Advances in Anxiety Management:
We Can Do Better Than The White-Knuckle Technique!

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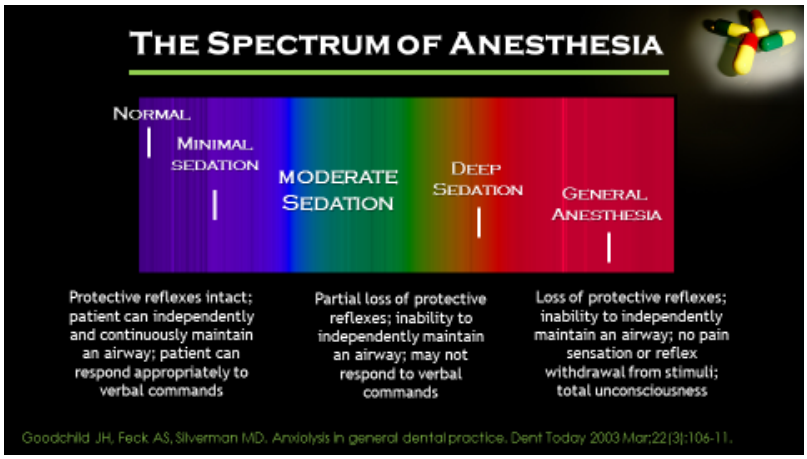
Our Clinician:

Dr. Mark Donaldson BSP, RPH, PHARMD, FASHP, FACHE received his baccalaureate degree from the University of British Columbia and his Doctorate in Clinical Pharmacy from the University of Washington. He completed a residency at Vancouver General Hospital, and has practiced as a clinical pharmacy specialist, clinical coordinator and director of pharmacy services at many healthcare organizations in both Canada and the United States. He is currently the Associate Principal of Clinical Pharmacy Performance Services for Vizient, in Whitefish, Montana.

Dr. Donaldson is a Clinical Professor in the Department of Pharmacy at the University of Montana in Missoula, and Clinical Associate Professor in the School of Dentistry at the Oregon Health & Sciences University in Portland, Oregon. He has a special interest in dental pharmacology and has lectured internationally to both dental and medical practitioners. He has spent the last 22 years focusing on dental pharmacology and dental therapeutics, and is a leader in the field.

Dr. Donaldson has published numerous peer-reviewed works and textbook chapters. He currently serves on the Editorial Board for the Journal Healthcare Executive and the Journal of the American Dental Association, and is a reviewer for over ten other different journals. He is board certified in healthcare management and is the Past-President and current Regent of the American College of Healthcare Executives' Montana Chapter. Dr. Donaldson was named as the 2014 recipient of the Bowl of Hygeia for the state of Montana and is the 2016 recipient of the Dr. Thaddeus V. Weclew Award. This award is conferred by the Academy of General Dentistry upon an individual who has made outstanding contributions to the medical, dental and pharmacy literature. In 2019, Dr. Donaldson was conferred by the Canadian Dental Association (CDA) in Ottawa with the, "Special Friend of Canadian Dentistry Award." This award is given to an individual outside of the dental profession in appreciation for exemplary support or service to Canadian dentistry and/or to the profession as a whole.

Minimal Sedation & Sedative Agents

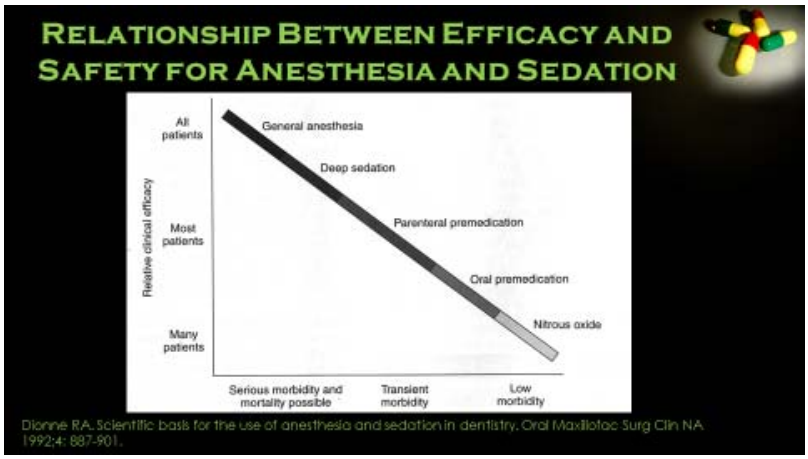


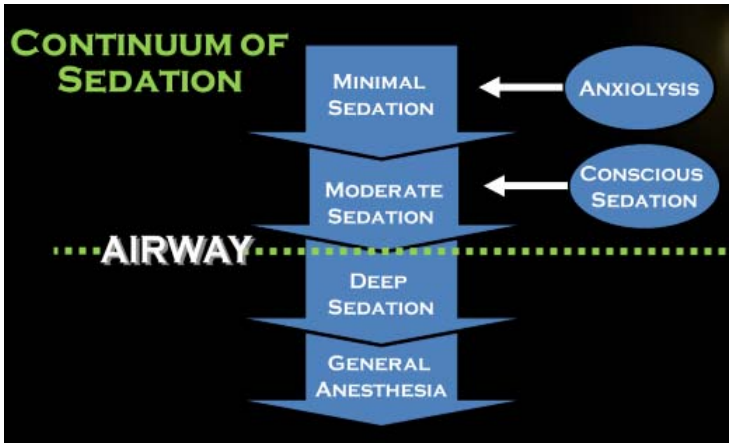
Anxiolysis is a minimal level of sedation whereby the patient has decreased anxiety to facilitate coping skills while retaining interaction ability (minimal sedation).

Conscious sedation is a moderate level of sedation whereby the patient retains their protective reflexes as well as their own airway, and can respond to physical and verbal stimuli (moderate sedation).

Dionne R, Yagiela J, Donaldson M et al. Balancing efficacy and safety in the use of oral sedation in dental outpatients. J Am Dent Assoc 2006; 137: 502-513.

Yageila JA, Malamed SF, Donaldson M, et al. Academy of General Dentistry White Paper on Enteral Conscious Sedation. General Dentistry 2006, Sept-Oct;301-304.





All things considered equal, the lower the sedation level, the less chance for a serious adverse event to occur. The adage, "go low and go slow" is an excellent philosophy for the practice of sedating dental patients.

Infosino A. Sedation of pediatric patients. In: Weiner-Kronish JP, Gropper MA. Conscious sedation. Philadelphia: Hanley & Belfus; 2001:89-104.

Other Notes or Questions to Ask:

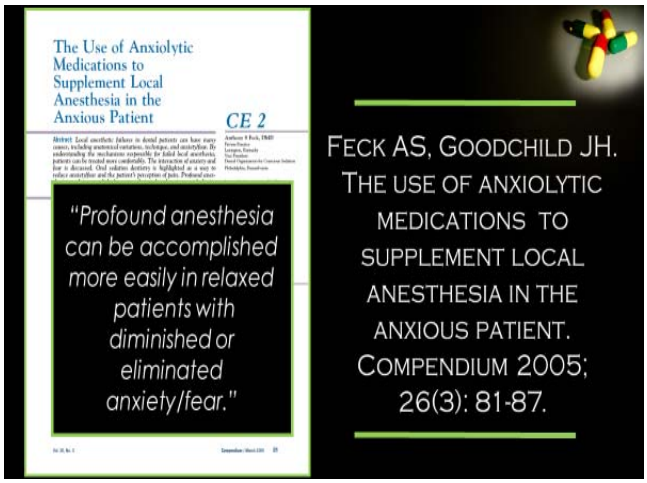
Who is a candidate for oral sedation?

Good

- Patients who have difficulty achieving profound local anesthesia
- Gaggers
- Fearful or anxious patients
- Patients needing longer procedures
- Helpful with invasive procedures

Difficult

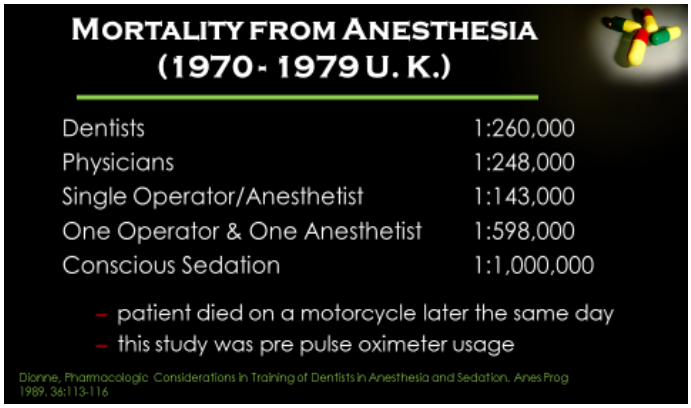
- Patients with complex medical histories
- Patients taking medications which may cau adverse reactions
- Severely depressed patients
- Patients with a severe mental handicap
- Pregnant patients



Randall CL, Shulman GP, Crout RJ, McNeil DW. Gagging and its associations with dental care-related fear, fear of pain and beliefs about treatment. J Am Dent Assoc. 2014 May;145(5):452-8.

The Drugs

The goal of conscious sedation dentistry is to create a patient who is calm, and comfortable enough to receive dental care, and who can maintain a patent airway without assistance. Medications used for anxiolysis or conscious sedation should carry an inherent margin of safety such that overdose or unconsciousness is unlikely.



Because there are many medications that are anxiolytic (reduces anxiety) and hypnotic (involves the induction and increase of sleep duration), there may be instances that alternate regimens may be indicated.

Other Notes or Questions to Ask:

The decision to use drugs other than triazolam should be based on the practitioners' level of training and should take into account many factors. The factors that may influence drug selection include:

- Medical History
- Drug interactions
- Allergies
- Length of appointment
- Depth of sedation needed
- Adverse reactions

Medications used for minimal or moderate sedation should carry an inherent margin of safety such that overdose or unconsciousness is unlikely: "First, Do No Harm!" Anxiolytic and Sedative agents are not new to the practice of medicine. Alcohols have been used for centuries to "numb" the mind to both painful as well as anxiety producing procedures. The use of opium has been traced back to Ancient Egypt. In the nineteenth century, drugs such as bromide (1853), chloral hydrate, paraldehyde, urethane and sulfonal (all pre-1970) were employed with varying degrees of success. Early in the twentieth century, the barbiturates were discovered (Barbital – 1903 and Phenobarbital – 1912), and the age of modern anesthesia was born. While these early drugs were effective, their level of safety was questionable.

