

What single drug is the most efficacious for oral conscious minimal sedation in adults?

Neil Gupta, Yi Jin, Yang Heon Kang, Karen Man, Sari Novack

A b s t r a c t

As many as 1 in 6 Canadians report fear and anxiety regarding dental treatment. One way of managing patients with mild to moderate levels of dental anxiety is through the use of oral conscious sedation. Unfortunately most systematic reviews on this subject have focused on children rather than adults. The objective of this literature review was therefore to evaluate the existing evidence for the use of oral medications for conscious minimal sedation in adults in order to determine which drug and dosage provides the most efficacious care. Trials were identified by computerized searches of the Cochrane Collaboration: Cochrane Reviews, MEDLINE, EMBASE up to January 2010. The Cochrane Reviews were hand searched and the reference lists were checked for additional studies. Nine studies were included with 614 subjects in total. Triazolam emerged as the drug most often compared. Eight studies measured sedation and patient co-operativity with Triazolam; six of these studies showed increased sedation with Triazolam measured against placebo; while two studies showed no significant difference. Overall quality of studies was found to be fair with participation selection, dosage, type of dental procedure intervention, and blinding often being the main problems as they may introduce both bias and confounding factors into the studies. Compared to placebo, six studies showed triazolam was an effective anxiolytic and amnestic agent. In conclusion, triazolam at a dosage of 0.25mg appears to be effective at producing anxiolysis, amnesia, and sedation. However, more studies (blinded parallel-RCT) that controlled for confounding variables before a clear recommendation on this subject can be made.

MeSH Key Words: *adult, dental, oral sedation, anxiolysis, diazepam (Valium®), lorazepam (Ativan®), triazolam (Halcion®), zaleplon (Sonata®), zipresidone (Zeldox®).*

According to Statistics Canada, approximately 40% of the Canadian population do not receive professional dental care (Statistics Canada, 1996). One reason patients may not seek dental care may be due to fear and anxiety regarding dental treatment, as these emotions have long been associated with dental visits (Malamed, 2006). Anxiety regar-

ding dental treatment is a common occurrence and refers to the anticipation of potential danger, including feelings of worry or dread (Maggirias, 2002; Armfield, 2006). In Canada, dental anxiety may affect up to 1 in 6 Canadians, as recent investigations regarding the prevalence of dental anxiety has been

reported to be in the range of 4.4% to 16.4% (Chanpong, 2005).

Dental patients experience varying levels of anxiety (Chanpong *et al*, 2005). The majority of patients experience low levels of anxiety and are able to manage this anxiety by various cognitive or behavioural techniques. However, a small, but considerable, portion of patients (9.8%) present with moderate levels of anxiety. Although these patients are sometimes able to accept minor dental treatment, they may have a higher level of anxiety for more complicated types of treatment. Interestingly, patients who self-identify as having low levels of anxiety for most dental procedures also report an increased demand for sedation services when specific dental treatments are of a more invasive nature, such as root canal therapy (Chanpong *et al*, 2005). This is important because when anxiety is present, cognitive and behavioural approaches may be insufficient for cooperation. Under these circumstances, a pharmacological approach is usually required (Dionne, 1998).

Although often ineffective in highly anxious patients (Dionne, 1998), sedation with oral medications can help the majority of patients with mild to moderate levels of dental anxiety. The use of oral sedatives in healthy adults has many advantages provided the proper dosage is prescribed and taken by the patient at an appropriate time. Additional benefits of oral sedatives are that they are inexpensive, painless, effective, and easy to administer (Donaldson, 2007). One group of oral medications that are particularly amenable to oral sedation are the benzodiazepines. The major inhibitory neurotransmitter in the central nervous system is gamma-aminobutyric acid (GABA). Benzodiazepines promote the binding of GABA to receptors on the GABA-complex, which is associated with chloride ion channels, thus reducing the excitability of the cell. They bind to benzodiazepine (BZ) receptors on the GABA-complex, located separately from the receptor for GABA. The activation the BZ receptors only potentiates the chloride

ion's response to GABA, and no effect is produced if GABA is not present. As a result, benzodiazepines have a wide margin of safety. The most commonly used benzodiazepine derivative is Diazepam (Valium), which has been available for 47 years. Other derivatives include Lorazepam (Ativan) and Triazolam (Halcion). Although this class of drugs is the ideal sedative agents of choice in dentistry, non-benzodiazepine GABA agonists such as the short-acting Zaleplon (Sonata) are also used in practice (Donaldson, 2007).

The goal of oral conscious sedation is to reduce anxiety and calm behaviour in order to assist in the completion of the dental treatment and provide a positive experience for the patient. Sedation is defined as the decreased level of activity and excitability of the patient, whereas hypnosis refers to drowsiness that may precipitate sleep or a state of unconsciousness. Patients who become unconscious using pharmacological methods may experience compromises in airway patency, respiratory function and cardiovascular function. Therefore maintaining a state of conscious sedation is desirable. Oral medications have the ability to produce varying levels of conscious sedation, which may be minimal or moderate. Minimal conscious sedation is a minimal depression of consciousness where the patient responds normally to verbal commands and physical stimulation. Moderate conscious sedation is a moderate depression of consciousness where the patient may not respond to verbal commands but will respond to physical stimulation. In minimal and moderate conscious sedation, the patient's airway and cardiovascular functions are typically normal, however, their cognition and coordination is moderately attenuated (RCDSO, 2009). The ideal orally administered sedatives for conscious sedation provides anxiolysis, sedation, amnesia of the dental procedure, and does not induce hypnosis. It should have the following properties: rapid absorption and onset of action, high therapeutic index, and rapid recovery

without prolonged psychomotor impairment (Loeffler, 1992).

The efficacy of various drugs for conscious sedation has been studied on numerous occasions. Unfortunately, most of these systematic reviews have focused on the behaviour management in children rather than adults (Matharu, 2009). Therefore, the objective of this literature review was to investigate the following question: What is the most efficacious drug for oral conscious minimal sedation in adults. This paper summarizes the strongest published literature regarding this matter.

Objective

To evaluate the relative efficacy of oral medications for conscious sedation in adult patients undergoing dental procedures. To meet this objective, we asked the following specific questions:

What evidence is available to direct the use of oral medications for conscious sedation in adult patients undergoing dental procedures?

Based on the available evidence, what is the most efficacious drug for oral conscious sedation in adults?

