedation, lorazepam, alprazolam, and diazepam should not be re-dosed, despite their relatively short time of onset (less than 1.0 hour).

Table 2. Assumptions and parameters used to calculate cumulative maximum dose (CMD) of sedation medications for in-office OCS.

Only adults 18 years or older are eligible

OCS dosing is based on patient age and weight: Older patients will need a smaller amount of medication than younger patients; smaller patients will require less medication than heavier patients

The lowest proposed dose of triazolam is 0.125 mg

The largest proposed cumulative maximum dose of triazolam is 2.0 mg

Calculated dose will always be rounded down to accommodate the closest available tablet size

In addition to changes based on age, doses must be reduced 50% for patients with ASA Physical Status Classification 3

Patients who are ASA Physical Status Classification 4 or greater should not receive OCS

to administer additional dosing of oral sedatives is based on direct patient assessment.

The cumulative maximum dose

The 24-hour cumulative maximum dose proposed in this article is not a goal and under no circumstances should it be administered as a single dose. The cumulative maximum dose could be reached only when the patient is a hypo-responder to the sedative medication or when a long appointment requires repeated doses of medication to maintain patient comfort. The authors emphasize that OCS should be accomplished with the smallest effective dose of medication at all times. No additional medication should be administered as long as the patient displays signs of conscious sedation and is tolerant of dental treatment. Patient factors that could require increasing

sedative medication include high anxiety or fear, liver enzyme induction, increased body mass or fat, use of stimulants (such as caffeine or tobacco), drug tolerance because of past use, and noncompliance with preoperative instructions.¹

The cumulative maximum dose is both a do-not-exceed dose and the cumulative absolute maximum dose (if it is reached). When the cumulative maximum dose has been administered, the dentist can choose either to terminate the dental appointment or to continue it, provided the patient is comfortable and has normal vital signs and the depth of sedation is consistent with either anxiolysis or conscious sedation. In either case, no further sedative should be administered. If a dental visit is terminated because the cumulative maximum dose has been reached, all routine dismissal procedures (including releasing the patient to a

responsible adult companion for travel) must be followed. If OCS is unsuccessful for a particular patient, he or she should be informed of the situation and referred for a different or deeper level of sedation.

It is important to remember that standard or typical doses of an oral medication will be effective for approximately two-thirds of patients (based on a typical Gaussian population distribution curve). For the other one-third of patients, doses that are smaller or larger than the standard may be needed to increase tolerance of dental treatment. Patients who are extreme hypo-responders (and thus candidates for a deeper level of sedation) should be recognized early on in an oral sedation procedure and referred appropriately.

Calculating the cumulative maximum dose

The 24-hour cumulative maximum dose is determined by using a formula based on the pharmacokinetic characteristics of the drug used and the patient's weight (see Tables 1 and 2).^{1,17-20}

Triazolam's metabolism and elimination follow first-order pharmacokinetics; as a result, dosage increases result in proportional increases in plasma drug levels. As described previously, a 2.0 mg dose of triazolam is considered to be an absolute maximum and is the highest possible cumulative maximum dose in these proposed guidelines.^{8,9,21-23}

As with the total anxiolytic dose described previously, it is necessary to lower the proposed maximum cumulative doses based on patient weight. The maximum weight for the calculation of