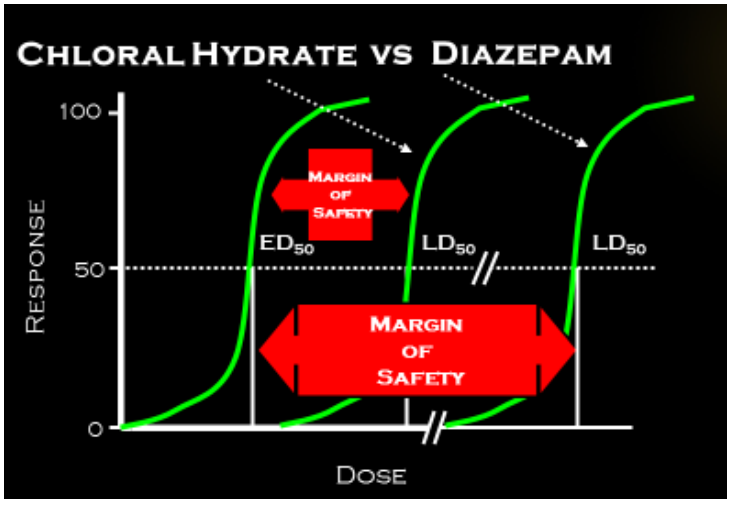
CHLORAL HYDRATE-INDUCED ARRYTHMIAS

Age	Dose (grams)	Arrythmia	Cardiac Arrest	Antiarry. Drug Res.	Outcome
2	1.5	PVC	No	No	Survived
9	0.6	SVT	No	Yes	Survived
17	14	PVC, VT	No	Yes	Survived
19	17.5	PVC, VF	Yes	Yes	Survived
21	20	VT	No	No	Survived
29	10	PVC, VT	No	-	Survived
32	20	PVC, VF	Yes	-	Survived
33	40	PVC	Yes	-	Died

In large doses it shortens the cardiac refractory period and may sensitize the heart to circulating catecholamines. *Jastak. JADA 1988 (vol.116)*

Safety of a given medication can be measured pharmacologically by determining the **Lethal Dose 50 (LD50)**. The LD50 is that dose of a given drug that will result in mortality of 50% of the population when administered. Likewise, the **Effective Dose 50 (ED50)** is the dose of a given drug that will cause the desired results in 50% of a population.

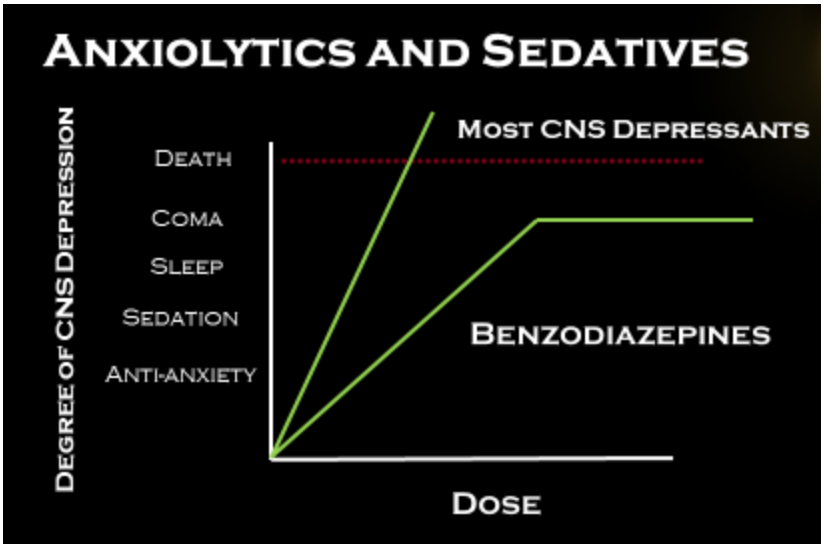
The two terms can be related to one another by the Therapeutic Index (TI = LD50/ED50), which is a relative measurement of drug safety. The greater the Therapeutic Index of a drug, the greater the margin of safety.



Chloral Hydrate, a drug that has been used as a sedative for over a century, when compared to a drug in the benzodiazepine class (Diazepam - early 1960s), is an example of the lower degree

Other Notes or Questions to Ask:

of safety as demonstrated by drugs of the past. One of the attributes that make newer classes of drugs safer than those in the past is their ability to more selectively depress areas of the central nervous system that affect consciousness. Most anxiolytic and sedative agents, if given in inappropriate doses, have the capacity to elicit undesired effects, including coma and death.



Chlordiazepoxide (1957) was the first drug in the benzodiazepine class to be synthesized. The benzodiazepines, being more selective in their effects on the central nervous system, are much less likely to induce coma and death; therefore they have a much higher LD50 and Therapeutic Index than drugs in other anxiolytic/sedative classes.

The "Ideal" Oral Agent should have the following properties:

- ✓ Fast onset
- ✓ No adverse effects – large margin of safety (respiratory, cardiovascular, others)
- ✓ "Short" acting (for office use)
- ✓ Anxiolytic with some amnesic properties
- ✓ Reversal agent available

Donaldson M, Chanpong B, Gizzarelli G. Oral Sedation: A Primer on Anxiolysis for the Adult Patient. Anesth Prog 2007;54:118-129.

Benzodiazepines meet these requirements and have the following properties:

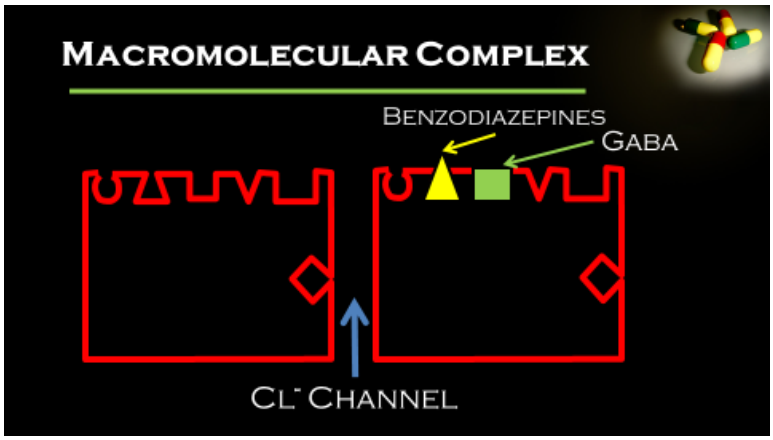
- ✓ Sedative-Hypnotic
- ✓ Muscle Relaxant
- ✓ Anxiolytic
- ✓ Anticonvulsant
- ✓ Antidepressant
- ✓ Anterograde Amnesia

Goodchild JH, Donaldson M. The American Dental Association's updated sedation and general anesthesia guidelines—is minimal sedation all about triazolam? Gen Dent 2017;65(2):6-11.

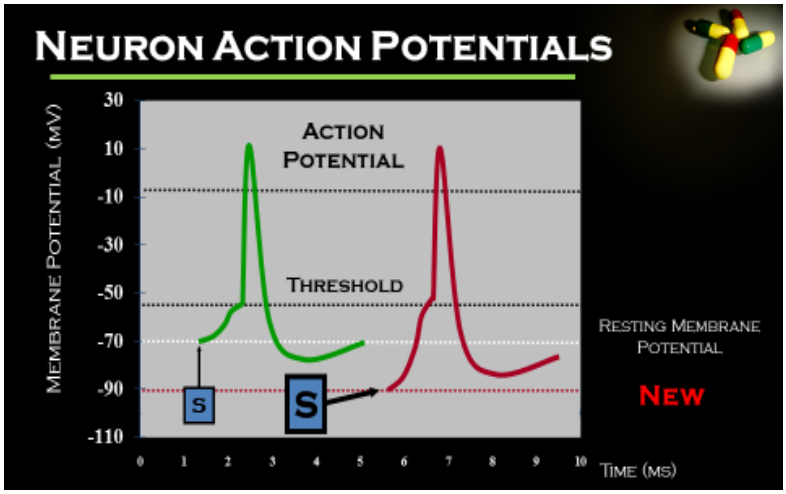
Other Notes or Questions to Ask:

Medications for Oral Conscious Sedation

The family of medications most commonly used for oral conscious sedation is the benzodiazepines. They were first introduced in the early 1960's, and are among the most widely prescribed drugs in the world. Like members of your own family they are closely related and share very similar properties due to a common mechanism of action on the gamma amino butyric acid (GABA) receptors in the brain.



These GABA receptors are the neuroreceptors responsible for levels of alertness, so the shared pharmacological property of this family of drugs denotes them as sedatives or hypnotics: they cause relaxation, can induce sleep and may even allow for post-hypnotic suggestions. The interaction of the benzodiazepines at the GABA molecule occurs in the limbic, thalamic and hypothalamic levels of the CNS. Specific high-affinity benzodiazepine receptors have been identified. When the benzodiazepine and GABA molecules interact, a macromolecular complex is formed. The complex results in an influx of chloride ions as the chloride ionophore channel in the nerve axon increases in diameter, causing hyperpolarization, and an associated new resting membrane potential.

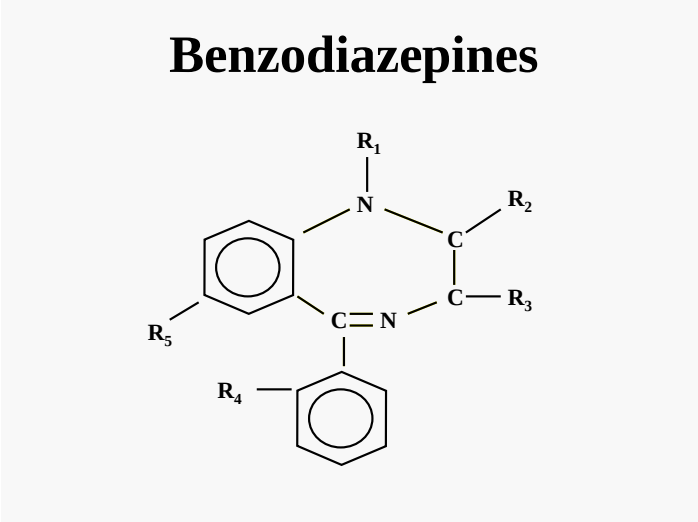


To further the familial analogy, these medications still maintain their own uniqueness despite their underlying similarity. Each medication may or may not have active metabolites, such as diazepam (Valium), and their individual plasma half-lives and mean peak concentrations vary among agents, which gives rise to different medication properties. It is only through experience that practitioners learn how to match the best medication and dose with each clinical situation and patient.

Other Notes or Questions to Ask:

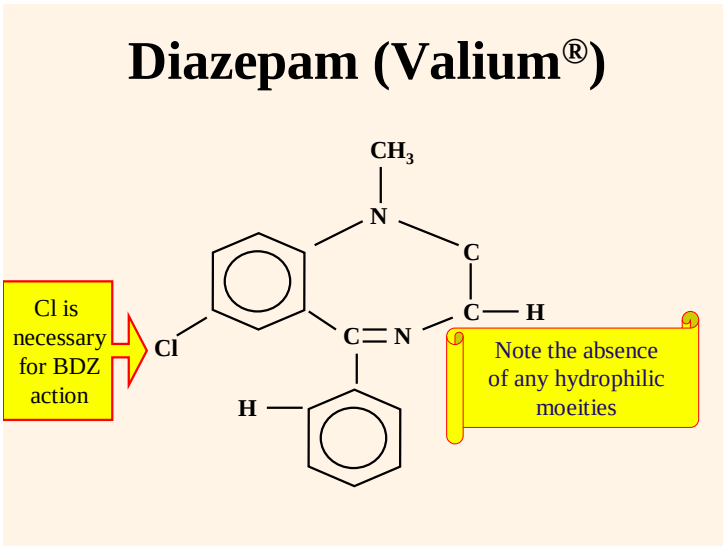
The Benzodiazepine Family of Medications

All of the benzodiazepine drugs have a similar chemical structure:



Diazepam (Valium)

- Produces mild sleep and mild amnesia
- Onset: 30-60 minutes
- Half-Life: 50 hours (20-100) due to active metabolites
- Duration of action can be 6-8 hours
- Supplied in 2, 5, and 10 mg tablets
- Usual Dosage is 2-40 mg
- FDA approved anxiolytic
- High Lipid Solubility



Indications for use of diazepam as listed in the Physicians' Desk Reference (PDR):

- Preoperative anxiolytic
- Night-time sleep (hypnotic)
- Anticonvulsant

THE BLOOD-BRAIN BARRIER

A complex group of blood-brain barrier mechanisms closely controls both the kinds of substances which enter the extra-cellular space of the brain and the rate at which they enter. This mechanism is not a true "barrier" but acts like a selective gatekeeper, and comprises both anatomical structures and physiological transport systems which handle different classes of substances in different ways. The blood-brain barrier mechanisms precisely regulate the chemical composition of the extra-cellular space of the brain and prevent harmful substances from reaching neural tissue, and gives rise to a second and third compartment model for the benzodiazepines.