Methods

Electronic data bases are used to locate potentially relevant articles: Ovid MEDLINE (1950 to Jan Week 2 2010) EMBASE (1980 to 2010 Week 03) Cochrane Collaboration: Cochrane Reviews. Furthermore, hand search was conducted on Cochrane Collaboration: Cochrane Reviews. The Cochrane Reviews were handsearched and the reference lists were checked for additional studies.

Types of Studies to be Included

In accordance with our question, to be included in our review, the primary intervention had to be a parenteral (oral or sublingually delivered drug) rather than enteral (intravenous or intramuscular). We sought randomized controlled trials (RCTs) as the primary study type for inclusion in this review,

however, we did not specifically limit our search to any study design. One single-site prospective study was included. Studies on common drugs used for sedation in dentistry (Donaldson, 2007) were noted, but the search was not limited exclusively to these medications.

Types of Participants

Adult dental patients were the participants included in this review. All adults were included, regardless of baseline anxiety, although studies showing pre-existing anxiety would be ideal if present. Studies that focused exclusively on paediatric or geriatric patients were not included in this study.

Types of Outcome Measures

The major outcome studied in this review is the relative efficacy of oral sedatives to facilitate or promote anxiolysis in dental treatment, before and during treatment. Efficacy was defined as the ability to cause a reduction in anxiety (distressful feelings of worry or nervousness) and/or sedation (change in behaviour to a calm, cooperative state) and/or amnesia (suppression of recall of the dental treatment). Studies include those that showed physiological affects related to anxiolysis – including heart rate and blood pressure, as well as studies that used visual analog scales (VAS) to measure patient apprehension and relaxation.

Types of Interventions

Oral, conscious, anxiolytic pre-medication for dentistry available in North America for parenteral administration (orally or sublingually). Each trial needed to compare the anxiolytic effects of orally administered anxiolytic drugs using a control (placebo) or another commonly used anxiolytic drug in dental procedures. Sedative agents administered enterally (iv or im) were not included in this study.

Data Synthesis

Meta-analysis of collected data was not performed due to: heterogeneity of studies: insufficient numbers of similar studies with regard to agents, doses, techniques of procedure and assessment used; missing sample size for intervention vs. control; non-validated/standardized measures; gender mismatch; some studies only draw qualitative conclusion rather than providing numerical data values of statistical significance.

Elimination Process

Studies were rejected at the title, abstract, and full copy level by 3 people based on inclusion and exclusion criteria: Only oral conscious sedation (tablet, liquid, or sublingual), no i.v. or i.m.; only adults; only dental procedures; only drugs available in North America; exclusion of studies on paediatric or geriatric patient population.

Search Result

The electronic search was conducted in the following databases: Ovid MEDLINE (1950 to Jan Week 2 2010), EMBASE (1980 to 2010 Week 03), and the Cochrane Collaboration: Cochrane Reviews. Our initial search yielded 136 original results – 130 of which were eliminated at different stages of exclusion. The terms for our original search for Ovid MEDLINE and EMBASE were “diazepam (Valium®)”, “lorazepam (Ativan®)”, “triazolam (Halcion®)”, “zaleplon (Sonata®)”, “zipresidone (Zeldox®)”, “anxiolysis”, “oral sedation”, and “dental”. Our combination of search terms were (Triazolam OR Lorazepam OR Zaleplon OR Ziprisidone) AND Dental, Diazepam AND Dental AND Oral Sedation, and Diazepam AND Dental AND Anxiolysis. (For search strategy and results see figure 1).

Our search identified 136 results. 109 articles were eliminated at the title stage, seventeen at the abstract stage, and four at full text stage. (Appendix A) Ultimately, six relevant articles were found that fit our inclusion/exclusion criteria (Appendix B).

Hand searching of the Cochrane Reviews returned one relevant study that was used as background information and back searching. From this review, one randomized controlled trial was found that appeared to fit the inclusion criteria. Upon further investigation, this article was excluded at the full-text stage because it failed to measure any anxiolytic-related effects of Triazolam. However, hand-searching through this study revealed two Triazolam-related studies that were relevant and thereby included in this review.

One article included in the review reported on two separate studies. These two studies are therefore reported separately in the evidence table as Kaufmann 2002a and Kaufmann 2002b. In total, nine studies from eight articles (six from electronic database and two from hand searching) met the inclusion criteria for this review.

Study Rating

The level of evidence was assigned to each study based on Canadian Task Force on Preventive Health Care and Azarpazhooh *et al.* (2008) checklist to assess efficacy of oral sedation (Appendix C). The score out of 18 was converted to a score out of 10. Level A study indicates *good* evidence which received a score greater than or equal to 8.0. Level B study indicates *fair* evidence which received a score between 7.9 and 6.0. Level C study indicates *poor* evidence which received a score less than or equal to 5.9.

Types of Studies

This review includes seven double-blinded, randomized-control trials (one crossover and six parallel studies) one prospective study, and one dose response/comparative study.

Description of Studies

Dates of publications ranged from 1997-2005, with the majority of the publications in 2002 (37.5%). All studies were from the USA.

What single drug is the most efficacious for oral conscious minimal sedation in adults?

