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Calculating and justifying total anxiolytic doses of medications for in-office use

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[Editor's note: 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, through an expert panel of educators, has drafted a White Paper on sedation issues, including patient safety and dosing. The AGD Board of Trustees and the AGD House of Delegates will be asked to ratify this position in the coming months. The AGD encourages continuing education in sedation modalities for general dentists.]

Providing anxiolysis (diminution of anxiety and/or fear) for patients is a popular technique for improving a patient's tolerance of invasive dental procedures. Currently there are no guidelines for helping dentists select the appropriate amount of oral medication for a patient who requires anxiolysis. Besides the availability of inherently safe drugs, pulse oximetry, and emergency equipment, conservative dosing guidelines should be established for the oral medications used most commonly. This article proposes guidelines for calculating and justifying the total anxiolytic doses of medications used in-office, with an emphasis on triazolam and lorazepam.

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In recent years, the use of oral triazolam and lorazepam for the diminution of perioperative anxiety and fear in dental patients has increased.¹ State dental boards generally agree that anxiolysis by pharmacological means does not require an advanced level of training or certification. Despite the consonance of these state regulations for the provision of in-office anxiolysis, guidelines to help calculate and justify selected doses of a sedative medication for individual patients have not been defined clearly in the literature.

As medications designed to alleviate patient anxiety are used more frequently, it is essential to protect patients by establishing conservative dosing guidelines. A typical pharmacological strategy for producing anxiolysis may include a small dose of an oral benzodiazepine administered one hour before a dental appointment.² The goal is to abate patient anxiety, increasing tolerance of invasive or prolonged dental procedures without outward signs of sedation.

Determining the correct anxiolytic dose of sedative medication is challenging. Currently, dentists must empirically figure

the one oral dose of the one oral medication that should be successful without having to reappoint or refer the patient. If either the practitioner or the patient deems the judged anxiolytic dose ineffective, the dental appointment may not be as successful and the patient's original fear/anxiety may be further compounded. This cycle of fear has been well-documented in the literature.³ Failure to alleviate anxiety or fear with anxiolysis can result when the right patient is not matched with the right drug at the right dose.

The evolution of guidelines for the safe practice of anxiolysis by pharmacological means will decrease the likelihood of adverse events and failed appointments. Based on a typical Gaussian population distribution curve, a standard or usual dose of an oral medication will be effective for approximately two-thirds of patients. The other patients may require doses that are either smaller or larger than usual to increase tolerance of dental treatment. It is difficult for the dentist to determine which patients need an increased dose and which will accept a lower dose before the first anxiolysis appointment has taken place.

In the case of triazolam and lorazepam, no maximum dose has been established for in-office anxiolysis during a dental appointment. This article is designed to propose guidelines for calculating and justifying total anxiolytic doses of medications for in-office use. Selecting the correct anxiolytic dose will prevent patients from underdosing or overdosing.

Anxiolysis by pharmacological means maintains an impeccable safety record, as evidenced by a lack of reported morbidity and the absence of specialty permit requirements.⁴

According to the ADA, "the use of anxiolytic sedative and anesthetic techniques by appropriately trained dentists in the dental office and other settings continues to have a remarkable record of safety."⁵

With the addition of clinical guidelines or "guardrails" to help dentists select the proper doses of anxiolytic medications, dental appointments can be more successful and patient safety may increase.

Rationale

It is understood that sedative medications can cause a varied response based on the dose provided. Anxiolysis by pharmacological means is based on clinical response.

The American Society of Anesthesiologists (ASA) defines anxiolysis as: "A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected."⁶

The anxiolytic doses proposed in this study should be considered the ultimate clinical guideline or "guardrail" for selecting the correct amount of medication. A 2004 article by Quarnstrom and Donaldson reported on 270 cases of anxiolysis over 15 years. The total doses reported were consistent with the

Table 1. Pharmacokinetics of triazolam and lorazepam.^{15,24-26}

	Average time to maximum concentration (T_{max} (hr))	Elimination half-life* ($T_{1/2\text{ elim}}$ (hr))	Site of metabolism	Pharmacologic antagonist
Triazolam	1.25	2.5 (1.7–4)	CYP 3A4, 5–7	Flumazenil
Lorazepam	1.2	15.7 (14–16)	Hepatic glucuronidation	Flumazenil

*The time required for a 50% reduction in plasma concentration

Table 2. Total triazolam anxiolytic dosing guidelines (in mg).