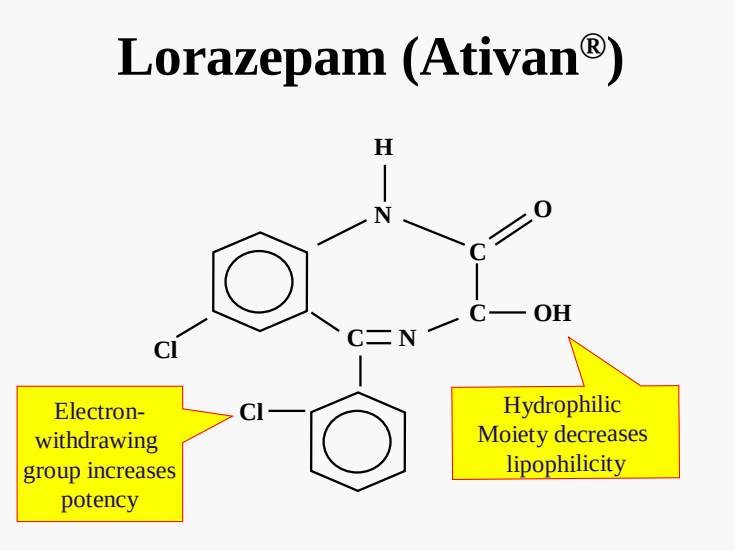
Other Notes or Questions to Ask:

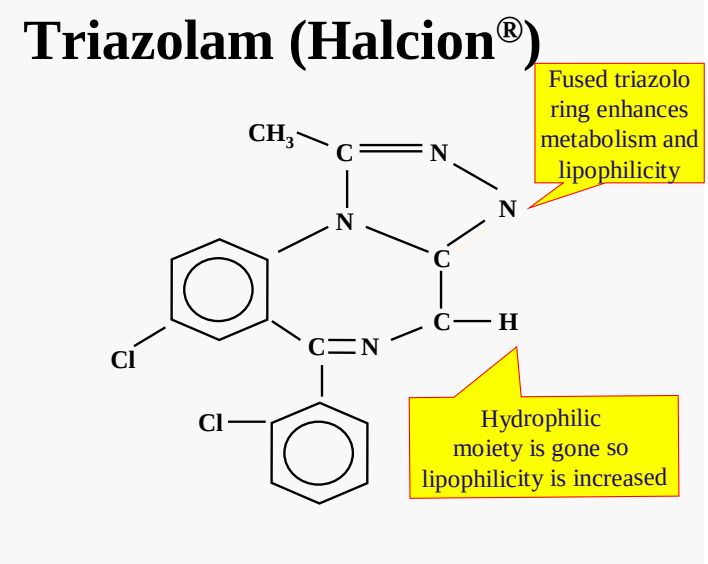
Lorazepam (Ativan)

- Produces mild/moderate sleep with moderate amnesia
- Onset: 60-120 minutes
- Half-Life: 10-20 hours
- No active metabolites
- Duration: 6-8 hours
- Supplied in 0.5, 1, and 2 mg tablets
- Dosage: 0.5-2.0mg
- Moderate Lipid Solubility

Indications for use of lorazepam as listed in the Physicians' Desk Reference (PDR):

- Preoperative anxiolytic
- Night-time sleep (hypnotic)
- Anticonvulsant





Triazolam (Halcion)

- No active metabolites
- Plasma half-life is 1.5 – 2.5 hours
- Wide effective dose range
- Mean peak concentration is achieved at 1.3 hours
- Has anticonvulsant properties – can be used with the epileptic patient
- May act as a respiratory depressant at very high doses (greater than 2mg)
- Relaxation for adequate pain control – important for hard to numb patients
- Does not cause nausea (unlike nitrous oxide)
- LD_{50} is 5 grams per kilogram in rats (very safe)*

Respiratory depression represents the principal negative that is introduced with conscious sedation and left unrecognized and untreated is the cause of the most serious complication!

Other Notes or Questions to Ask:

Indications for use of triazolam as listed in the Physicians' Desk Reference (PDR):

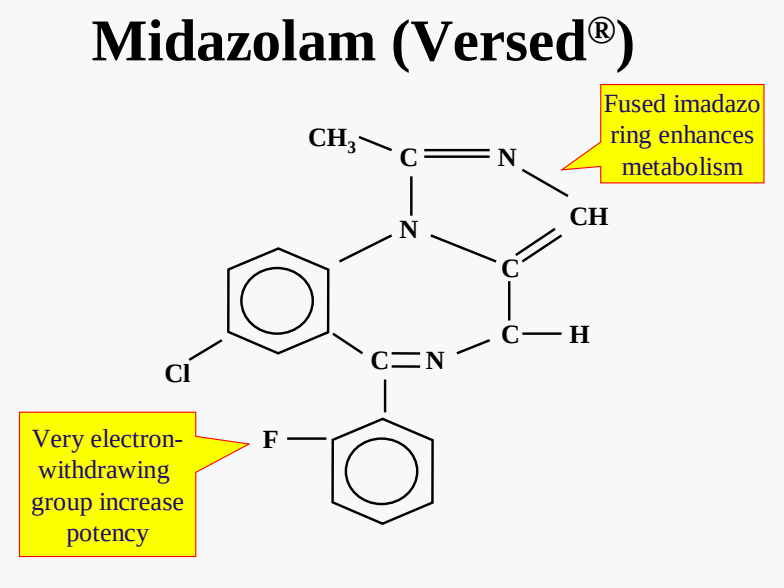
- Preoperative sedation
- Night-time sleep
- Onset: 1 hour
- Peak effect: 1.3 hours
- Duration: 2-3 hours

Dosage (PDR):

- Adult: 0.5 mg Healthy adult
- Elderly or debilitated 0.125 mg
- Always use the lowest effective dose
- Child: Safety and efficacy not tested for patients below the age of 18

Midazolam (Versed)

- Produces moderate sleep and high amnesia
- Onset: 15-30 minutes
- Half-Life: 1.5 - 5 hrs.
- No active metabolites
- Duration: 1 hr.
- Supplied in 118 ml bottles, each mL contains 2mg midazolam
- Dosage: 0.25 to 0.75 mg/kg in children >6 months (relative maximum at 10 mg)
- High Lipid Solubility
- Not an FDA approved anxiolytic



Indications for use of midazolam as listed in the Physicians' Desk Reference (PDR):

- Preoperative anxiolytic
- Night-time sleep (hypnotic)
- Anticonvulsant

Some licensing bodies may consider the intranasal administration of midazolam so similar to the intravenous delivery that IV sedation certification is required. Delivering the medication intranasally requires a MAD® (Mucosal Atomization) Device.

Other Notes or Questions to Ask:

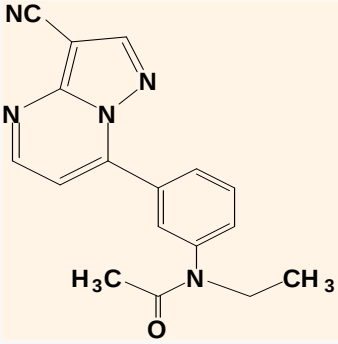
Other Medications (non-Benzodiazepines)

Zaleplon is a pyrazolopyrimidine, differing in structure from the benzodiazepines but still acting selectively at the benzodiazepine receptor. The benefits of this medication are in producing sedation without many of the other effects seen with benzodiazepines. It has modest anxiolytic, myorelaxant, and anticonvulsant properties. Significant drug interactions are uncommon, and synergy with ethanol does not occur. Patients with zaleplon overdose generally do well with supportive care alone. Overdose information for zaleplon is limited and no fatalities have been reported with ingestions of up to 100 mg. Adverse effects with therapeutic use include anterograde amnesia and transient visual hallucinations.

Zaleplon (Sonata, Starnoc)

- Produces high sleep with only mild amnesia
- Onset: 30 minutes
- Half-Life: 1-2 hours
- No active metabolites
- Duration: up to 6 hours
- Supplied in 5 and 10 mg capsules
- Dosage: 10 mg (start at 5mg in the elderly or patients with liver disease)
- Overdosage can be treated with flumazenil
- Not an FDA approved anxiolytic (approved for treatment of insomnia in adults only)

Zaleplon (Sonata)



Pyrazolopyrimidine Family

Cautions:

- hypersensitivity to zaleplon products
- depressed patients
- elderly or debilitated patients
- hepatic or severe renal impairment
- compromised respiratory condition
- concurrent use of alcohol
- tartrazine sensitivity
- Coadministration with the following medications can effect metabolism: cimetidine, digoxin, and rifampin (diphenhydramine may augment zaleplon's effects)
- Pregnancy: risk category C

Donaldson M, Goodchild JH. Pregnancy, breast-feeding and drugs used in dentistry. J Am Dent Assoc 2012;143(8):858-71.

Other Notes or Questions to Ask:

Drug	Lipid Solubility	Onset (mins)	$T_{1/2}$ (hrs)	Site of Metabolism	Active Metabolite	Working Time (hrs)	Usual Dosing
Diazepam	High	30-60	>24	CYP 1A2, 2C8, 2C19, 3A3-4	Yes	n/a	2-(40) mg per day
Lorazepam	Moderate	60-120	10-20	Hepatic glucuronidation	No	4	2-(6) mg
Triazolam	High	15-30	1.5-2.5	CYP 3A4, 5-7	No	2	0.125-0.5 mg
Midazolam	High	0 (IM) 15-30 (PO)	1.5-5	CYP 3A3-5	No	1	0.25-0.75 mg/kg
Zaleplon	Moderate	30	1-2	Aldehyde oxidase, CYP 3A4	No	1	10-20mg

Triazolam is a near ideal sedative agent due to it's pharmacological properties, which make it not only highly effective for dental sedation purposes, but it also comes with a high margin of safety.