Authors	Sample Characteristics Surgery type and sample size	Intervention Study type, drug, dosages	Outcome Measures	Outcome Results				Conclusion & Level Evidence
				Anxiety	Amnesia	Sedation	Other	
Lieblich <i>et al.</i> , 2002	Impacted third molar extraction n= 12 (18-40y, 50-100kg)	Randomized, double blind, parallel-group study comparing 0.25mg triazolam (T) vs. placebo preoperatively.	1. Anxiety 2. Amnesia 3. Sedation (patient cooperation and relaxation) 4.CV response	Trend showing anxiety (STAI) for P at baseline (2 wks prior) < day of surgery, NSD. T at baseline (mean=39.0) > day of surgery (mean 35.0) p<0.05.	Self-reported recall of surgical procedure measured but not reported	T>P observer (VAS) for patient cooperation and relaxation .	HR: P > T upon arrival (mean=105 vs. 80, p<0.007) and in treatment room (mean=90 vs. 75, p<.048) Arrhythmia: Sinus tachycardia (HR>100) in all P patients vs. 1/3 rd of T patients (P=6/6, T=2/6; ventricular ectopy P=4/6 vs. T=1/6)	Conclusion: Triazolam 0.25 mg is appears to reduce pre-op anxiety better then placebo. Comment: Clinical effect represents approximately 5% change in anxiety from baseline Level of Evidence: I-A
Wilner <i>et al.</i> , 2002	Minor dental surgery n= 90 (18-50y, 50-100kg; Patients ±15% ideal BMI) (M>>>F)	RCT, double-blinded, parallel-group study comparing ziprasidone (Zi) 20 mg, diazepam (D) 10 mg and placebo (P).	1. Anxiety 2. Sedation 3. Adverse effects	Anxiety (VAS) D < Zi=P at 1hrs, but Zi>P=D at 3hrs (p ≤ 0.05).	N/A	Drowsiness (NSM) at 1- 1.5 hrs post-dose D > Zi=P (p<0.05).	No significant adverse effects.	Conclusion: Ziprasidone 20 mg produces similar anxiolytic effects at 3 hrs as Diazepam 10 mg at 1 hr, but with less sedation. Comment: Late onset of clinical effects for ziprasidone limits its clinical application. Level of Evidence: I-A
Ehrich <i>et al.</i> , 1997	Endodontic treatment n=79	RCT, double-blinded, parallel-group study comparing triazolam (T) 0.25mg, diazepam (D) 5mg and placebo (P)	1. Anxiety 2. Amnesia 3. Sedation based on patient's compliance 4. Cognitive function	Anxiety (VAS) for T < D < P (p < 0.05) from baseline self-report pre-treatment to intra-operative observation.	T > than D=P for treatment recall (p < 0.02) and memory cards (p < 0.03). For T patient intra-operative recall was 80% for LA, but only 50% for endow tax.	Patient intra-operative cooperation rated by observer T=D=P (NSM). 24 hours post-operative patient's rated T > D > P (p <0.05).	Psychomotor function (DSST) at 30, 60 and 90 minutes T < D < P (P < 0.05). Patient self reporting of pain (VAS) T=D=P.	Conclusion: Triazolam 0.25 mg appears to be a more effective anxiolytic agent and amnestic agent then Diazepam 5mg. Comment: Triazolam patients may fail to recall up to 50% of clinical events Level of Evidence: I-A

What single drug is the most efficacious for oral conscious minimal sedation in adults?

Authors	Sample Characteristics Surgery type and sample size	Intervention Study type, drug, dosages	Outcome Measures	Outcome Results				Conclusion & Level Evidence
				Anxiety	Amnesia	Sedation	Other	
Berthold <i>et al.</i> , 1997	Molar extraction surgery n=77 (19-31y, 118.7-180.5kg)	RCT, double-blind, study comparing 0.25mg oral triazolam (T _o), 0.25mg sublingual triazolam (T _{SL}) and placebo (P)	1. Anxiety 2. Amnesia 3. Patient evaluation of drug efficacy 4. Cognitive-psychomotor function 5. Serum drug concentration	Anxiety (VAS) T _{SL} < T _O < P (p<0.05)	NS amnesia to clinical events, but decreased recall (pictures cards) T _{SL} intra-operatively (p<0.05).	Patient evaluation of sedation rated T _{SL} > T _O > P (p<0.05). Observer evaluation of patient cooperation (NSM) T _{SL} =T _O =P.	NS Cognitive-psychomotor (DSST) impairment. Self-reported pain (VAS) T _{SL} < P (p<0.05). Mean plasma levels both during (NS) and after surgery (p<0.05) T _{SL} > T _O .	Conclusion: Sublingual Triazolam 0.25 mg appears to provide greater anxiolysis, amnesia and sedation Comment: 20% reduction in anxiety from baseline reported after 0.25mg sublingual Triazolam Level of Evidence: I-A
Kaufman <i>et al.</i> , 2002	Surgical removal of impacted third molars n=48	Study A: Dose response trial examining the difference between 50% N ₂ O/O ₂ and placebo (P), 0.125 mg triazolam (T), 0.25mg T, and 0.5mg T (n=12/group).	1. Anxiety 2. Amnesia 3. Patient cooperation 4. Cognitive-psychomotor function 5. Pain	Anxiety (Corah's dental scale) NSD all groups.	Decreased recall (clinical events) in half of the T=0.5mg patients (p<0.01). 80% decrease in recall (picture words) T=0.25mg and T=0.5mg (p < 0.01).	Observer rated efficacy of sedation (NSM) and patient cooperation (NSM) T0.25mg > P (P<0.05). Alertness (NSM) at 60 min P > T0.125mg > T0.25mg > T0.5mg (<0.05).	Cognitive-psychomotor skill (DSST) impairment T0.5mg > T0.25mg > T0.125mg > P (p < 0.001). Ambulatory function remained impaired 2hrs post-surgery T=0.5mg. Pain was 'slight' for all groups.	Conclusion: 50% N ₂ O + Triazolam 0.125 or 0.5 mg appears to show a dose-response reduction in alertness and impairment in cognitive-psychomotor function. Comment: 50% N ₂ O + 0.5mg triazolam appears to negatively influence patient cooperation. Level of Evidence: I-B
Kaufman <i>et al.</i> , 2002	Surgical removal of impacted third molars n=75	Study B: Comparison of 0.25 mg triazolam (T), 40% N ₂ O, 0.25mg T + N ₂ O, placebo (P) and i.v. diazepam (D) titrated to Verrill's sign	1. Anxiety 2. Sedation 3. Cognitive-psychomotor function 4. Pain	Reduction in anxiety (Corah's dental anxiety scale) compared to baseline for T + N ₂ O (p<0.05) and T alone (p< 0.01).	N/A	Similar rating of intra-operative observed sedation and patient cooperation across all interventions (NSM).	Cognitive-psychomotor skill (DSST) was significantly impaired with D more than the other interventions (p <0.01); i.v. D > T > T + N ₂ O > Placebo > N ₂ O. Only i.v. D significantly impaired alertness (p < 0.01) and ambulatory function (p	Conclusion: Triazolam 0.25 mg (±40% N ₂ O) appears to be an effective anxiolytic with less cognitive psychomotor impairment than i.v. Diazepam. Comment: 40% N ₂ O not required to achieve clinically effective anxiolysis if given 0.25mg Triazolam.

What single drug is the most efficacious for oral conscious minimal sedation in adults?