Weight (lb./kg)	Age (years)		
	18–40	41–64	65 and older
≤100/≤45	0.3125*	0.250*	0.1250*
110/50	0.3438	0.275	0.1375
120/55	0.3750	0.300	0.1500
130/60	0.4063	0.325	0.1625
140/65	0.4375*	0.350	0.1750
150/70	0.4688	0.375*	0.1875*
160/75	0.5000*	0.400	0.2000
170/80	0.5313	0.425	0.2125
180/85	0.5625*	0.450	0.2250
190/90	0.5938	0.475	0.2375
200+/95+	0.6250*	0.500*	0.2500*

*Indicates possible triazolam dosing increments, based on available tablet strength. Note: Always round down to the nearest tablet strength.

Table 3. Total lorazepam anxiolytic dosing guidelines (in mg).

Weight (lb./kg)	Age (years)		
	18–40	41–64	65 and older
≤100/≤45	1.250*	1.0*	0.50*
110/50	1.375	1.1	0.55
120/55	1.500*	1.2	0.60
130/60	1.625	1.3	0.65
140/65	1.750*	1.4	0.70
150/70	1.875	1.5*	0.75*
160/75	2.000*	1.6	0.80
170/80	2.125	1.7	0.85
180/85	2.250*	1.8	0.90
190/90	2.375	1.9	0.95
200+/95+	2.500*	2.0*	1.00*

*Indicates possible lorazepam dosing increments, based on available tablet strength. Note: Always round down to the nearest tablet strength.

guidelines proposed herein.⁷

The literature has suggested several strategies and protocols describing the appropriate dosing of medications for anxiolysis.^{2,7,8} When both patient and procedural factors are considered, the practitioner is faced with the prescribing dilemma of which medication should be used for treating the patient and at what dose. Several authors have cited benzodiazepines as the ideal agents in this procedural realm, with triazolam and lorazepam receiving the most publicity.^{1,4,9} Perhaps the most important clinical distinction between triazolam and lorazepam is their duration of action; triazolam lasts two to four hours, compared to four to six hours for lorazepam.

Other than the FDA's suggestion of a maximum recommended dose when treating insomnia, dosing guidelines have never been recommended for these agents in the dental realm. This is unfortunate, as difficult dental cases can require more invasive treatments or longer

appointments and may induce a heightened level of anxiety or fear in patients.

It must be emphasized that the total anxiolytic doses proposed in this article are guidelines and should not substitute for good clinical judgment or direct patient assessment. The authors recognize that some patient factors could necessitate deviating from the proposed anxiolytic dosing guidelines, including high anxiety/fear, liver enzyme induction, increased body mass or fat, extremes of age, use of stimulants (such as caffeine or tobacco), drug tolerance because of past use, and noncompliance with preoperative instructions. If the patient displays signs of anxiolysis and will accept the proposed dental treatment, the anxiolysis should be judged successful.

If the calculated amount of medication is ineffective, the dentist can choose to terminate the dental appointment or continue, provided the patient is willing. If a dental visit is terminated after the total anxiolytic dose is administered be-

cause the patient's anxiety/fear is not sufficiently diminished or eliminated, the dentist must follow all normal dismissal procedures, including releasing the patient to a responsible adult travel companion. A referral for a different or deeper level of sedation should be considered.

The total anxiolytic doses proposed should be considered as both the "do not exceed" doses and the maximum possible doses. They may be achieved with divided doses or a single bolus dose, depending on the applicable state board regulations. It should be emphasized that the goal of anxiolysis is administering the lowest possible effective dose for each patient.

Calculating the total anxiolytic dose

The total anxiolytic dose is determined by a formula based on the pharmacokinetic characteristics of the drug used and the patient's weight. The relevant pharmacokinetic characteristics of both triazolam and lorazepam are outlined in Table 1.

Table 4. ASA physical status classification.¹⁸

Class	Physical status
1	A normal healthy patient
2	A patient with a mild systemic disease
3	A patient with a severe systemic disease that limits activity but is not incapacitating
4	A patient with an incapacitating systemic disease that is a constant threat to life
5	A moribund patient not expected to survive 24 hours with or without an operation

Table 5. Sample calculations of the total anxiolytic dose.

Age	Gender	Weight (lb.)	ASA classification	Planned anxiolytic medication	Total anxiolytic dose (mg)
41	F	104 (Round down to 100 for classification)	1	Triazolam	0.25
22	M	150	2	Triazolam	0.4375*
66	M	215 (entered as 200 into the calculation)	3	Triazolam	0.125 (reduced by 50% because of patient's ASA classification)
50	F	128	1	Lorazepam	1.25
35	M	160	3	Lorazepam	1.0 (reduced by 50% because of patient's ASA classification)
70	F	125	2	Lorazepam	0.5 (reduced by 50% because of the patient's age)

* Always round down to the nearest possible tablet strength.