Triazolam: Cautions and Contraindications (Nearly all of these cautions and contraindications apply to all benzodiazepines):

Absolute Contraindications

- ✓ Known hypersensitivity
- ✓ Pregnancy – benzodiazepines are known teratogens (esp. 1st trimester)
- ✓ Lack of Knowledge
- ✓ Inability to resuscitate
- ✓ Concurrent with CYP3A4 inhibitors: grapefruit juice, ketaconazole, itraconazole, nefazodone, cimetidine, and macrolide antibiotics

Relative Contraindications

(Risk benefit should be considered when the following medical conditions exist)

- Alcohol intoxication – additive CNS
- Glaucoma
- Drug abuse or dependence
- Pediatric patients
- Elderly (oversedation, dizziness, or impaired coordination)
- Psychiatric patients
- Renal impairment
- Severe hepatic impairment
- Lactating patients

Other Notes or Questions to Ask:

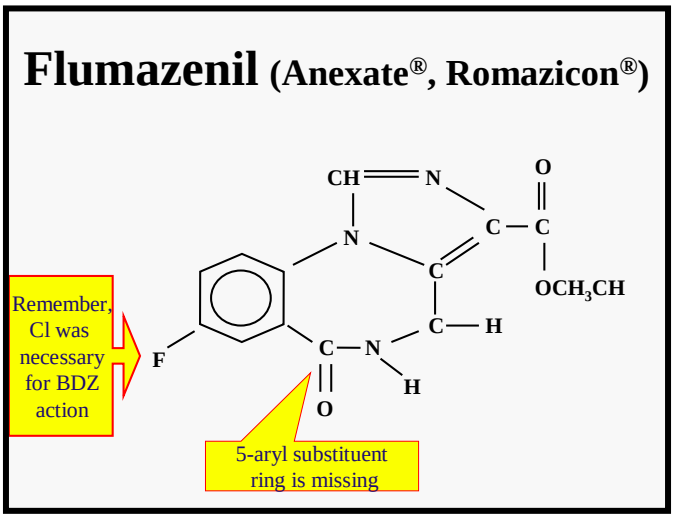
"Triazolam is chemically related to diazepam and is used for the short-term treatment of insomnia. its rapid onset, short duration of action, and lack of active metabolites also makes it a near ideal anti-anxiety medication for dental patients".

Dionne RA, Trapp LD. Oral and rectal sedation. In: Dionne RA, Phero JC, Becker DE. Management of Pain and Anxiety in the Dental Office. St. Louis, MO:WB Saunders;2002:229.

Benzodiazepine Reversal Agent

Flumazenil (Romazicon® in U.S., Anexate® in Canada):

- ✓ First clinical trials done in 1979
- ✓ Displaces BDZ's from their receptor site, reversing their sedative action
- ✓ Onset of reversal after I.V. injections is 1-2 minutes (neutral ligand)
- ✓ Duration of effect depends on the dose of flumazenil and the dose of the BDZ
- ✓ Adult dose is 0.2mg q1min up to 5 doses



Flumazenil, a nonspecific competitive antagonist of the benzodiazepine receptor, is used for reversal of benzodiazepine-induced sedation, and overdose. It binds to GABA-receptor sites, but has no agonist activity.

*** It is not recommended for **routine** reversal as seizures and cardiac dysrhythmias can occur with flumazenil administration, and although the majority of these effects are uncommon and well tolerated. Co-ingestion of drugs with proconvulsant properties is associated with an increased risk of seizures, presumably due to loss of the benzodiazepine's protective anticonvulsant effect when the antagonist is administered. Combined overdose of benzodiazepines with tricyclic antidepressants accounts for 50% of these seizures. Coingestants possessing prodysrhythmic properties, such as carbamazepine or chloral hydrate, may increase the likelihood of cardiac effects by a similar mechanism.

*** Although flumazenil reverses benzodiazepine-induced sedation, it does not consistently reverse respiratory depression. The initial adult dose of flumazenil is 0.2 mg given intravenously over 30 seconds. A second dose of 0.2 mg may be given, followed by 0.2mg

Other Notes or Questions to Ask:

doses at 45-60 second intervals, to a total of 1mg in twenty minutes. Most patients will respond to less than 1 mg.

*** In children, the initial dose is 0.01 mg/kg.

*** Because the duration of action of flumazenil is short (40-80 minutes), resedation occurs in up to 65% of patients and requires either redosing or continuous infusion (0.25 to 1.0 mg/hr).

In summary, flumazenil should be used for selected patients with significant symptoms from a known benzodiazepine overdose, and not routinely used on patients following an oral sedation procedure.

Flumazenil -- Other points to note are:

1. Insoluble in water
2. Slightly soluble in acidic solutions
3. Dilute concentration of 0.1mg/mL
4. 5 mL and 10 mL vials
5. One hour duration (triazolam's half-life is about 2 hours so patients could re-sedate)
6. Can be given sublingual in the canine to first molar area, 2-3 mm under the mucosa, not in the midline
7. Buy the 5mL vials and be aware of expiry dates!

Contraindications:

- Known hypersensitivity to benzodiazepines
- Patients with known seizure disorders treated with a benzodiazepine

Several studies support the use of flumazenil in the treatment of benzodiazepine overdose. :

✓"Respiratory depression mediated by benzodiazepines can be reversed using the specific antagonist flumazenil (Romazicon). It can be titrated intravenously or injected sublingually in 0.2 mg increments every 2-3 minutes, up to 1 mg. Flumazenil should not be administered to patients with a history of seizure disorder or dependence on benzodiazepines."

✓"Clinical trials using flumazenil to reverse the CNS depression associated with intravenous diazepam sedation for third molar extractions have demonstrated its efficacy."

Other Notes or Questions to Ask:

Some Definitions

- ***Synergism:*** When two or more drugs with similar pharmacologic effects act together to produce a greater effect than either drug alone. Synergism can either be additive or potentiating.
    - ***Additive:*** The combined drug effects are essentially the algebraic sum of their individual effects (e.g., 1 + 1 = 2).
    - ***Potentiating:*** The combined drug effects are greater than the sum of their individual effects (e.g., 1 + 1 > 2).

Antihistamines

There are several other drugs that are effective for oral sedation, but don't fall into the previous drug classes that have been discussed. The H_1-receptor antagonist hydroxyzine (Atarax) has both sedative and hypnotic properties. The OTC anti-histamine diphenhydramine (Benedryl) have hypnotic properties and can be an inexpensive and safe adjunct to sedation. Both Atarax and Benadryl are useful in allergic rhinitis and urticaria, and are antiemetic.

Antihistamines

Generic Name	Trade Name	Half-Life (hrs)	Dose Range
Diphenhydramine	Benadryl	2-8	25-50 mg
Dimenhydrinate	Dramamine	4-6	50-100 mg
Hydroxyzine	Atarax, Vistaril	3-7	50-100 mg
Promethazine	Phenergan	2-6	25-50 mg

Hydroxyzine (Atarax or Vistaril)

- Diphenylmethane, unrelated to benzodiazepines, phenothiazines, or opiates
- H1-receptor antagonist
- Bronchodilator
- Antisialogogue (anticholinergic)
- Antiarrhythmic
- Anxiolytic
- Even at high doses produces minimal CV and respiratory depression
- High therapeutic index
- Produces moderate sleep with no amnesia

Other Notes or Questions to Ask:

Antihistaminic, Decongestant, and Anti-emetic actions

- Onset: 1 hour
- Half-Life: 3-7 hours
- No active metabolites
- Duration: 3-6 hours
- Supplied in 10, 25, and 100 mg tablets and a 10mg/5mL syrup
- Dosage: Adults 50-100 mg, Children 10-50 mg
- Overdosage: No specific antidote
- FDA approved anxiolytic and as a pre- and postoperative adjunctive medication

Contraindications:

- Early Pregnancy
- Known Hypersensitivity
- Nursing Mothers
- Children <1 year
- Acute narrow angle glaucoma
- Use with other CNS depressants cautiously

Phenergan is from the phenothiazine class but has H_1-receptor effects. It has strong antihistamine properties and is commonly used in conjunction with opioid anesthesia, due to its antiemetic properties. Phenergan's antiemetic protection is primarily due to its interaction with dopaminergic receptors in the CTZ (Chemotactic Trigger Zone).

Some important points about Phenergan:

- Will not produce unconsciousness, and even at higher doses will not cause respiratory or CV depression
- Sedative
- Antisialagogue (Anticholinergic effects)
- Strong antiemetic

Nitrous Oxide

"I am sure the air in heaven must be this wonder working gas of delight"
- Robert Southey, about Nitrous Oxide

Historical Perspective

The discovery of nitrous oxide (and also oxygen) is credited to Joseph Priestley in 1793. During experiments with iron filings, ammonium nitrate, and water, he found that a residual gas was given off which later became known as nitrous oxide.

Other Notes or Questions to Ask:

$$NH_4NO_3 + H_2O + Fe \rightarrow N_2O + Fe(OH)_2 + H_2O$$

Ammonium nitrate is heated in the presence of iron filings. The resultant gas is then passed through water to remove toxic by-products. The result is nitrous oxide.

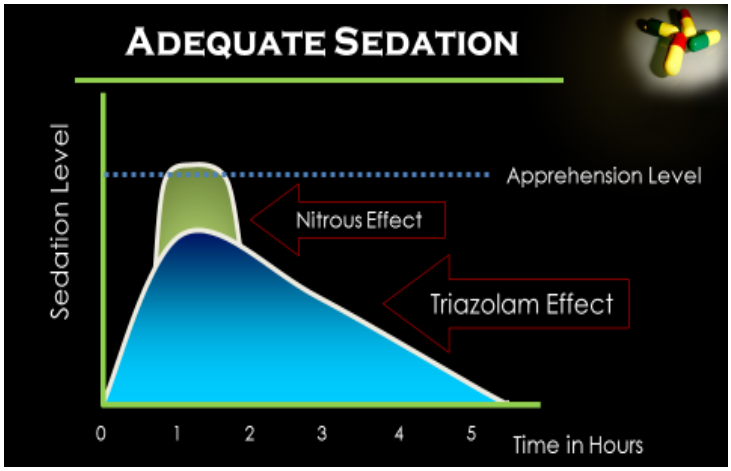
The first to person to inhale pure nitrous oxide was Humphrey Davy (at the Pneumatic Institute in Bristol, England), in 1798. At that time, nitrous oxide (N2O) was thought to be responsible for many diseases, however after breathing the gas he reported a euphoric feeling, and "overwhelming joy."

For the first half of the 19th century, the analgesic properties of N2O went unnoticed and nitrous was widely used as a recreational drug. It was not until the mid-1840's that a dentist named Horace Wells while attending a demonstration was exposed to N2O. During this demonstration a man named Samuel Cooley, after inhaling the gas, injured his leg. Dr. Wells noticed that Mr. Cooley appeared to be unaware of the injury to his leg, and he instantly envisioned the gas as an adjunct to the field of dentistry. Horace Wells in fact became the first person to have a tooth extracted while under N2O anesthesia. He termed this revelation the "greatest discovery ever made," and tried over the next year to prove the efficacy of N2O to the medical community. After a failed experiment at Harvard Medical School in 1845 in which the patients "felt some discomfort," Wells was labeled as a "charlatan" and a "fake." He died some years later, never receiving the credits for his discovery.