Authors	Sample Characteristics Surgery type and sample size	Intervention Study type, drug, dosages	Outcome Measures	Outcome Results				Conclusion & Level Evidence
				Anxiety	Amnesia	Sedation	Other	
		(drooping eyelids) (D) (n=15/group).					< 0.01). Pain was 'slight' for all groups.	Level of Evidence: I-B
Milgrom <i>et al.</i> , 1994	≥1 dental restoration n= 31 (21-58y, mean:75.7kg, SD=18.4kg) (F>M)	RCT, double-blind, parallel-group study examining triazolam (T) (n=15; 0.375 mg ≤80kg, or 0.50 mg >81 kg) vs. placebo (P) (n=16)	1. Anxiety 2. Amnesia 3. Sedation 4. Safety	Self-report anxiety (VAS) for T < P (p =0.04).	Recall (pictures and word pair recognition) showed T < P (p<0.05) and recall 24 hrs later (word-stem completion) T <P (p<0.05).	NSD between patient's pre- or post-op patient preference for drug intervention (p=0.32). Observer rating of patient behaviour (NSM) P > T for disruptive movements (p=0.02).	No adverse effects aside from sleepiness and mild headache were reported. No subjects dropped below 91% O ₂ saturation	Conclusion: Triazolam appears to impair memory, reduces anxiety and improves patient's in-treatment behaviour. Comment: Results showed that blinding was ineffective and may have affected the observation scores Level of Evidence: I-B
Ganzberg <i>et al.</i> , 2005	Extraction of impacted third molars n= 14 (18-40y)	Double-blinded, RCT, cross-over control comparing zaleplon (Z) 10mg with triazolam (T) 0.5mg	1. Anxiety 2. Amnesia 3. Sedation based on self-report comfort level 4. Recovery	T=Z NSD from baseline to pre- or post-operative.	Recall (picture scores) NSD T vs. Z (p<0.99). Most patients recalled some or all of the procedure.	T patients experienced a greater level of self-reported comfort (NSM) during the 2 nd surgery vs. Z patients (27.6 ±20.8 for the T vs. 49.6±22.1 for Z; p> 0.05).	Recovery time faster Z (64%) < T (24%). Less Z-treated patients expressed feelings of lingering sedative effects throughout the day (p<0.016).	Conclusion: Triazolam 0.5mg and Zaleplon 10mg have equivalent effects. Comment: Neither drug appeared to be effective at reducing intra-operative anxiety or amnesia from baseline. Level of Evidence: I-C
Quarnstrom <i>et al.</i> , 2004	Private dental practices for 270 appointments n= 188 (7-78y).	Prospective descriptive study reporting the clinical effects of triazolam (T). Mean dosage: 0.0063 + 0.0021mg/kg for a 70kg	1. Anxiety 2. Amnesia 3. Success initial T dose and proportion of patients required augment with N ₂ O/O ₂ .	Progressive decrease in anxiety (NSM) with largest decrease at 30 min following T administration	132 patients assessed using memory symbols reported some level of amnesia. 30% of patients remembered the LA injection 60 min following T administration.	Supplemental dosage (1/2 initial T dose) was required in 10% of patients after 30 min. A further 19% of patients required N ₂ O/O ₂ mixtures during the procedure. Overall success (NSM) achieved in	No changes in CV parameters detected, except slight trend in high pulse rate at 60 min corresponding with admin of LA.	Conclusion: 98.4% success using a weight based dosage formula for oral triazolam Comment: Measures not validated. Observers not calibrated; Large age range but no sub-analyses provided among descriptives

What single drug is the most efficacious for oral conscious minimal sedation in adults?

Authors	Sample Characteristics	Intervention	Outcome Measures	Outcome Results				Conclusion & Level Evidence
	Surgery type and sample size	Study type, drug, dosages		Anxiety	Amnesia	Sedation	Other	
		adult 0.153 mg (dose range 0.125-1.25mg)	4. CV response			98.4% of patients.		Level of Evidence: III-C

**For numerical results, mean with standard deviation and associated p-values from the inferential statistical test are described where reported or could be extrapolated from graphical figures. Absence of test and significance values from table indicates a failure to report these details within the reviewed publication.

Legend: BP: Blood pressure; CV: Cardiovascular; DSST: Digital Substitution Symbol Test; HR: Heart Rate; HVAS: Horizontal Visual Analogue Scale; LA: Local anaesthetic; N2O/O2: Nitrous oxide/ oxygen ; N2O: Nitrous oxide; NSD: No Significant Difference; NSM: Non-standardized measure (no empirical evidence of validity or reliability); OCS: Oral Conscious Sedation ; RCT: Randomized Controlled Trial; STAI: Spielberger State-Trial Anxiety Inventory; VAS: Visual Analogue Scale; wrt: with respect to

Age of participants ranged from 7-78 years of age. The mean number of participants was 68.2, with 614 in total.

Participant Selection

Out of nine studies, eight studies selected participants 18 years and older. Another study used a sample of participants that ranged from 7-78 years old. Three studies used anxiety for dental treatment as inclusion criteria, however the remaining studies did not recruit participants based on dental anxiety. Four studies excluded patients, who were pregnant or lactating, had known drug allergies, psychological or neurological disorders, were smokers, or had history of drug or alcohol abuse, mental disability, glaucoma, or were on benzodiazepines, opioids, or antidepressants. The remaining five did not mention exclusion criteria.

Type of Intervention

A wide variety of drugs, either singly or in combination, were used. Delivery was orally or sublingually.

Dosage

Of the eight studies that used Triazolam, seven used 0.25mg as the standard dose of measure, and two studies used 0.5mg. Two studies used derived formulas to calculate the dose of Triazolam, one of which used 0.375mg for people who weight under or equal to 80kg, and 0.5mg for people who weighed over 80kg, and the other of which used a range of Triazolam from 0.125-1.25mg according to the formula $0.0063 + 0.0021\text{mg/kg}$.

Two studies used Diazepam, one of which used 5mg and one of which used 10mg as the standard dose.

The only study that looked at Ziprasidone used 20mg, and the only study that looked at Zaleplon used 10mg as the standard dose.

Three out of the nine studies provided an explanation for the rationale behind drug dosage either based on evidence from previous

studies or based on an attempt to limit weight dependent affects.

Board Approval and Informed Consent

Of the nine studies included, only six studies stated that they had sought informed consent, and only four had gained board approval. Two studies did not indicate any informed consent or board approval. Funding for all researchers was not stated.

Dental Procedure Intervention

A wide variety of surgical procedures were documented, with four studies examining extraction, four of which were impacted third molars and one of which were any molars. One study examined endodontic treatment, one examined more than one dental restoration, one examined minor dental surgery, and one examined general dental procedures.