Both lorazepam's and triazolam's metabolism and elimination follow first-order pharmacokinetics; as a result, increasing the dosage increases the plasma drug level proportionally. The rate of elimination is proportional to the amount of drug that is present, which implies that the elimination half-lives are reasonably constant, and differences in mean values for both half-life and the clearance of either drug have been demonstrated only at extremes of age.¹⁰⁻¹⁵

As stated previously, no maximum dose for lorazepam or triazolam has been established for anxiolysis in the dental setting; however, the literature cites a daily cumulative maximum for lorazepam of 8.0 mg for other deeper levels of sedation.^{9,16} This level is considered to be

equal to 2.0 mg of triazolam in terms of efficacy.¹⁷ Therefore, a ratio of 4:1 describes the relative potency of these medications and underscores the scientific basis for equal efficacy when considering lorazepam and triazolam. In Quarnstrom and Donaldson's study, 0.625 mg of triazolam seldom was exceeded in the clinical setting over a 15-year period.⁷ This dose was determined to be the maximum anxiolytic dose for triazolam. By extension, the maximum anxiolytic dose for lorazepam would be 2.5 mg.

Maximum doses are not appropriate for all patients, so it is necessary to adjust such doses downward based on weight. The maximum weight for the calculation of the total anxiolytic dose is 200 lb. (95 kg). Regardless of the patient's actual

weight, 200 lb. will be the maximum weight entered into the formula. The weight is divided by a factor individualized for each drug using the 4:1 ratio described above; the divisor is 400 for triazolam, and 100 for lorazepam. This computation yields the total anxiolytic dose based on weight for patients aged 41–64 (see Tables 2 and 3).

Two other components contribute to the calculation of the total anxiolytic dose: patient age and ASA physical status classification (see Table 4).¹⁸ The literature offers evidence that age-related changes to cytochrome enzymatic activity can impair or enhance benzodiazepine metabolism.^{12,13} Decreased clearance of benzodiazepines among elderly patients is due to changes in hepatic metabolic processes (for example, cytochrome enzyme expression) and hepatic blood flow.^{12,13} The clinical result is higher plasma concentrations and more pronounced psychomotor effects.^{14,15,19} By contrast, younger adult patients may have accelerated metabolic processes, resulting in lower plasma concentrations and decreased clinical effects of sedative medications. Although other patient-specific parameters have been investigated, studies have concluded that gender differences in kinetics are not apparent, while age-dependent differences are significant and influence the pharmacodynamics of benzodiazepines.¹³ The total anxiolytic dose for elderly patients should be reduced by 50%.¹⁴

Younger adult patients (aged 18–40) will need a small increase in medication to account for age-related enzymatic induction. The total anxiolytic dose for patients aged 18–40 is increased by 25% over the 41–64 age group (see Tables 2 and 3).

The second component influencing the total anxiolytic dose is the medical complexity of the dental patient. It has been demonstrated that 20–30% of patients seeking dental treatment have a significant medical history that may influence the provision of dental care.^{20,21} The administration of anxiolytic medications to a patient with serious or possibly multiple medical conditions can increase operative risk. Accordingly, patients with a complex medical history also may be taking multiple medications. In a population-based survey of 2,590 subjects, Kaufman et al found that approximately 20% of individuals aged 65 and older were taking five or more prescription medications during the

one-week period preceding the interview.²² A study by Johnson et al determined that patients taking five medications have a 50% chance of a significant drug interaction; for a patient taking eight drugs, that likelihood increases to 100%.²³

For patients with an ASA Physical Status score of 3 (that is, a severe systemic disease that is not incapacitating), medical consultation should be sought before anxiolysis by pharmacological means begins. The total anxiolytic dose for ASA Physical Status 3 should be reduced by an additional 50%, regardless of age-specific dosing. Patients with an ASA Physical Status of 4 should not receive anxiolysis by pharmacological means.

There are times when the total anxiolytic dose as calculated will fall between available tablet strengths. In such instances, the dentist always should round the total anxiolytic dose downward to the nearest available tablet strength. Table 5 contains sample calculations of the total anxiolytic dose.

Summary

Guidelines exist to aid dentists with clinical decision-making. In the case of triazolam and lorazepam, empirical dosing has been the norm for anxiolysis. As the popularity of pharmacological techniques for anxiolysis increases, conservative guidelines should be established to ensure patient safety and improve clinical success. These proposed total anxiolytic dosing guidelines would provide dentists with sufficient latitude to account for interpatient variability while also maintaining safety. Before either drug is prescribed for any anxiolytic technique, dentists must satisfy all state laws and regulations regarding the provision of this service. Additional clinical research is needed to fortify and validate these guidelines.

Disclaimer

Drs. Goodchild and Donaldson are lecturers for the Dental Organization for Conscious Sedation.

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