Table 3. Drug interactions with triazolam.³⁰

Contraindicated	Major	Moderate
Amprenavir	Alfentanil	Aprépitant
Atazanavir	Amobarbital	Clarithromycin
Bifonazole	Butabarbital	Dehydroepiandrosterone
Butoconazole	Butalbital	Delavirdine
Clotrimazole	Carisoprodol	Diltiazem
Croconazole	Chloral hydrate	Erythromycin
Econazole	Chlorzoxazone	Fluvoxamine
Efavirenz	Codeine	Modafinil
Fenticonazole	Dantrolene	Nefazodone
Fluconazole	Fentanyl	Omeprazole
Fosamprenavir	Hydrocodone	Ranitidine
Indinavir	Hydromorphone	Rifampin
Itraconazole	Levorphanol	Rifapentine
Ketoconazole	Meperidine	Roxithromycin
Lopinavir	Methohexital	St. John's Wort
Miconazole	Mibefradil	Theophylline
Nelfinavir	Morphine	Troleandomycin
Omoconazole	Oxycodone	
Oxiconazole	Oxymorphone	
Ritonavir	Pentobarbital	
Saquinavir	Phenobarbital	
Sulconazole	Primidone	
Terconazole	Propoxyphene	
Tioconazole	Remifentanil	
Tipranavir	Secobarbital	
Voriconazole	Sufentanil	
	Thiopental	

the cumulative maximum dose is 200 lb, even if the patient's actual weight exceeds 200 lb. The patient's weight is divided by a factor individualized for each drug (the divisor for triazolam is 100); this computation yields the cumulative maximum dose based on weight for a given patient. Extremes of age and the patient's overall medical complexity (that is, the American Society of Anesthesiologists' physical status score) are other factors involved in calculating the cumulative maximum dose.²⁴ For patients older than 65 and individuals judged to be ASA 3, the maximum cumulative dose should be reduced by an additional 50%. OCS should not be provided to patients with an ASA score of 4 or higher. Although other patient-specific parameters have been investigated, gender differences

in kinetics are not apparent; however, age-dependent differences are significant and influence the pharmacodynamics of benzodiazepines.²⁵

It has been demonstrated that 30% of patients receiving dental treatment will have a history of at least one medical condition.^{26,27} Administering sedative medications to a patient with serious or multiple medical conditions can increase operative risk. Accordingly, patients with a complex medical history also may be taking multiple medications.²⁸ Kaufman *et al* studied nearly 2,600 subjects and found that approximately 20% of individuals 65 and older were taking five or more prescription medications.²⁸ Another study determined a 50% chance of a significant drug interaction for a patient taking five medications, while the likelihood for a patient taking

eight prescription drugs is 100%.²⁹ Table 3 lists some of the more common drug interactions with triazolam.³⁰

Using the cumulative maximum dose

The cumulative maximum dose provides dosing guidance for dentists who need additional time to complete dental treatment or when the sedation level has waned to the point that the provision of treatment is no longer tolerable to the patient. The cumulative maximum dose outlines the dosing interval; specifically, the amount of time between triazolam doses that is necessary for the dentist to assess clinical effects.

The cumulative maximum dose also outlines the amount of any subsequent doses. If additional doses of triazolam are needed (regardless of the size of the initial dose), 0.25 mg and 0.125 mg are the only possible increments. Based on age and weight, a 200 lb, 30-year-old man with an ASA score of 1 should receive an initial triazolam dose of 0.5 mg. If additional triazolam is needed (after an assessment period of not less than 90 minutes), the dose should not exceed 0.25 mg; if the sedation level is judged appropriate, no additional medication should be administered. The choice between possible doses is based on direct patient assessment, whereas the larger dose is intended to increase sedation.

The cumulative maximum dose may be reached only during unusually long dental appointments. To reach the cumulative maximum dose for the healthy 200 lb individual cited above, a nine-hour dental appointment would be necessary (0.5 mg triazolam at the outset, then 0.25 mg given every 90 minutes). Since the vast majority of dental appointments are short, the cumulative maximum dose provides ample scope for dentists while also describing safe absolute maximum dosing guidelines.