Blinding

Seven out of nine studies utilized blinding, of which only two studies indicated blinding of both the observer and the patient. Three studies showed blinding for patient only, and two studies stated that they performed double blind but did not state who was blinded or the method of blinding.

Methods of Statistical Analysis

All studies (nine) except for one reported significant differences with p-values of $p < 0.05$. No studies accounted for beta error.

Dropout and Follow-up

Only three studies reported drop out, and out of the three only two accounted for the drop out. The remaining six studies did not indicate drop out in their reports.

Results

Triazolam appears to reduce anxiety and serves an effective anxiolytic drug compared to placebo. Triazolam also appears to provide greater amnesia versus both diazepam and

placebo, both on memory recall of picture cards, as well as clinical events. It appears to increase sedative effects and cause psychomotor impairment. The exception to these findings was one study comparing Triazolam and Zaleplon (Ganzberg), of which neither drug appeared to be effective at reducing intra-operative anxiety or causing amnesia when compared to baseline.

Ziprasidone had lower sedative effects than Diazepam, but equal anxiolytic effect as Diazepam three hours post-drug administration.

Anxiety

Anxiety was measured in all studies included (nine), four studies measured anxiety using the VAS scale, two studies used the Corah's dental scale, one used the STATI scale one used the analogue scale (0-6), and one used the a non-validated scale (0-42).

Decrease in anxiety with Triazolam use was shown in six studies, five of which compared Triazolam to placebo and one compared against Diazepam. One study demonstrated the need for nitrous oxide supplementation for effective sedation. Another study showed that sublingual Triazolam induced greater decrease in anxiety than oral Triazolam, with both greater than placebo. Contrarily, two studies showed no significant difference of anxiolytic effects of Triazolam, one compared to placebo and one to Zaleplon and placebo. Lastly, one study showed that Diazepam had a greater anxiolytic effects than Ziprasidone at 1hr post-administration, and Ziprasidone greater than Diazepam at three hrs post-administration, both significantly greater effects compared to placebo.

Amnesia

Amnesia was measured in seven of the studies included, of which four studies were measured with picture or word memory recall, and six studies with clinical recall by self-report.

Six studies showed an increase in amnesia with Triazolam, three of which clinical event

recall was decreased compared to placebo, one compared to Diazepam. Four showed increase in amnesia affects of decreased image recall compared to placebo (one which showed only with sublingually administered Triazolam), and one compared to Diazepam. One study showed no difference in clinical recall compared to placebo and one studied measured amnesia but had no further report on the subject. Lastly, one study showed no significant difference of amnesia affects with Triazolam or Zaleplon compared to placebo and each other.

Sedation

Sedation was measured in all of the studies included (nine), six of which measured patient cooperation by an observer, five of which measured self-reported cooperation. Eight studies used non-standard measures and only one used a VAS scale.

Patient self-rating showed increased sedation and patient cooperation with Triazolam in five studies, all of which were measured against placebo. In addition, of these studies, one showed greater effect of triazolam compared to diazepam, one showed greater effect using sublingual triazolam over oral administration of triazolam, and one showed greater effect of triazolam compared to Zaleplon. Diazepam was shown to have greater sedative effects than Ziprasidone.

Observer ratings showed increased sedation and patient cooperation with Triazolam in 4 studies, all of which were measured against placebo. One study showed sedative effectiveness of Triazolam used in conjunction with nitrous supplement, while two studies showed no significant difference between Triazolam (sublingual and oral administration) compared to placebo, or between Triazolam and Diazepam and placebo.

Others

Psychomotor cognitive function impairment was also measured using the DSST scale

in four studies. Three studies showed an increased in impairment with Triazolam compared to placebo. Two other studies had opposite results with one showing Triazolam impairment greater than Diazepam and the other study vice-versa.

As well, three studies showed no significant difference in self-reported pain with Triazolam or Diazepam compared to placebo and each other, while one study reported decreased self-reported pain with sublingual Triazolam use.

Furthermore, of the two studies that examined heart rate, one study reported increased heart rate and tachycardia in placebo patients compared to those given Triazolam, and one study reported of significant change in cardiovascular rates.

Adverse Effects

Of the five studies that examined adverse effects, varying results were reported, ranging from no adverse effects (two studies), mild headaches and sleepiness (one study), lingering sedative effects reduced by replacement with Zaleplon (one study) and ambulatory function impairment two hrs post-surgery (one study).

Discussion

Our literature search revealed few studies addressing the use of oral medications for conscious sedation in adults. Although we consider a randomized controlled trial the best study design to answer our question, we chose to include one study reported as a prospective trial. We chose to include this study for two reasons. First, by including this study, to the best of our knowledge it allowed us to represent the entire range of literature available that has been published on this subject. Secondly, this study used a unique dosing formula, and a critique of this paper is relevant to the future of investigation in this subject area. The most recent date of publication was 2005, five years before this review (2010). This concerns the authors, as this suggests that

follow-up studies are not occurring. The lack of ongoing research in this area prevents firm conclusions to guide clinical practice in terms of what is the most effective form of oral sedative. Dental anxiety however, is still an issue faced by clinicians every day in practice. The fact that all of the publications searched regarding this topic were published in the USA may serve as both a language and location bias. The age range covered is acceptable for adult treatments, however, it is discerning to see that only 614 total participants out of 6 studies were examined throughout the span of eight years.

Only six of nine studies sought informed consent, five of which had gained approval from a university ethics board. It may be that these additional studies did not undergo any ethics peer process, although this could also simply be due to a failure to report ethics approval. We base this second postulate on our impression that reporting of methodology and results was generally poor amongst all studies. Regardless, ethical issues should always precede scientific research, to protect the safety and well being of study participants, and it would have been more reassuring to know that all study designs had undergone an ethics process.

Participant Selection

Participant selection criteria and eligibility widely ranged between the studies, which introduces the potential for bias and confounders. For example, four studies examined healthy patients regardless of other factors, but did not indicate history of past medications that could cause possible drug interactions, or possible past history of benzodiazepines use for other illnesses that could decrease sensitivity to oral sedative benzodiazepines during dental treatment. Also, there was often a large discrepancy in the number of female and male participants, not accounted for in the studies. On the other hand, it is encouraging to see that four other studies

did state their exclusion factors clearly to ensure that the effect found in their studies can in fact be mainly contributed to the intervention in question.