Nitrous oxide lost favor and was very seldom used outside of dentistry until the 1930's. It was then that medical schools began teaching the techniques of N2O sedation. From that time until the late 1950's, the medical field predominately used N2O as a preanesthetic gas for Halothane. Dental schools began teaching inhalation anesthesia in the early 1960's and it is estimated that "56% of GP's and 85% of oral surgeons" use N2O in their practice today.

Advantages of Combination Oral-Inhalation Sedation

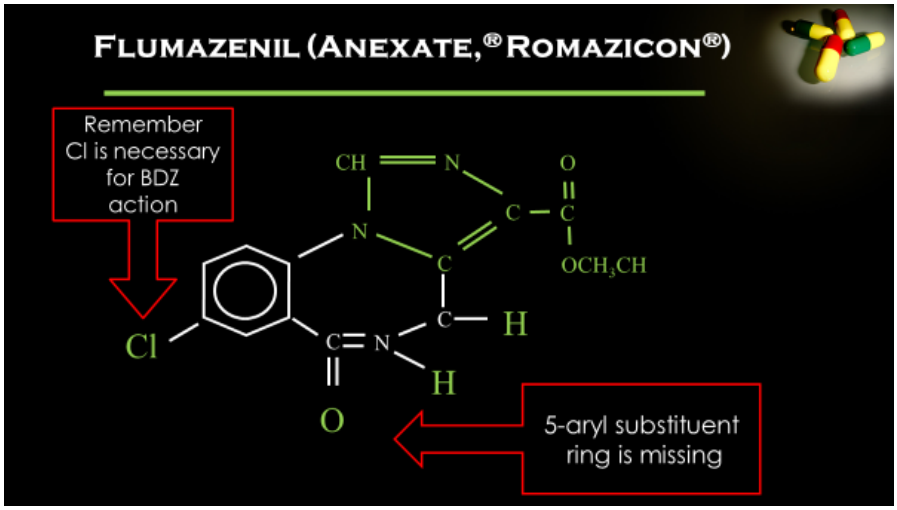
- Decreased dose required of either medication alone
- Decreased overall side effects
- Potentiation vs Synergy

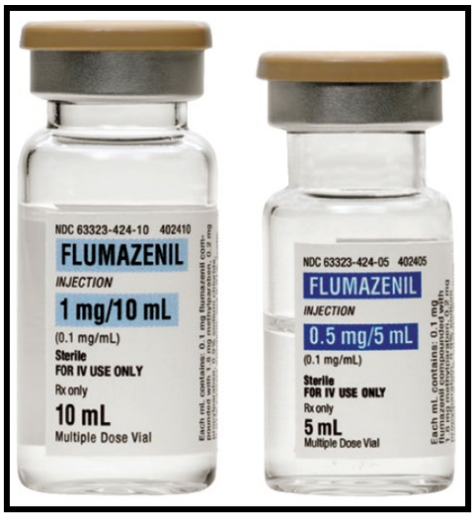


Other Notes or Questions to Ask:

	T_{max} (hr)	$T_{1/2\ elim}$ (hr)	Site of metabolism	Pharmacologic antagonist	Usual PO dose	Duration of action (hr)
Triazolam (Halcion®)	1.25	2.5 (1.7-4)	CYP 3A4, 5-7	Flumazenil	0.125-0.5 mg	2-4
Midazolam (Versed®)	0.5-1	1-2	CYP 3A3-5	Flumazenil	0.5 mg/kg	1-2
Lorazepam (Ativan®)	1.2	15.7 (14-16)	Hepatic gluronidation	Flumazenil	1-3 mg	6-8
Alprazolam (Xanax®)	1.45	14.5 (12-15)	CYP 3A4	Flumazenil	1 mg	6-8
Diazepam (Valium®)	1.12	33 (20-100)	CYP 1A2, 2C8, 2C19, 3A3-4	Flumazenil	5-10 mg	6-8
Zaleplon (Sonata®)	0.5-1.5	1	Aldehyde oxidase, CYP 3A4	Flumazenil	10 mg	4
Zolpidem (Ambien®)	1.6	2.5	CYP 3A4, 2C9, 1A2	Flumazenil	10 mg	8
Ramelteon (Rozerem®)	0.3	0.5-2.6	CYP 1A2, 2C, 3A4	Unknown	8 mg	24
Eszopiclone (Lunesta®)	1-1.5	6	CYP 3A4, 2E1	Flumazenil	2-3mg	6
Zopiclone (Imovane®)	1-1.5	3.5-6.5	CYP 3A4, 2E1	Flumazenil	7.5mg	< 24
Promethiazine (Phenergan®)	2-3	7-15	CYP 2D6, 2B6	None	25 mg	2-8
Hydroxyzine (Atarax®, Vistaril®)	2.1	7-20	CYP 2D6	None	50 mg	24

Keeping Patients Safe: Flumazenil & Naloxone





Flumazenil (Romazicon in U.S., Anexate in Canada, multiple generics now available):

Flumazenil, a nonspecific competitive antagonist of the benzodiazepine receptor, is used for reversal of benzodiazepine-induced sedation, conscious sedation, and overdose. It binds to GABA-receptor sites, but has no agonist activity. In the emergency room it can quickly confirm a clinical diagnosis, thereby obviating the need for time-consuming and expensive interventions. In the dental office, with patients undergoing conscious sedation with benzodiazepines, it speeds return to baseline alertness in emergency situations.

It is not recommended for routine reversal as seizures and cardiac dysrhythmias can occur with flumazenil administration, and although the majority of these effects are well tolerated, fatalities have been reported. Coingestion of drugs with proconvulsant properties is associated with an increased risk of seizures, presumably due to loss of the benzodiazepine's protective anticonvulsant effect when the antagonist is administered.

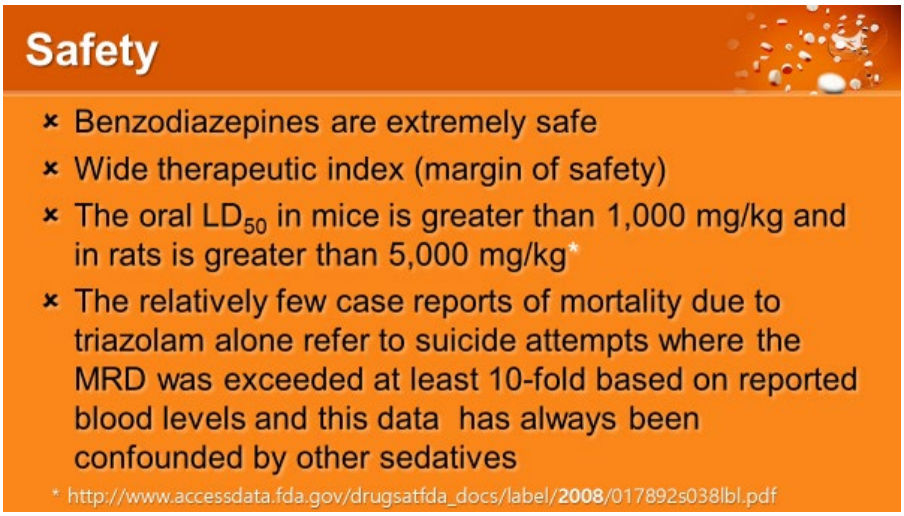
Triazolam Absolute Contraindications

- Known hypersensitivity
- Pregnancy – benzodiazepines are known teratogens (especially 1st trimester)
- Lack of knowledge
- Inability to resuscitate
- Concurrent treatment with CYP3A4 inhibitors: (i.e., grapefruit juice, ketoconazole, itraconazole, nefazodone, cimetidine, macrolide medications and others)

Triazolam Relative Contraindications

- Risk benefit should be considered when the following medical conditions exist:
  - Drug/Alcohol intoxication - additive CNS depression
  - Drug Abuse or dependence
  - Glaucoma

Other Notes and Questions to Ask:

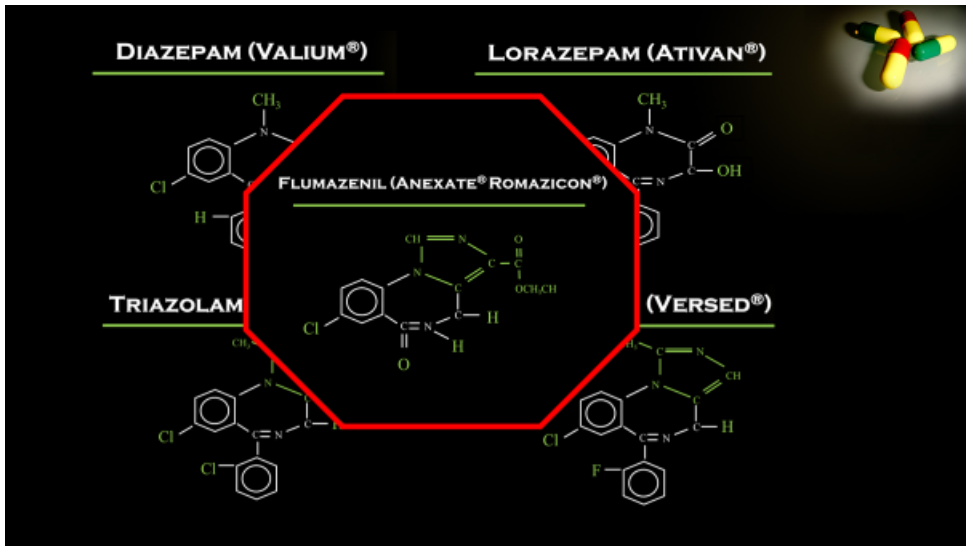


In and of themselves, benzodiazepines are very safe and have a large inherent margin of safety. Combined overdose of benzodiazepines with tricyclic antidepressants accounts for 50% of these seizures. Coingestants possessing prodysrhythmic properties, such as carbamazepine or chloral hydrate, may increase the likelihood of cardiac effects by a similar mechanism.

Because the mechanism of action of flumazenil is specific to the benzodiazepine receptor in the central nervous system, other medications that work via this receptor can also be reversed with this antagonist. Examples include zolpidem (Ambien), zopiclone (Imovane), eszopiclone (Lunesta) and zaleplon (Sonata, Starnoc).

Contraindications to flumazenil are minimal:

- Known hypersensitivity to benzodiazepines
- Patients with known seizure disorders currently controlled with a benzodiazepine

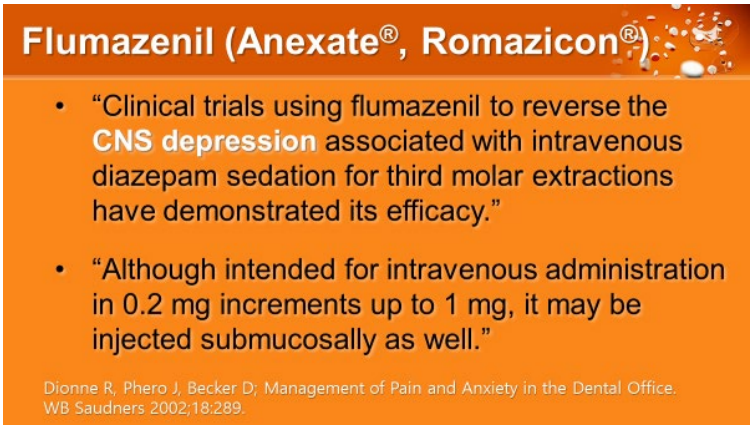


Although flumazenil reverses benzodiazepine-induced sedation, it does not consistently reverse respiratory depression. The initial adult dose of flumazenil is 0.2 mg given intravenously over 30 seconds. A second dose of 0.2 mg may be given, followed by 0.2mg doses at 1-minute intervals, to a total of 1mg in twenty minutes. Most patients will respond to less than 1 mg. In children, the initial dose is 0.01 mg/kg. Because the duration of action of flumazenil is short (0.7 to 1.3 hours), re-sedation occurs in up to 65% of patients and requires either re-dosing or continuous infusion (0.25 to 1.0 mg/hr). In summary, flumazenil should be used for selected patients with significant symptoms from a known benzodiazepine overdose and not routinely used in patients with altered mental status.