Summary

Guidelines exist to aid dentists with clinical decision-making. In the case of triazolam, empirical dosing has been the norm for OCS. With the increased popularity of OCS techniques, conservative guidelines have been proposed to establish "guardrails" to ensure patient safety. In a 1998 study by Skatrud and Busch, 2.0–4.0 mg of triazolam did not induce respiratory depression in awake human subjects.³¹ In studies dating back to 1977, triazolam

(in doses up to 3.0 mg) was found to be safe and effective with no adverse effects despite the increased doses.³² By creating an absolute 24-hour cumulative maximum dose for triazolam, dentists will have sufficient latitude for dosing to account for inter-patient variability while also maintaining safety. Clinical research is needed to test the safety of OCS and to validate the proposed guidelines. Before triazolam is prescribed or any oral conscious technique is utilized, dentists must satisfy all state laws and regulations for the provision of this service.

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DART Exercise No. 188

Subject Code: 132 Anesthesia and Pain Control

The 15 questions for this exercise are based on the article, "Maximum cumulative doses of sedation medications for in-office use," on pages 143–148. This exercise was developed by Thomas V. Dembski, DDS, FAGD, in association with the *General Dentistry* DART committee.

Reading the article and successfully completing the exercise will enable you to:

- understand the need for in-office oral conscious sedation guidelines;
- appreciate the conservative use of oral medication for reducing patient anxiety in the dental office; and
- recognize the patient factors that influence the effectiveness of oral sedatives.

Answer form and instructions are on pages 167–168. Answers for this exercise must be received by February 15, 2008.

- Concern for which of the following procedures prompted a co-sponsored workshop in 2006?
 - Parenteral sedation
 - Conscious sedation
 - Oral titration
 - Oral premedication
- For approximately what percentage of patients is a single dose of oral sedation likely to be effective?
 - 10%
 - 22%
 - 33%
 - 66%
- What rationale justifies the need for multiple sedation doses in the dental office?
 - Anxious patients may require many hours of treatment
 - A 24-hour cumulative dose is the ideal goal
 - A patient may be a hyper-responder
 - Oral sedation maintains an impeccable record
- Which dose should be used to achieve successful oral conscious sedation?
 - A 24-hour cumulative maximum dose (CMD)
 - The minimum effective dose
 - A single standardized dose below the CMD reduced for the length of the appointment
 - The maximum recommended dose for short-acting benzodiazepines
- Which action is most appropriate once the 24-hour cumulative maximum dose (CMD) has been reached for a single oral medication?
 - Continue treatment if the patient is comfortable
 - Switch to a different medication
 - Increase the nitrous-oxide-to-oxygen ratio
 - Dismiss the patient who reports not feeling sedated
- No cumulative maximum dose for triazolam has been established for oral conscious sedation. The literature commonly cites an upper limit of 8.0 mg for triazolam.
 - Both statements are true.
 - The first is true; the second is false.
 - The first is false; the second is true.
 - Both statements are false.
- According to the proposed guidelines, what is the maximum weight for calculating the cumulative maximum dose?
 - 200 lb, regardless of the patient's actual weight
 - 200 lb, to be divided by 25 for triazolam
 - 200 lb, to be divided by 2 for triazolam
 - The patient's actual weight
- Which factor is not considered when calculating a patient's CMD?
 - Weight
 - Age
 - ASA category
 - Gender
- What is the likelihood of a significant drug reaction for a patient taking eight prescription medications?
 - 20%
 - 30%
 - 50%
 - 100%
- Approximately what percentage of all patients over 65 take five or more prescription medications?
 - 10
 - 20
 - 30
 - 50
- By how much should the CMD be reduced for patients over the age of 65?
 - 20%
 - 30%
 - 50%
 - 100%
- What is the absolute 24-hour CMD proposed for triazolam?
 - 0.25 mg
 - 0.5 mg
 - 2.0 mg
 - 2.5 mg
- What is the half-life of triazolam?
 - 1.25 hours
 - 1.7–4.0 hours
 - 14–16 hours
 - 24 hours
- Which reversal agent is effective for both triazolam and lorazepam?
 - Naloxone
 - Ativan
 - Flumazenil
 - Interferon
- Which parameter may be identical in both anxiolysis and oral conscious sedation?
 - Dose
 - Medications
 - Dosing regimen
 - Titration