Type of Intervention

A wide variety of drugs were used in these nine studies, ranging from three types of benzodiazepines to two types of non-benzodiazepines. It is hard to examine the full effect of any one specific drug because of this large variation, particularly since some studies only compared against another drug and some studies only compared against a placebo.

Dosage

Dosage was a main concerning factor in examining the effectiveness of the drugs used. There was a broad range of dosage measured, especially when comparing two drugs with each other. For example, one study compared 0.5mg of Triazolam to 10mg of Zaleplon. With 1 dosage being 20 times as much as the other, it is difficult to differentiate whether clinical effects examined, if any, was due to the drug alone, or because of differentiating doses.

Dental Procedure Intervention

As a wide range of procedures were examined, it is difficult to make conclusions and apply clinical use of the effects of a particular drug in question to a specific procedure. Error is introduced into these studies because for example, anxiety levels of a patient who is undergoing normal, minor dental treatment (ex. small cavity filling) to that of surgery (ex. lengthy tooth extraction) varies greatly. Thereby a reduction in anxiety of the two cannot be validity comparable with each other.

Blinding

Most of the studies (seven out of nine) claimed that double blinding was performed. However, rarely was the method of blinding clearly stated, nor who was being blinded.

Only two studies indicated that both the dispenser and patient were blinded. This will inevitably introduce bias into the data as the placebo effect has been proven to be effective in a board range of studies and this makes it more difficult to attribute findings, even if significant, to the drug intervention independent of the placebo effect.

Methods of Statistical Analysis

All studies, except for one, reported significant findings with p-values of $p < 0.05$. This is encouraging to see, as it can be safely concluded that should differences fall within this range, they can be statistically accepted as truly significant. However, no studies accounted for beta errors when no significant findings were found. This suggests that the studies were mainly concerned with positive findings, and that possible statistically insignificant differences were overlooked. This makes it is difficult to state whether the drug interventions really caused a difference at all compared to control studies.

Dropout and Follow-up

Very few studies (2) accounted for the loss of follow-up. This suggests that there might be possible inclinations towards positive findings, and it was difficult to know whether this claim of loss to follow-up was due to patient drop out, complications or side effects, or simply an exclusion of data that did not fit well into statistically significant calculations.

Applicability

The single study that examined the effectiveness of Zaleplon did not show any positive effects over benzodiazepines, and is not suggested for current clinical use. Although the single study with Ziprasidone did show greater effects over Diazepam for longer onset, further studies of both drugs should be made to test their relative effectiveness, both against another drug, or no drug at all. Oral Triazolam appears to reduce anxiety, serve as

an affective amnesic drug, increase sedation, as well as increase psychomotor function impairment. Clinically, these findings suggest that the use of Triazolam over other oral sedatives will help increase patient cooperation in the dental clinic. Furthermore, Triazolam also appears to be the most researched drug out of those available for oral sedation in dentistry. However, it is suggested that use should be according to an “absolute need” basis, as the collective data of these studies are only suggestive. Strong evidence is still lacking in terms of actual clinical credibility, and many bias and confounding factors have yet to be accounted for. Furthermore, the possible adverse effects of oral Triazolam are still not well known, if reported at all.

Assessment Scales for Measuring Outcome

Recognized scales that have been proven to be valid tests in measuring anxiety, sedation, amnesia, and psychomotor cognitive function impairment have been shown in Appendix D. Importance of recognized validity testing is essential to have a standard comparison between studies on these reported factors.

Anxiety

Contradictory outcomes have been shown for the use of Triazolam in anxiolysis. However, more positive outcomes have been indicated, and the two studies that did not report any positive findings also did not show any contra-indications, but merely stated that there were no significant differences compared to no drug at all. This suggests that even if Triazolam was used, the benefits could possibly outweigh the risks in anxiety reduction. The study comparing Diazepam with Ziprasidone, showed Ziprasidone anxiolysis at three hours post-dose which questions its application in dentistry.

Amnesia

The measures of amnesia were relatively consistent in all nine studies, that being either

picture or word memory recall. Of the nine studies, six also had self-reported recall of clinical procedures, which is a less accurate measure of amnesia, since individual memory ability is hard to control and standardize for. Nonetheless, six out of nine studies showed Triazolam to be effective in the impairing memory recall, both over Diazepam and placebo. These findings can be applied clinically to help improve patient cooperation during procedures, and help create a positive experiment that encourages future treatment if necessary. No significant differences were found for Zaleplon, and it is not effective at reducing recall.

Sedation

The effects of sedation are poorly researched. All studies, except one, used non-standard measures to assess levels of sedation, and it was mainly either self-reported or assessed by an observer, which can lead to patient variation. As well observer bias is a problem with self-reported sedation, especially since only two papers stated that observer blinding was performed. Nonetheless, overall, five studies showed increased sedation and patient cooperation with Triazolam use. The degree difference contributed to by any placebo effect was not accounted for.

Others

Psychomotor cognitive function impairment showed contracting results, which reflects that the use of Triazolam for impairment is still debatable. Three studies showed no difference in self-reported pain upon dosing with Triazolam or Diazepam compared to placebo. Thus it should not be used as an analgesic during dental treatment.

Adverse Effects

Only five studies examined adverse effects, mainly short-term, with varying results reported. There was a broad range of observations, from no effect to functional

impairment. This strongly indicates that further observations should be made with the use of these oral sedatives, in short term and especially in long-term studies to ensure overall safety.

Confounding Factors

No studies accounted or controlled for confounding factors. Differences in dosage, weight, and gender, are all factors that may present misleading results to seemingly relevant findings.

Conclusion

In summary, the results of this literature review suggest that the evidence available to direct the use of oral conscious sedation for dental procedures is level C (fair) evidence. Based on the available evidence, Triazolam was the most reported drug, and also appears to be the most efficacious drug for oral conscious minimal sedation in adults. The reviewed studies suggest that a dosage of 0.25mg is the most effective in producing anxiolysis, amnesia, and sedation. However, caution is advised in applying this finding to clinical practice. In addition to variable study results, there was also a large amount of individual variation among patients that were not well-reported in the studies. Further research should be conducted in order to draw conclusions for the usage of Ziprasidone and Zaleplon in clinical practice, and additional evidence gathered on appropriate Triazolam dosing for desired effects. At this time, a meta-analysis of the studies we reviewed is not recommended due to the heterogeneity of the study findings, individual variation in the sedative effects, poor reporting, and use of non-validated outcome measures. Future work

in this area would benefit from consideration of methods of randomization, board approval and informed consent, participation selection, dosage, dental procedure intervention, allocation concealment, and the use of standardized assessment scales for

measuring outcome. There also needs to be improvements in reporting variables such as gender, weight, time of onset, drop outs, and follow-up. In regards to blinding, the operator, patient, and assessor should all be blinded to the sedative agent.