Other Notes and Questions to Ask:

Other points of note about flumazenil include:

- Insoluble in water
- Slightly soluble in acidic solutions
- Dilute concentration of 0.1mg/mL
- 5mL and 10mL vials
- One hour duration (triazolam's half-life is about 2 hours so patients could re-sedate)
- Can be given sublingual in the canine to first molar area, 2-3 mm under the mucosa, not in the midline
- Be aware of expiry dates!
- Not to be used for routine sedation reversal



Growing Body of Evidence for Sublingual Use: References with Summaries

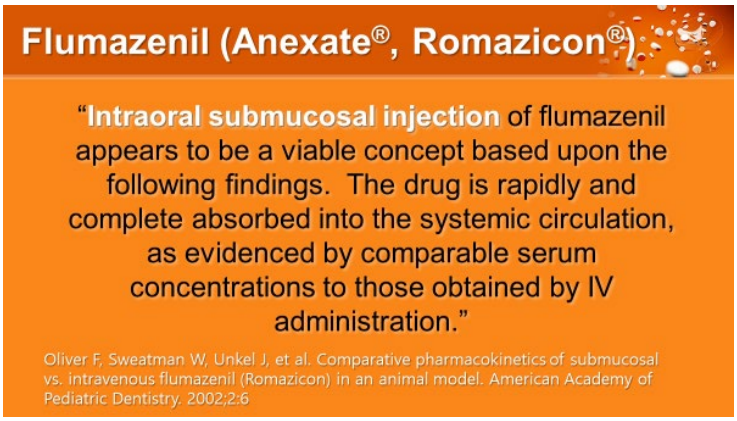
Unkel JH, Brickhouse TH, Sweatman TW, Scarbecz M, Tompkins WP, Eslinger CS. A comparison of 3 routes of flumazenil administration to reverse benzodiazepine-induced desaturation in an animal model. Pediatr Dent. 2006 Jul-Aug;28(4):357-62.

PURPOSE: The purpose of this study was to examine intralingual (IL) and submucosal (SM) delivery of flumazenil as viable alternatives to immediate intravenous (IV) administration for reversing benzodiazepine sedation in an animal model. METHODS: A dog animal model was chosen based upon comparable body weight to children (12-17 kg) and the ease of oral access in this species. Research design was a non-randomized matched pair study. This type of "before and-after study" allowed the dogs to receive 3 different routes of flumazenil administration (IV, IL, and SM) following an initial dose of midazolam (0.5 mg/kg IV). Blood samples were obtained (at 0, 2, 4, 8, 15, and 30 minutes) for high performance liquid chromatography (HPLC) analysis of flumazenil and midazolam, and oxygen saturation values were recorded. RESULTS: Both IL and SM delivery of flumazenil were determined to be viable alternatives to immediate IV administration for reversing benzodiazepine-induced oxygen saturation (SaO2) desaturation. For flumazenil to be able to reverse the SaO2 desaturation, the plasma levels must be greater than 5ng/ml, which was exceeded by IL and SM drug delivery. CONCLUSION: In a benzodiazepine-induced desaturation, the submucosal and intralingual routes are viable alternatives to intravenous administration of flumazenil in an animal model.

Other Notes and Questions to Ask:

Oliver FM, Sweatman TW, Unkel JH, Kahn MA, Randolph MM, Arheart KL, Mandrell TD. Comparative pharmacokinetics of submucosal vs. intravenous flumazenil (Romazicon) in an animal model. Pediatr Dent. 2000 Nov-Dec;22(6):489-93.

PURPOSE: This study was performed to determine the bioavailability and local tissue toxicological safety of flumazenil (Romazicon) when administered by oral submucosal (SM) as opposed to intravenous (i.v.) injection. METHODS: Six dogs each received SM flumazenil (0.2mg), and their serum was collected at predetermined time intervals (0-2 h) and frozen (-70 degrees C). Seven days later, the dogs received an identical dose of i.v. flumazenil, and serum samples were again collected, as above. Comparative quantitation of flumazenil levels (i.v. vs.SM) was made using a sensitive HPLC assay (UV detection). Direct/local drug toxicity was visually scored by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. An oral pathologist examined slides processed from control and treatment tissues (hematoxylin and eosin staining) taken (punch biopsy) 1 week following SM injection to compare with direct clinical scores. RESULTS: Serum flumazenil levels reached a plateau (8.5 +/- 1.5 ng/mL, mean +/- SD) within 4 min of SM drug injection and declined thereafter to -2 ng/mL by 2 h. Bioavailability of SM flumazenil was 101 +/- 14%, based upon measuring the area under the serum concentration-time curves over 1.5 h (AUC 0-1.5 h, SM vs. i.v. drug). Thus, serum drug levels following SM drug administration were broadly comparable to those obtained during the elimination phase of corresponding i.v. drug delivery. Regarding drug tissue toxicity, no evidence of direct drug toxicity was observed by unbiased raters of color photographs (test and control mucosa) taken at 1, 2, and 7 days following SM flumazenil injection. Following pathologic review, no difference was seen in the degree of inflammation between treatment and control tissue. CONCLUSION: At the quantity and concentration used, SM drug flumazenil administration appears to be both a safe and a viable alternative to bolus i.v. drug delivery and worthy of further investigation.



Heniff MS, Moore GP, Trout A, Cordell WH, Nelson DR. Comparison of routes of flumazenil administration to reverse midazolam-induced respiratory depression in a canine model. Acad Emerg Med. 1997 Dec;4(12):1115-8.

OBJECTIVE: To determine whether flumazenil, a drug used to reverse benzodiazepine-induced respiratory depression and approved only for i.v. use, is effective by alternative routes. METHODS: A randomized, controlled, nonblinded, crossover canine trial was performed to evaluate reversal of midazolam-induced respiratory depression by flumazenil when administered by alternative routes. Mongrel dogs were sedated with thiopental 19 mg/kg i.v., then tracheally intubated. With the dogs spontaneously breathing, tidal volume, end-tidal CO2, and O2 saturation were observed until a stable baseline was achieved. Incremental doses of midazolam were administered until respiratory depression (30% decline in tidal volume, 10% decrease in O2 saturation, and 15% increase in end-tidal CO2) occurred. Flumazenil was administered by a randomly selected route [0.2 mg followed 1 minute later by 0.3 mg i.v., sublingual (s.l.) or intramuscular (i.m.); or 1 mg followed 1 minute later by 1.5 mg per rectum (PR)]. Time to return to baseline respiratory functions was recorded ("time to reversal"). Each of 10 dogs was studied using all 4 routes of flumazenil administration with a washout period of at least 7 days. An additional dog served as a control (no flumazenil). RESULTS: The control time to reversal was 1,620 seconds. The i.v. route was significantly faster (mean 120 +/- 24.5 sec) than the other 3 routes ($p<0.005$). The SL route was the second fastest (mean 262 +/- 94.5 sec),

Other Notes and Questions to Ask:

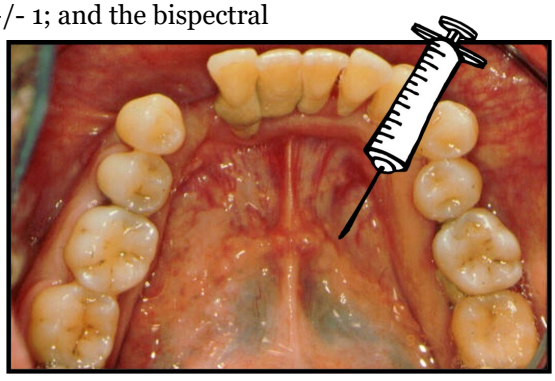
the IM route was the third fastest (mean 310 +/- 133.7 sec) and the PR route was the slowest (mean 342 +/- 84.4 sec). The SL, IM, and PR routes did not differ significantly from one another. CONCLUSIONS: Flumazenil administered by all 4 routes reversed midazolam-induced respiratory depression in a dog model. For the selected dosages used, the i.v. route was significantly faster than all 3 other routes, and SL was the second fastest.

Roncari G, Timm U, Zell M, Zumbrunnen R, Weber W. Flumazenil kinetics in the elderly. Eur J Clin Pharmacol. 1993;45(6):585-7.

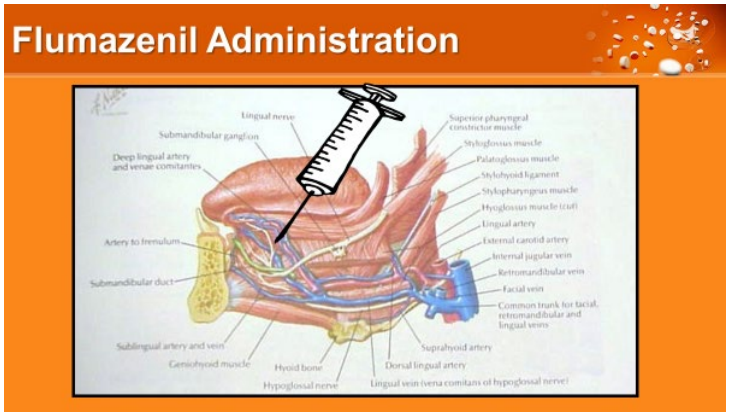
In an open design, randomised, two-way cross-over study, a single 2 mg i.v. dose and a single 30mg oral dose of flumazenil were each administered to a group of healthy young (n = 6) and elderly (n = 12) volunteers (male: female 2/1). Plasma samples were collected at intervals and intact drug was assayed. Both the i.v. and oral doses of flumazenil were very well tolerated by both age groups and no severe or unexpected adverse effects were observed. The main complaints were dizziness and headache, mainly after oral dosing, probably due to the higher Cmax and AUC following this route of administration. After 2 mg i.v. the disposition parameters in the two age groups (elderly/young) were very similar: volume of distribution (Vss): 0.88/0.90 L/kg; total body clearance (ClPL): 0.86/0.99 L/min; terminal elimination half-life (t1/2 beta): 1.02/0.91 h. After the 30 mg oral dose the mean Cmax of 87.6 ng/mL (elderly) and 78.4 ng/mL (young) were generally reached within 0.5 to 1 h. In 26% (elderly) and 23% (young), the absolute bioavailability of flumazenil was very similar. It is concluded that the absorption and disposition parameters of flumazenil were not significantly affected by aging.