Acknowledgement: *The authors thank Dr. Carilynne Yarascavitch for her invaluable guidance and ideas.
The authors have declared no financial interests.*

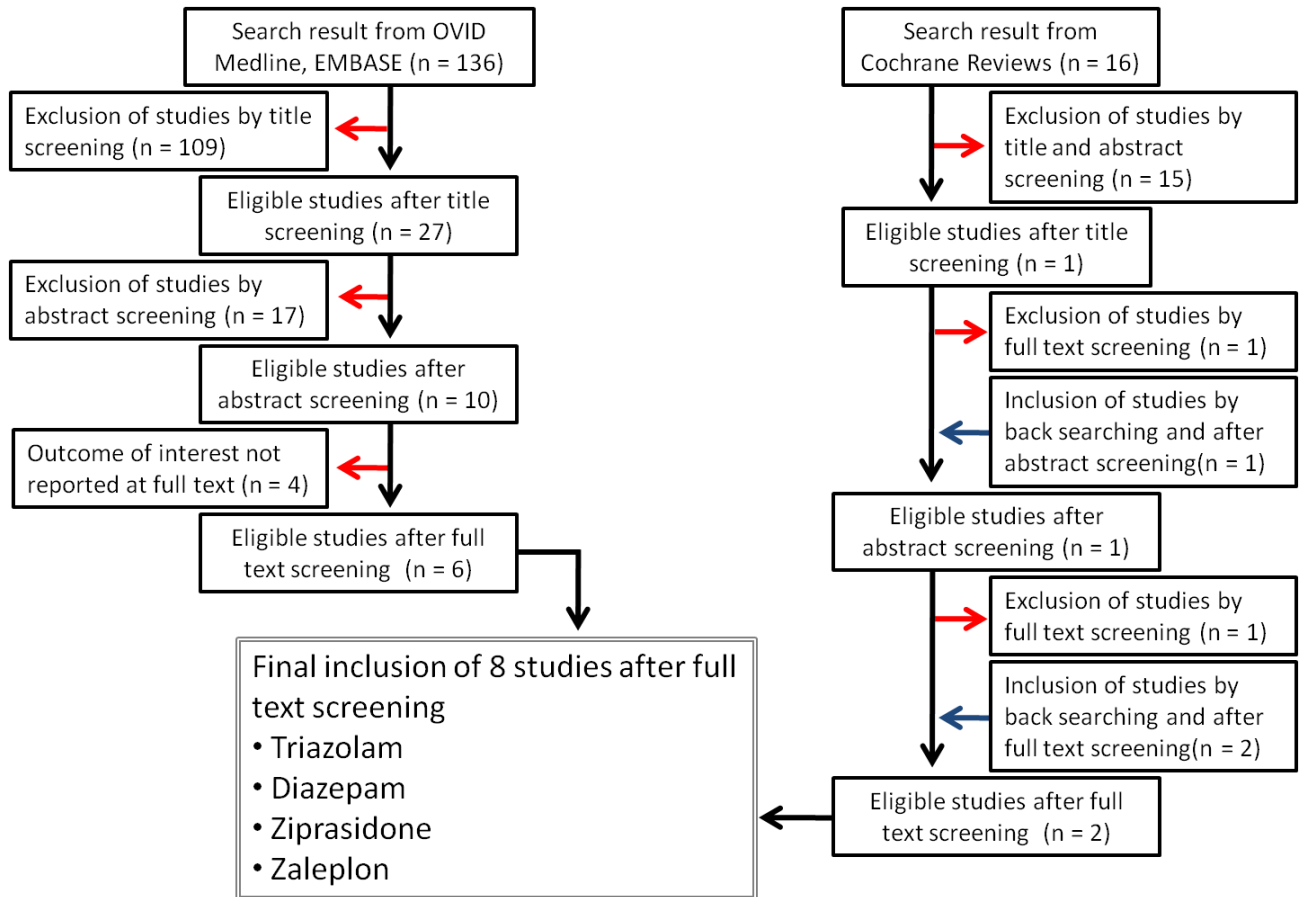
References

1. Armfield JM, Spencer AJ, Stewart JF. Dental fear in Australia: who's afraid of the dentist? *Aust Dent J* 2006;51(1):78-85.
2. Azarpazhooh A, Mayhall JT, Leake JL. Introducing dental students to evidence-based decisions in dental care. *J Dent Educ.* 2008 Jan;72(1):87-109.
3. Berthold CW, Dionne RA, Corey SE. Comparison of sublingually and orally administered triazolam for premedication before oral surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endo* 1997;84:119-24.
4. Chanpong B, Haas DA, Locker D. Need and demand for sedation or general anaesthesia in dentistry: a national survey of the Canadian population. *Anesth Prog Spring* 2005;52(1):3-11.
5. Dionne RA, Yagiela JA, Coté CJ, Donaldson M, Edwards M, Greenblatt DJ, Haas D
6. Balancing efficacy and safety in the use of oral sedation in dental outpatients. *J Am Dent Assoc* 2006;137:502-13.
7. Donaldson M, Gizzarelli G, Chanpong B. Oral sedation: a primer on anxiolysis for the adult patient. *Anesth Prog* 2007;54:118-29.
8. Ehrlich DG, Lundgren JP, Dionne RA, Nicoll BK, Nutter JW. Comparison of triazolam, diazepam, and placebo as outpatient oral premedication for endodontic patients. *J Endod* 1997;23:181-4
9. Ganzberg SI, Dietrich T, Valerin M, Beck FM. Zaleplon (Sonata) oral sedation for outpatient third molar extraction surgery. *Anesth Progr* 2005;52(4):28-31.
10. Kaufman E, Hargreaves KM, Dionne RA. Comparison of oral triazolam and nitrous oxide with placebo and intravenous diazepam for outpatient premedication. *Oral Surg* 1993;75:156-64.
11. The Canadian Task Force on Preventive Health Care, Levels of Evidence- Research Design Rating Table, Available from <http://www.ctfphc.org/ctfphc&methods.htm>
12. Liebllich SE, Horsell B. Attenuation of anxiety in ambulatory oral surgery patients with oral triazolam. *Oral maxillofac Surg* 1991;49:792-6.

What single drug is the most efficacious for oral conscious minimal sedation in adults?

13. Locker D, Liddell A, Burman D. Dental fear and anxiety in an older adult population. *Community Dent Oral Epidemiol* 1991;19(2):120–4.
14. Loeffler P. Oral Benzodiazepines and Conscious Sedation: A Review. *J Oral Maxillofac Surg* 1992;50:989-97.
15. Maggiri J, Locker D. Psychological factors and perceptions of pain associated with dental treatment. *Community Dent Oral Epidemiol* 2006;30(2):151-9.
16. Malamed SF. Sedation and safety: 36 years of perspective. *Alpha Omegan* 2006;99(2):70–4.
17. Milgrom P, Quarnstrom FC, Longley A, Libed E. The efficacy and memory effects of oral triazolam premedication in highly anxious dental patients. *Anesth Prog* 1994;41(3):70-6.
18. Quarnstrom FW, Donaldson M. Triazolam use in the dental setting: a report of 270 uses over 15 years. *Gen Dent* 2004;52(6):496-501.
19. Royal College of Dental Surgeons of Ontario. Guidelines: of sedation and general anaesthesia in dental practice. Available from http://www.rcdso.org/sedationAnaesthesia_pdf/Guidelines_sedation_06_09.pdf. Accessed January 20, 2010.
20. Statistics Canada National population health survey. Available from <http://www.phac-aspc.gc.ca/ph-sp/phdd/pdf/report/stats/eng15-29.pdf>. Accessed January 20, 2010.
21. Wilner KD, Anziano RJ, Johnson AC, Miceli JJ, Fricke JR, Titus CK. The anxiolytic effect of the novel antipsychotic ziprasidone compared with diazepam in subjects anxious before dental surgery. *J Clin Psychopharmacol* 2002;22(2): 206-10.

Appendix A: Flow Chart



What single drug is the most efficacious for oral conscious minimal sedation in adults?

Appendix B: Articles Included for Review

1. Triazolam use in the dental setting: A report of 270 uses over 15 years
2. Comparison of Triazolam, Diazepam, and Placebo as Outpatient Oral Premedication for Endodontic Patients
3. Oral Sedation: A Primer on Anxiolysis for the Adult Patient
4. The Anxiolytic Effect of the Novel Antipsychotic Ziprasidone Compared With Diazepam in Subjects Anxious Before Dental Surgery
5. Balancing efficacy and safety in the use of oral sedation in dental outpatients
6. Zaleplon (Sonata) Oral Sedation for Outpatient Third Molar Extraction Surgery
7. Triazolam use in the dental setting: A report of 270 uses over 15 years
8. Pharmacokinetics and Clinical Effects of Multidose Sublingual Triazolam in Healthy Volunteers
9. Comparison of sublingually and orally administered triazolam for premedication before oral surgery
10. The Efficacy and Memory Effects of Oral Triazolam Premedication in Highly Anxious Dental Patients

Appendix C: Levels of Evidence - Research Design Rating

I	Evidence from randomized controlled trial(s)
II-1	Evidence from controlled trial(s) without randomization
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Adapted from The Canadian Task Force on Preventive Health Care

Checklist for assessing evidence for relevant articles

1. Was the study ethical?
2. Was a strong design used to assess efficacy?
3. Were interventions validly and reliably measured?
4. Were outcomes validly and reliably measured?
5. Was the sampling frame complete, or were all members of the cohort entered at the beginning?
6. Was the response rate 80% or higher? Was loss to follow-up low – less than 20%?
7. Are the age/sex distributions similar?
8. Is there evidence of no systematic differences in prevalence or trends in disease between this group and your patients?
9. Did the survey use valid measures of success/failure?
10. Was there a control group?
11. Were all patients who entered the trial properly accounted for and attributed at its conclusions?
12. Was the study longer than 5 years?
13. Were patients, health workers, and study personnel “blind” to treatment?
14. Was care received outside the study identified and controlled for?
15. Were all clinically important outcomes considered?
16. Are the likely benefits of treatment worth the potential harms and costs?

Adapted from Azarpazhooh *et al.* (2008)

Appendix D: Validated Scales of Outcome Measurements

- 1) **Horizontal visual analogue scale (HVAS)**- Wilson J. A preliminary evaluation of analogue scoring in sedation. *Br J Anaesth* 1969; 41:792-3.
 - Used by Berthold (1997), Ehrich (1997)
- 2) **Vertical visual analogue scale (VVAS):**
 - a. Gracely RH, Dubner R. Reliability of validity of verbal descriptor scales of painfulness. *Pain* 1987; 29:175-85
 - b. Walther DJ, Gracely RH. Ratio scales of pleasantness and unpleasantness affective descriptors. *Am Pain Soc Abstra* 1986;6,34.
 - Used in Berthold (1997), Kaufman (2002), Lieblich (2002), Ehrich (1997), Ganzberg (2005)
- 3) **Digital Symbol Substitution Test (DSST)**- Wechsler D. Manual for the Wechsler Adult Intelligence Scale. New York: The Psychological Corporation; 1955. p.110.
 - Used in Berthold (1997), Kaufman (2002), Ehrich (1997)
- 4) **Spielberger State-Trait Anxiety Inventory (STAI)**- Spielberger CD, Gorsuch RL, Lushene RE: STAI Manual for the State-Trait Anxiety Inventory. Palo Alto, CA, Consulting Psychologist Press, 1970.
 - Used in Lieblich (2002)
- 5) **Cognitive Self report of anxiety (0-42)**- Corah NL, Zielezny, MA, O'Shea RA, Thines, RM, Terrance J, Mendola P: Development of an interval scale of anxiety response. *Anesth Prog* 1986; 33: 220-224
 - Used in Milgrom (1994)
- 6) **Corah's Dental Anxiety Scale**- Corah NL, Gale EN, Illig SJ. Assessment of a dental anxiety scale. *J Am Dent Assoc* 1978; 97: 816-9.
 - Used in Kaufman (2002)
- 7) **Corah's Interval Scale of anxiety response**- Mendola P, O'Shea RM, Zielezny MA, Thines TJ, Corah NL. Validity and reliability of the interval scale of anxiety response. *Anaesth* 1984; 56:179-85.
 - Used in Kaufman (2002)