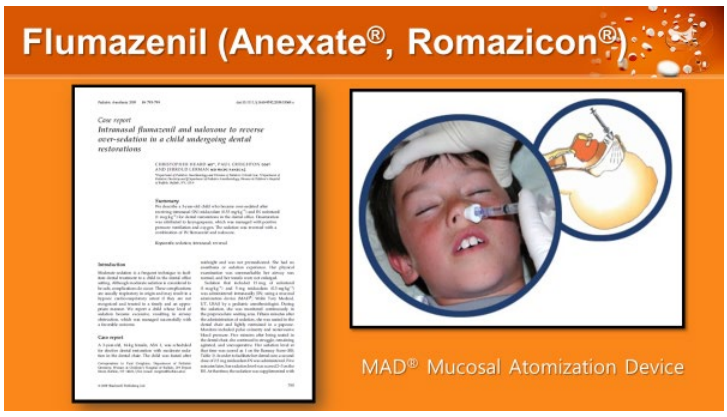
Jackson DL, Milgrom P, Heacox GA, Kharasch ED. Pharmacokinetics and clinical effects of multidose sublingual triazolam in healthy volunteers. J Clin Psychopharmacol. 2006 Feb;26(1):4-8.

Triazolam is increasing in popularity as a premedication prescribed by dentists to help their fearful and anxious patients tolerate the potentially aversive nature of some dental procedures. Recent anecdotal reports suggest that incremental sublingual dosing of triazolam may be an effective technique for producing conscious sedation in the dental setting. Although promising, no laboratory or clinical data have been available to evaluate the efficacy or safety of this approach. This study was designed to determine the pharmacokinetics and sedative effects of incremental sublingual dosing of triazolam (total, 1.0 mg) in healthy adults. Ten healthy adult volunteers received sublingual triazolam (0.25 mg) followed by additional doses after 60 (0.50 mg) and 90 (0.25 mg) minutes. Plasma triazolam concentrations, clinical effects (Observer's Assessment of Alertness/Sedation score), and processed electroencephalogram (bispectral index score) were measured intermittently for 3 hours. Plasma triazolam concentrations (mean +/- SD, 5.1 +/- 1.1 ng/mL) and drug effects (Observer's Assessment of Alertness/Sedation score, 2 +/- 1; and the bispectral index score, 62 +/- 16) were greatest in all subjects at the end of the 3-hour evaluation period. Eight of the subjects had Observer's Assessment of Alertness/Sedation scores consistent with the definition of deep sedation or general anesthesia (Observer's Assessment of Alertness/Sedation score, <3) at some of the later time points in the 180 minutes of data collection. In comparison, 4 of the subjects had bispectral index scores less than 60 during these later time points of data collection. Given the considerable intersubject variability in triazolam concentrations and effects, additional research is needed to assess this multidosing strategy before it can be endorsed as a useful and safe sedation technique for managing fearful and anxious patients in dental practice.

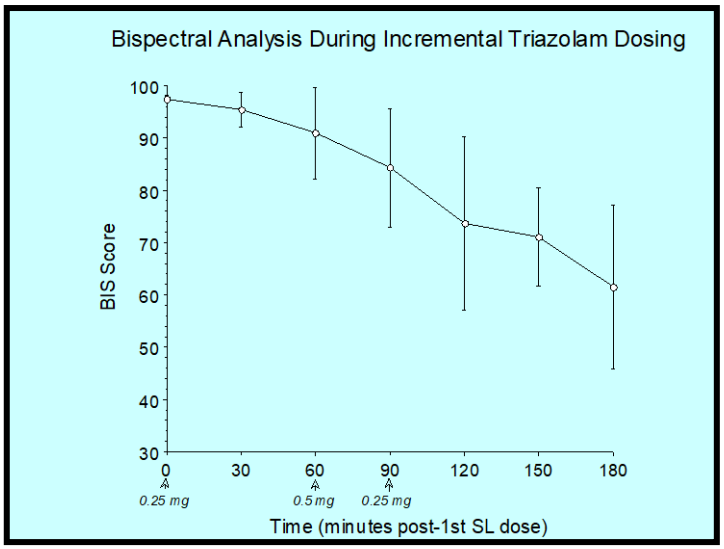


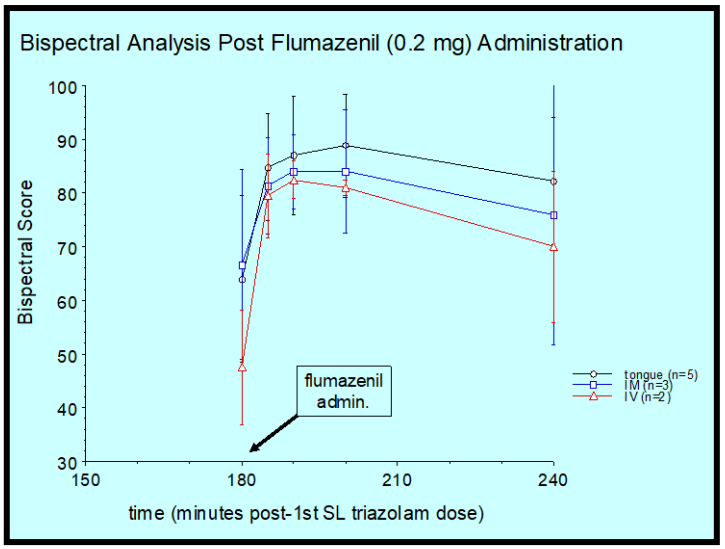
Other Notes and Questions to Ask:





Can we make sedation even safer?

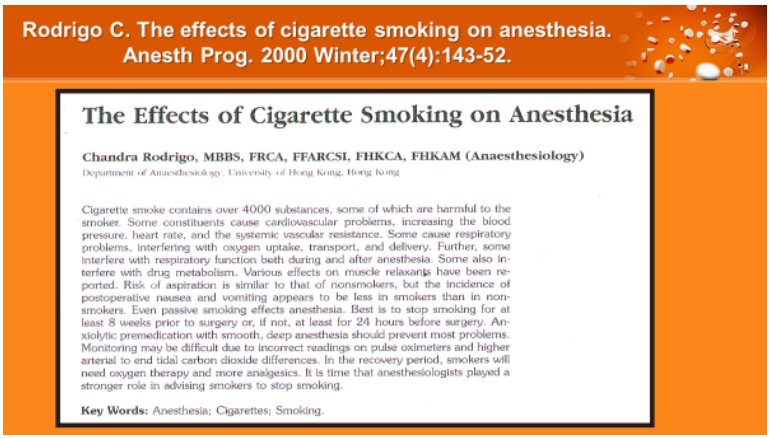




Jackson DL, Milgrom P, Heacox GA, Kharasch ED. Pharmacokinetics and clinical effects of multidose sublingual triazolam in healthy volunteers. J Clin Psychopharmacol 2006;26(1):4-8.

- Start with intrinsically safe medications that have the best evidence for use.
- Have an up to date medical emergency kit with all of the medications you need.
    - *Donaldson M, Goodchild JH. Making dentistry even safer: understanding the proper choice and use of emergency medications. Calif Dent Assoc J 2019;47(7):455-463.*
- Ensure that you and your staff are well-educated, trained and up to date with your certifications (BLS, HCPBLS, ILS, PALS, ACLS).
- Practice, practice, practice
- Monitoring will keep your patients safer too: Blood pressure, pulse, heart rate, oxygen saturation (pulse oximetry).
- Regardless, you need to know what to look for clinically, and how your monitoring equipment works.

Other Notes and Questions to Ask:


Rodrigo C. The effects of cigarette smoking on anesthesia. Anesth Prog. 2000 Winter;47(4):143-52.

The Effects of Cigarette Smoking on Anesthesia

Chandra Rodrigo, MBBS, FRCA, FFARCSI, FHKCA, FHKAM (Anaesthesiology)

Department of Anaesthesiology, University of Hong Kong, Hong Kong

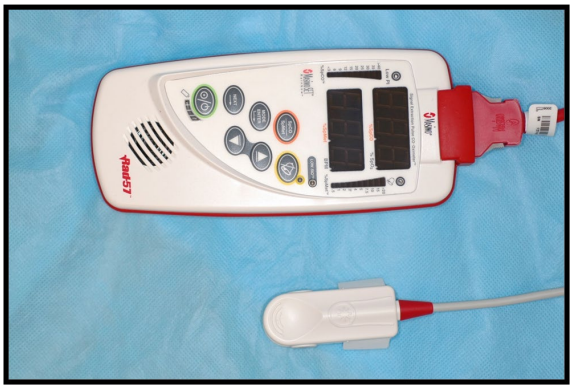
Cigarette smoke contains over 4000 substances, some of which are harmful to the smoker. Some constituents cause cardiovascular problems, increasing the blood pressure, heart rate, and the systemic vascular resistance. Some cause respiratory problems, interfering with oxygen uptake, transport, and delivery. Further, some interfere with respiratory function both during and after anesthesia. Some also interfere with drug metabolism. Various effects on muscle relaxants have been reported. Risk of aspiration is similar to that of nonsmokers, but the incidence of postoperative nausea and vomiting appears to be less in smokers than in nonsmokers. Even passive smoking effects anesthesia. Best is to stop smoking for at least 8 weeks prior to surgery or, if not, at least for 24 hours before surgery. Anxiolytic premedication with smooth, deep anesthesia should prevent most problems. Monitoring may be difficult due to incorrect readings on pulse oximeters and higher arterial to end tidal carbon dioxide differences. In the recovery period, smokers will need oxygen therapy and more analgesics. It is time that anesthesiologists played a stronger role in advising smokers to stop smoking.

Key Words: Anesthesia; Cigarettes; Smoking.

- In the blood, carbon monoxide combines with hemoglobin to form carboxyhemoglobin (COHb).
- In smokers, the amount of COHb in the blood ranges from 5-15%.
- In non-smokers the level is 0.3-1.6%.
- Affinity of carbon monoxide for hemoglobin is 200x that of oxygen.
- Causes a left shift in the oxyhemoglobin dissociation curve – more difficult for tissues to extract oxygen.
- Result is chronic tissue hypoxia – body compensates with more RBC:

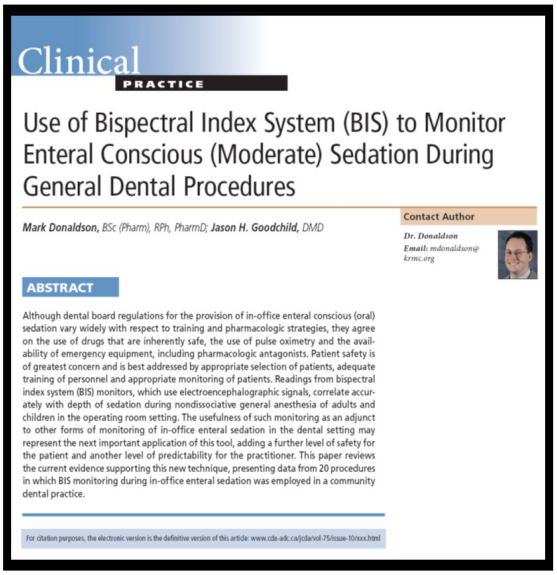
Net effect = increased oxygen availability at the expense of plasma viscosity

- Currently pulse oximeters can only measure oxyhemoglobin (HbO2) and deoxyhemoglobin (HHb); carboxyhemoglobin (COHb) is not being measured.
- The pulse oximeter will grossly overestimate the oxygen saturation in chronic smokers!
- Pulse oximeter shows the combination of HbO2 + COHb, not the individual components.
- Example: Pulse oximeter reads 99% on a chronic smoker. If they have 10% COHb then the true reading of HbO2 is 89%!!!



New, non-invasive co-pulse oximetry measures:

- Oxyhemoglobin
- Reduced Hemoglobin
- Methemoglobin
- Carboxyhemoglobin


Clinical PRACTICE

Use of Bispectral Index System (BIS) to Monitor Enteral Conscious (Moderate) Sedation During General Dental Procedures

Mark Donaldson, BSc (Pharm), RPh, PharmD; Jason H. Goodchild, DMD

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ABSTRACT

Although dental board regulations for the provision of in-office enteral conscious (oral) sedation vary widely with respect to training and pharmacologic strategies, they agree on the use of drugs that are inherently safe, the use of pulse oximetry and the availability of emergency equipment, including pharmacologic antagonists. Patient safety is of greatest concern and is best addressed by appropriate selection of patients, adequate training of personnel and appropriate monitoring of patients. Readings from bispectral index system (BIS) monitors, which use electroencephalographic signals, correlate accurately with depth of sedation during nondissociative general anesthesia of adults and children in the operating room setting. The usefulness of such monitoring as an adjunct to other forms of monitoring of in-office enteral sedation in the dental setting may represent the next important application of this tool, adding a further level of safety for the patient and another level of predictability for the practitioner. This paper reviews the current evidence supporting this new technique, presenting data from 20 procedures in which BIS monitoring during in-office enteral sedation was employed in a community dental practice.

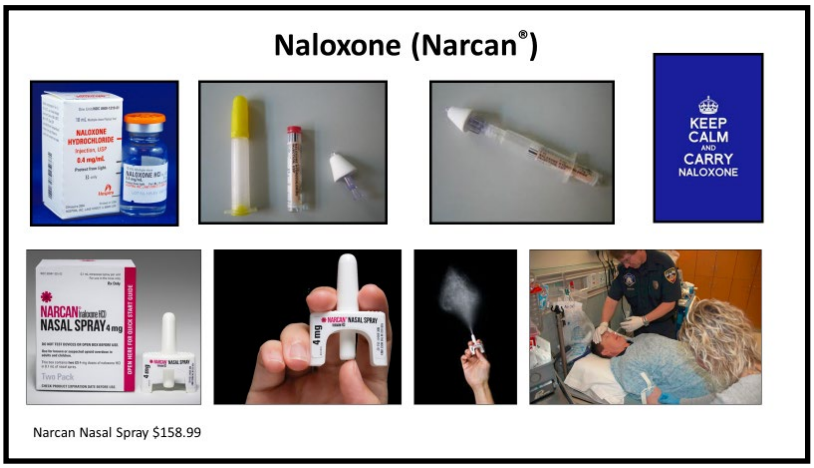
For citation purposes, the electronic version is the definitive version of this article: www.cda-adc.ca/jcda/vol-75/issue-10/xxx.html

Other Notes and Questions to Ask:

Naloxone (Narcan®) – Narcotic Antagonist

Indications:

- Reversal of narcotic depression including respiratory depression induced by opioids, (both natural and synthetic narcotics), propoxyphene, and narcotic-antagonist analgesics
- Diagnosis of suspected acute narcotic overdosage
- Not effective in counter-acting depression due to barbiturates, tranquilizers or other non- narcotic anesthetics or sedatives



Routes of Administration:

- IM, SC - when IV route not feasible; onset of action not as prompt as with IV and may be delayed in patients who are hypotensive and have impaired peripheral circulation
- IV direct - slowly over at least 1 minute

Rando J, et al. Intranasal naloxone administration by police first responders is associated with decreased opioid overdose deaths. Am J Emerg Med. 2015 Sep;33(9):1201-4.

Dosage, Adults:

- Known or suspected overdose: 0.4-2 mg IV; if no response, repeat 2-4 mg in minutes; in cases of large narcotic overdoses, or methadone, pentazocine, propoxyphene overdose, higher doses may be required; if no response after 10mg, reassess diagnosis; effective dose may repeat every 20-60 mins
- Post-operative respiratory depression: 0.1-0.2 mg at 2-3 minute intervals until desired response is obtained; repeat doses may be required at 1-2 hour intervals
- Partial reversal of opioid-associated respiratory depression in palliative patient: if respiratory rate < 6/minute, administer 0.1-0.2mg IV q2-3 minutes or 0.1-0.2mg SC q5-10minutes until respiratory rate > 10/minute. Continue to monitor respiratory rate q15minutes until no naloxone given x 1 hour.

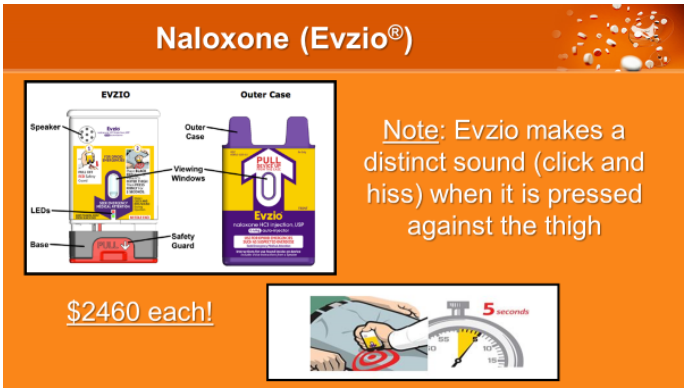
Dosage, Children:

Known or suspected overdose:

- Birth to 5 yrs or 20 kg: 0.1 mg/kg/dose; repeat at 2-3 minute intervals until desired response obtained
- > 5 yrs or > 20 kg: 2 mg; repeat as above

Post-operative respiratory depression: 0.005-0.01 mg/kg IV repeated if necessary at 2-3 minutes intervals

- Onset of effect: within 1-2 minutes following IV, within 2-5 minutes following IM or SC
- Duration of effect: 45 minutes to 3-4 hours
- Since duration of action of narcotic agent may exceed that of naloxone, repeated doses or administration of naloxone via IV infusion may be required



Edwards ET, et al. Comparative Usability Study of a Novel Auto-Injector and an Intranasal System for Naloxone Delivery. Pain Ther. 2015 Jun;4(1):89-105.

Other Notes and Questions to Ask:

Box 1. Opioid epidemic timeline.[3-7]

- Early 1990s: The American Pain Society suggests that there is a national epidemic of untreated pain and that pain should be classified as the fifth vital sign.
- 1995: New emphasis is placed on the aggressive treatment of pain.
- 1995: OxyContin is introduced to the US market.
- 1996: Prescriptions for opioids begin a sharp upsurge.
- 1999: The Veterans Health Administration launches the "Pain as the 5th Vital Sign" initiative.
- 2005: Hydrocodone becomes the most prescribed drug in the United States.
- 2010: Prescriptions for opioids peak.
- 2013: Drug overdose becomes the leading cause of accidental death in the United States.
- 2014: Hydrocodone combination products are reclassified as Schedule II by the US Drug Enforcement Administration.
- 2015: Heroin surpasses prescription drugs as the foremost cause of opiate overdose death.
- 2016: Synthetic opioids (eg, fentanyl and its analogs) become the foremost cause of opiate overdose death.
- 2017: The highest total number of drug overdose deaths is recorded.

Goodchild JH, Donaldson M, Malamed SF. Should naloxone be considered an essential medication in dental emergency kits? *Gen Dent*. 2020 May-Jun;68(3):14-17.

PHARMACOLOGY

Should naloxone be considered an essential medication in dental emergency kits?

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Although it is often described as a new emergency, the opioid epidemic in the United States is not a recent development. Almost 10 years ago, the Centers for Disease Control and Prevention (CDC) determined that overdose deaths from painkillers had more than tripled in a decade, rising to the level of an epidemic.[1] Regardless of its origin, the opioid epidemic in the United States continues to challenge patients, families, healthcare professionals, and prescribers alike. According to the CDC, 68,400 drug overdose deaths occurred during the 12-month period ending in October 2017—up from 61,062 in the previous 12-month period (a 12% increase).[2] The estimated number of lives lost every day to drug overdoses in the United States is 142.[2] Even more tragically, drug overdoses have become the leading cause of unintentional deaths in the United States, surpassing motor vehicle accidents.[3] Many elements have contributed to the rise in unintentional opioid overdose deaths. Box 1 illustrates the timeline for the opioid epidemic in the United States.[3-7]

Proposed solutions to the opioid epidemic

Several strategies are being implemented to limit the improper use, overprescribing, and wide availability of prescription opioids (Box 2).[4,8,9,10] Beginning in 2016, the CDC issued evidence-based practice recommendations for prescribing opioids to patients 18 years or older in primary care settings, focusing on chronic pain treatment.[8] To date, however, no CDC guidelines exist for prescribing opioids for acute pain. Similarly, the American Dental Association (ADA) does not have specific guidelines for prescribing opioids to treat acute dental pain.[11] In January 2018, the ADA's president encouraged prescribers to take 4 steps to help opioids from harming patients: consider nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line analgesics, order fewer pills when opioids are indicated, counsel patients on the risks and benefits of opioids, and learn to recognize when a patient may have a substance use disorder or be prone to addiction.[12]

On April 5, 2018, the US Surgeon General released an advisory on naloxone and opioid overdose, stating[10]:

For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life.

Naloxone: history and pharmacology

Naloxone was synthesized by Jack Fishman in 1961 during attempts to develop a treatment for constipation following chronic opioid use.[4,10] By replacing the methyl group with an allyl group from the nitrogen atom in oxymorphone, the strong competitive and specific antagonist naloxone was formed.[4] In 1971, the US Food and Drug Administration (FDA) approved naloxone under the brand name Narcan (Adapt Pharma) for use by intravenous and intramuscular injection with a recommended initial dose of 0.4 mg.[10] In 1983, the World Health Organization added naloxone to its Model List of Essential Medicines.[4,10]

Naloxone has no clinical effects when given alone, but when it is administered to patients previously given opioid agonists, it competes for available opioid-binding sites, ultimately displacing the agonist and reversing its effects.[13] It can be used clinically to reverse respiratory depression in patients who breathe inadequately after opioid overdose or opioid anesthesia. In addition, naloxone can reduce or reverse opioid-induced nausea and vomiting, pruritus, urinary retention, rigidity, and biliary spasm associated with numerous opioid therapies.[4]

The onset of intravenous naloxone action is rapid—less than 2 minutes—and its half-life and duration of effect are short (30 and 60 minutes, respectively).[10] Because respiratory depression from opioids may outlast the effects of naloxone, repeated doses, bolus injections, or even a continuous infusion of naloxone may be required to maintain

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Other Notes and Questions to Ask: