Application to Add Midazolam to the Model List of Essential Medicines

Prepared by:

Enno D. Wildschut, MD, PhD Pediatric intensivist
Nienke J. Vet, MD, pediatric resident & PhD candidate
Saskia N. de Wildt, MD, PhD Pediatric intensivist, Clinical Pharmacologist

Erasmus MC Sophia Children's Hospital
Department of Pediatric Surgery & Intensive Care
Dr Molewaterplein 60
3015 GJ Rotterdam
The Netherlands

December 2010

1. Summary statement of the proposal for inclusion

The benzodiazepine midazolam has proven sedative, anxiolytic and amnesic properties. It is extensively used for premedication and procedural sedation in both adults and children.

In comparison to other benzodiazepine and non-benzodiazepine drugs, midazolam is equally or more effective for premedication/preoperative sedation. No evidence exists that premedication with midazolam prolongs discharge time from hospital. Its efficacy and safety have been extensively studied in both adults and children. This contrasts its comparator drug, diazepam for which data in children and elderly are scarce or lacking.
Midazolam is also effective for procedural sedation as a single drug or in combination with an opioid. As a single drug, adequate sedation for procedures in the emergency room, is achieved in over 90% of all procedures. Comparative efficacy was shown for propofol. Data are insufficient to determine comparative efficacy for procedural sedation for other drugs.

When administered with the appropriate precautions, e.g. titration to effect, adequate monitoring and personnel to support ventilation, midazolam is very safe. No major adverse events were seen in 847 adults who received midazolam for procedural sedation. Also, adverse effects can be antagonized with an effective antagonist, flumazenil.

As midazolam is off-patent, drug costs are relatively low. Drug costs per procedure range from approximately 0.15 US$ to 2.6 US$ in an adult, depending on dose and country, with significantly lower costs in developing countries.

2. Name of the focal point in WHO submitting or supporting the application

3. Name of the organization(s) consulted and/or supporting the application

Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands

4. International Nonproprietary Name (INN, generic name) of the medicine

Midazolam

5. Formulation proposed for inclusion; including adult and paediatric

Intravenous formulation: injection: 1 mg/mL
Oral formulation: tablet, 7.5 mg, suspension 2 mg/mL

6. International availability - sources, if possible manufacturers

Please see addendum 1

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

8. Information supporting the public health relevance

Invasive procedures are part of daily adult and pediatric practice. Many of these procedures are painful, stressful, and impossible to perform without immobilizing the patient. Therefore, procedural sedation is required to enable these procedures to be performed. Procedural sedation can be defined as the use of sedative, analgesic, or dissociative drugs in order to provide anxiolysis, analgesia, sedation, and motor control during painful or unpleasant procedures [1].
Indications for procedural sedation and analgesia can be divided into three categories: minor trauma (e.g. wound care, incisions and drainage, fractures and dislocations), instrumentation (e.g. lumbar puncture, renal biopsy, intravenous access, endoscopic procedures and cardiothoracic procedures)

and diagnostic imaging (ultrasonography, MRI and CT scan) [1]. These procedures are routinely performed outside the operating room, for example at the emergency department and at nursing wards.

Effective procedural sedation guarantees predictable procedural success and timing (procedural point of view) and optimal procedural comfort and minimizing procedural stress and failure (patient's point of view). The primary goal of procedural sedation is patient comfort. The ideal sedation endpoint would be one at which the procedure can be successfully accomplished with as little distress to the patient as possible and with cardiopulmonary stability and retention of protective airway reflexes. Currently, intravenous midazolam is one of the drugs routinely used for procedural sedation.
Registry data from the United States and Canada indicate that midazolam is used in 15-42% of all episodes of procedural sedation [2-4].

Besides procedural sedation, midazolam is also used as pre-operative medication to provide sedation and anxiolysis. Many patients are anxious before surgery. Since increased pre-operative anxiety is associated with poor postoperative behavioral and clinical recovery, up to 75% of anesthesiologists in the United States routinely administer sedative premedication to healthy adult patients who undergo surgery [5]. It is shown that patients treated with midazolam pre-operatively not only exhibit lower levels of anxiety, but they also report improved post-operative psychological and pain recovery [6]. Thus, in addition to beneficial pre-operative effects, midazolam has also beneficial postoperative effects on patients undergoing surgery.

9. Treatment details

Dosage regimen

Indication	Adults <60 yrs of age	Adults >60 yrs of age and debilitated or chronically ill patients	Children
"Conscious sedation"	i.v. Starting dose: 2-2,5 mg Titration dose: 1 mg Total dose: 3,5-7,5 mg	i.v. Starting dose: 0,5-1 mg Titration dose: 0,5-1 mg Total dose: < 3,5 mg	i.v. 6 months - 5 years: Starting dose: 0,05-0,1 mg/kg Total dose: < 6 mg i.v. 6-12 years: Startdose: 0,025-0,05 mg/kg Total dosis: < 10 mg rectal > 6 months 0,3-0,5 mg/kg
Amnesia induction Anxiety Preoperative sedation	i.v. 1-2 mg titrated i.m. 0,07-0,1 mg/kg	i.v. Startdose: 0,5 mg Slowly titrate towards effect i.m. 0,025-0,05 mg/kg	rectal > 6 months 0,3-0,5 mg/kg i.m. 1-15 years 0,08-0,2 mg/kg Oral > 6 months 0.25-1 mg/kg

Clinical guidelines

1. WHO Pediatric Formulary:

Midazolam is included in the WHO pediatric formulary for palliative procedures, but not for the indications of this application (premedication, procedural sedation).

Formulary text:
ATC code: N05CD08
Injection: 1 mg/ml; 5 mg/ml
Indications: Palliative situations such as seizures, anxiety and agitation.
Contraindications: Consider the relevance of these listed contraindications in palliative care. Acute or severe pulmonary insufficiency; sleep apnoea syndrome; severe liver disease; myasthenia gravis.

Dose: For all indications in a palliative care setting.
SC or IV injection: Child all ages 0.05–0.15 mg/kg every 1–2 hours.
Continuous SC or IV infusion: Child all ages 10 micrograms/kg/hour by continuous SC or IV infusion, initially, and titrate to effect. There is considerable variability in the dose required.
Oral: Child all ages 0.3–0.5 mg/kg (maximum 15 mg) as a single dose. Use the parenteral form; bitter taste can be disguised in apple juice or chocolate sauce.
Buccal or intranasal: Child all ages 0.2–0.5 mg/kg per dose (maximum 10 mg) as required. Use the parenteral form.

2. Other guidelines
- Clinical policy from American College of Emergency Physicians: procedural sedation and analgesia in the emergency department:
Drug Administration Recommendations: The combination of fentanyl and midazolam is effective for procedural sedation and analgesia in the ED [7].

- AGA Institute Review of Endoscopic Sedation 2007 [8].
Recommendation: The majority of patients can be sedated adequately by using a combination of an opioid and a benzodiazepine.

Need for monitoring
Midazolam hydrochloride must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. Prior to the intravenous administration of midazolam hydrochloride in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, i.e., pulse oximetry. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately [9].

10. Summary of comparative effectiveness in a variety of clinical settings

Indication: premedication

- Identification of clinical evidence

Pubmed was searched from inception to July 2010. The following search strategy was used: Midazolam AND ((premedication OR pre-operative sedation) OR (preoperative sedation) OR (pre-operative medication) OR (preoperative medication) OR pre-operative). All case reports (unless specifically addressing adverse events), non systematic reviews, cohort studies, papers not reporting on midazolam were excluded. Two systematic reviews were identified. Cox et al. evaluated the efficacy of midazolam used as premedication and Dahmani et al. who reviewed efficacy of midazolam and clonidine as premedication in the pediatric population [10]. We also searched Micromedex Drug Evaluations and clinical guidelines for relevant papers. In addition, the Cochrane Database was searched using: midazolam OR premedication. One relevant Cochrane review was found for adults on the difference of time to discharge from hospital in patients who received anxiolytic medication for day surgery [11]. For children, no relevant Cochrane reviews were identified.

- Summary of available data

Adults

A Cochrane review found no evidence of a difference in time to discharge from hospital, assessed by clinical criteria, in patients who received anxiolytic premedication versus placebo for day case surgery [11]. Of the 17 studies identified in this review, overall quality was poor. Of these studies, seven involved midazolam, as single agent, in different dosages and administration routes [12-18]. Significantly deeper sedation, both preoperativaly and postoperatively was found for midazolam vs. placebo. Four of these studies specifically looked at discharge time, but did not show a difference in discharge time between midazolam and placebo [12-13, 15, 17].

In addition to these 7 studies on midazolam for premedication in adult day case surgery, another 18 studies comparing midazolam vs. placebo for premedication for a variety of surgical procedures were found [6, 19-35].
Midazolam doses ranged from 0.05 and 0.2 mg/kg IV, PO, IM or SL. For most studies, quality of study reporting of these studies was moderate to low, with often missing information on randomization and/or blinding procedures. All studies (n=16) with sedation and/or anxiety as outcome measure, showed significant preoperative sedation and/or anxiety reduction in patients receiving midazolam as premedication. In addition, midazolam was associated with amnesia and prolonged impairment when compared to placebo. In one of these studies, in elderly patients, prolonged discharge time was observed after midazolam premedication [20]. This difference with the other studies discussed above may be explained by prolonged plasma elimination and increased sensitivity to midazolam in the elderly population.

One study showed that midazolam as premedication (3.5 mg PO) blunts the hormonal stress response to surgical procedures [30]. Another study showed a significant reduction in preoperative oxygen consumption and energy expenditure, when midazolam (70 mcg/kg IV) was administered as premedication [29].

Most studies only looked at sedation, anxiety levels and amnesia as efficacy outcome measures. An additional, but maybe more important outcome for adequate sedation and anxiolysis, is the possible positive effect on postoperative clinical recovery. A well designed, but small study in 56 adult patients, showed a reduction in postoperative pain and anxiety, but could not identify a difference in most postoperative clinical outcomes, such as time to discharge from PACU, vomiting and nausea, overall health outcome and quality of life [6]. Interestingly, up to 7 days postoperatively, self-reported pain and analgesic consumption, were significantly decreased with midazolam versus placebo, respectively (0% versus 17%, p=0.03). Anxiety levels were also lower for midazolam up to 30 days postoperatively. The only significant between-group difference in clinical recovery was a reduction in self-reported infection at 1 week for midazolam versus placebo recipients (0% versus 16%, p=0.04).

In summary, the available evidence shows, that midazolam is effective in reducing anxiety and increasing sedation when given as premedication in adult patients undergoing invasive procedures. Although, psychomoter impairment may be present up to 4 hrs postoperatively, evidence appears to be lacking that midazolam premedication actually increases discharge time.

Children

A systematic review in 2006 by Cox at al. evaluated efficacy of midazolam as a premedication, focusing on behavioral outcomes. A total of 30 out of 171 randomized controlled trials (midazolam vs placebo or comparator) were identified. The authors concluded that; 'Premedication with midazolam 0.5 mg/kg administered 20–30 min preoperatively, is effective in reducing both separation and induction anxiety in children (grade A recommendation), with minimal effect on recovery times. However improved postoperative behavioural outcomes in the post-anesthesia care unit, or at home cannot be predicted on a consistent basis" [36].

Using the above mentioned search strategy, we identified 19 double blinded randomized controlled trials comparing efficacy of midazolam versus placebo. In most trials, primary outcome measurements were level of sedation and anxiety. In 18 out of 19 RCT's midazolam was shown to significantly decrease anxiety or increase the level of sedation prior to general anesthesia, as compared to placebo [37-55]. Midazolam dosage ranged from 0.25-0.75 mg/kg given either orally, rectally or buccal/sublingual. Only Bevan et al. did not find a difference in depth of sedation or anxiety of midazolam compared to placebo using an oral dose of 0.5 mg/kg [56].

Two studies addressed occurrence or reduction of postoperative vomiting and nausea after general anesthesia, comparing midazolam to placebo. Both Riad et al. and Splinter et al. showed a reduction in episodes of nausea or vomiting in children after strabismus correction or tonsillectomy using low dose intravenous midazolam (0.05-0.075 mg/kg) [57-58].

Several studies showed prolonged recovery after general anesthesia in children premedicated with midazolam although this did not lead to prolonged hospital stay [47, 49, 56, 59-60].

In summary, the available evidence shows, that midazolam is effective in reducing anxiety and increasing sedation when given as premedication in pediatric patients undergoing general anesthesia. Although, there seems to be an effect on delayed recovery, it does not prolong hospital stay.

- Summary of available estimates of comparative effectiveness

Adults

In adults, midazolam for premedication has been compared with many other drugs for premedication, such as benzodiazepines (temazepam [18, 61-63], diazepam [15, 27, 33-34, 64], triazolam [15] alprazolam [12]), alpha 2-adrenoceptor agonists (clonidine [23-24, 29], dexmedetomidine [32, 65-66], first generation antihistamines (droperidol [31, 67-68], phenothiazine [31], hydroxyxizine [35]), ketobemidone [69], butorphanol [70], zolpidem [28] and melatonin [19, 21-22].
Diazepam and midazolam are similar in efficacy for producing sedation prior to short surgical procedures. However, midazolam produces a greater degree of amnesia and, when given intramuscular, less pain on injection, and less phlebitis than diazepam [71]. Midazolam in doses between 5 and 15 mg IV/IM/PO was equally or more effective to induce sedation and anxiolysis when compared to these other drugs. Also, the amnesic properties of midazolam appear more evident than for other drugs.

Children

Several studies compare the efficacy of midazolam for premedication with other sedatives or analgesics. Midazolam is compared with melatonin [38, 41], fentanyl [72], clonidine [10, 44, 73-77] ketamine [78-87] , diazepam/meripidine [88], chloralhydrate [89-90] and dexmedetomidine [91].

A recent systematic review evaluated comparative efficacy of benzodiazepines and clonidine, including five trials that compared midazolam with clonidine. The authors conclude; “Premedication with clonidine, in comparison with midazolam, exhibited a superior effect on sedation at induction, decreased the incidence of emergence agitation and produced a more effective early post-operative analgesia” [10]. Critical evaluation of this review reveals that in two trials sedation with midazolam is significantly more effective in the pre operative setting compared to clonidine [44, 73], or, at least as effective as clonidine [74-75]. One study showed more effective sedation with clonidine compared to midazolam. However there was no significant difference in anxiety reduction or acceptance of mask ventilation between both groups. Moreover midazolam achieved its effect significantly faster compared to clonidine [76]. Only one RCT showed clonidine is superior to midazolam with regards to reduced anxiety, increased sedation and mask acceptance [77].

Several RCT’s addressed relative efficacy of midazolam and ketamine. Most studies find either no significant difference in efficacy [78-86] or favor midazolam in reduction of anxiety and increased sedation[87].

Several authors showed increased levels of sedation with midazolam premedication compared to rectal chloralhydrate [89-90]. Compared to diazepam in combination with meperidine, midazolam is as effective [92] or more effective [88]. Intranasal dexmedetomidine produces more sedation than oral midazolam, but with similar and acceptable cooperation [91].
Midazolam was found to be the drug of preference in comparison to fentanyl for the majority of patients [72]. Two RCT placebo controlled addressed melatonin and midazolam. Both studies showed midazolam is as effective or more effective [38, 41].

Indication: Procedural sedation

- Identification of clinical evidence

Pubmed was searched using the following search strategy: Midazolam AND ((procedural sedation) OR (short-term procedures) OR (short term procedures)). For pediatric studies the following search terms were added: child*[tw] OR infan*[tw] OR pediatr*[tw] OR paediatr*[tw] All case reports (unless specifically addressing adverse events), non systematic reviews, cohort studies and papers not reporting on midazolam use were excluded.

A 2008 systematic review was found in this search comparing safety and clinical effectiveness of midazolam versus propofol for procedural sedation in the emergency department [93].
Another 2008 systematic review was identified of clinical trials for sedation in gastrointestinal endoscopy [94].
One systematic review was identified comparing efficacy and safety of midazolam versus ketamine for procedural sedation in children in the emergency department[95]. In addition two reviews were identified evaluating drug efficacy in procedural sedation and analgesia in children [96-97].
Micromedex Drug Evaluations® and clinical guidelines were searched for relevant papers. In addition the Cochrane Library was searched using the following search terms: midazolam OR sedation. This search yielded 65 results. The following review was relevant for adults: Conscious sedation and analgesia for oocyte retrieval during in vitro fertilisation procedures [98]. For pediatric procedural sedation another two reviews were relevant: 'Sedation versus general anaesthesia for provision of dental treatment in under 18 year olds' [99] and 'Sedation of anxious children undergoing dental treatment' [100].

- Summary of available data

Adults

In 2008, Hohl at al performed a systematic review comparing midazolam with propofol for procedural sedation in the Emergency Room setting [93]. The secondary endpoint was the mean difference in the proportion of patients who were successfully sedated and for whom the indicating medical procedure could be performed.
Overall procedural success rate for patients sedated with midazolam was 89.9 (83.2, 94.6) %. When trials with a Jadad score <3 (poor study quality) were removed from the analysis, procedural success rate was even higher (93.5 (87.0, 97.8%)).

The American College of Emergency Physicians published the guideline: procedural sedation and analgesia in the emergency department. For this guideline, a systematic review was performed for all aspects of procedural sedation. A level B recommendation was made that the combination of fentanyl and midazolam is effective for procedural sedation and analgesia in the ED [7].

Another setting for frequent procedural sedation is gastrointestinal endoscopies. Most studies in this setting compared midazolam with placebo or another benzodiazepine. In 2007, the AGA Institute published a Review of Endoscopic Sedation [8]. Whenever possible, the statements and recommendations were developed systematically from an evidence-based analysis of the literature. The guidelines state that the majority of patients can be sedated adequately by using a combination of an opioid and a benzodiazepine, however, without mentioning the strength of evidence.
A 2008 systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures identified 16 trials comparing midazolam to placebo. Only 2 trials were of good quality (Jadad score ≥ 4) [94]. 91% of patients were satisfied with their level of sedation, vs. 85% of physicians.

Children

Two Cochrane systematic reviews were identified addressing continuous sedation in the pediatric patient during dental procedures. Both reviews concluded that there were insufficient good quality studies to make any recommendations concerning the choice of medication [99-100].
We could identify only eight placebo controlled randomized trials evaluating midazolam for procedural sedation in children [101-107]. These studies all show that midazolam is more effective than placebo for sedation for minor procedures.

- Summary of available estimates of comparative effectiveness

Adults
The efficacy of procedural sedation in the emergency room was compared for midazolam versus propofol in systematic review. Although there appeared to be a small advantage of propofol over midazolam in the point estimates of the proportion of successful PS in two RCTs, the pooled difference between the agents remained statistically insignificant in all sensitivity analyses [93].

The Cochrane review on conscious sedation and analgesia for oocyte retrieval during in vitro fertilisation procedures concluded that there is insufficient evidence to determine the effect of different methods of pain relief when compared with conscious sedation and analgesia used during oocyte recovery [98]. Hence, not one drug can be identified as superior for this indication.

The ACEP guideline for procedural sedation also provided a level B recommendation that propofol can be safely administered for procedural sedation and analgesia in the ED, which is a recommendation with similar strength of evidence as the combination benzodiazepine/opioid. Although diazepam is approved for sedation in adult patients by the FDA. strength of evidence (Category B) is less than for midazolam (Category A). While a Level C recommendation was made for etomidate in the same setting [7].

More than 98% of endoscopists in the United States routinely administer sedation during upper and lower endoscopies. Endoscopists prefer the use of midazolam instead of diazepam because of its favorable pharmacologic profile [108]. A systematic review comparing sedative regimens showed high level of physician and patient satisfaction and a low risk of serious adverse events with all currently available agents [94]. In addition, meta analysis of 8 studies showed that midazolam provided superior patient satisfaction to diazepam (RR Z 1.18, range 1.07-1.29) and less frequent memory of upper gastrointestinal endoscopy (RR Z 0.57, range 0.50-0.60) versus diazepam. No difference in patient satisfaction was found when midazolam was compared with propofol. There does not appear to be an advantage of sedation with a combination of midazolam and opiates compared with midazolam alone for upper gastrointestinal endoscopy.

Children

A systematic review conducted in 2007 evaluated the literature for comparison of efficacy and safety of midazolam and ketamine for procedural sedation in the emergency department. Four papers were included in the analysis. Based on these studies midazolam and ketamine have the same safety profile in the emergency department. Although midazolam reduces post operative vomiting there seems to be a preference for ketamine in parent surveys [95]. As noted in this review there are no single drug studies comparing midazolam and ketamine. Most studies evaluate treatment regimes including and comparing multiple drugs.

Liddo et al. compared efficacy and safety of etomidate and midazolam, showing shorter induction and recovery times for etomidate with higher efficacy compared to midazolam [109]. However etomidate is assocated with adrenal insufficiency and should therefore be used with care in children [110] and is not recommended in children below the age of 10 years [111].

There remains a paucity of high quality randomized controlled trials addressing efficacy and safety of single drugs. Since the indications of procedural anesthesia vary, several combinations of midazolam and morphine or morphine derivates have been published.
Two systematic reviews conclude that midazolam in combination with fentanyl or ketamine provides effective sedation and analgesia during painful procedures in children [96-97].
The systematic review from 2004 by Migita et al, evaluated efficacy and safety of several sedatives and analgesics frequently used in the emergency department. The authors concluded that midazolam in combination with fentanyl is effective in providing procedural sedation and analgesia in 91-100% of all patients (recommendation level B). However, this combination is associated with a higher rate of respiratory depression. Therefore adequate monitoring and facilities to secure respiration are essential (recommendations level B) [97]. The systematic review in 2006 by Russell et al concluded that midazolam in combination with ketamine provides adequate sedation and analgesia in fracture reduction in children and seems superior to fentanyl-midazolam and propofol-fentanyl [96].

Padmanabhan et al evaluated midazolam-ketamine versus propofol-ketamine, midazolam-tramadol and propofol-tramadol in pediatric dental patients. The combination of midazolam-ketamine was the most effective combination realizing adequate sedation levels in 81% of patients [112]. Two other RCT's evaluating midazolam-ketamine versus ketamine [113] or midazolam-fentanyl [114] published after 2006 show ambiguous results. However both studies show there is additional value of midazolam in procedural sedation.
A combination of midazolam with dexmedetomidine, pentobarbital/fentanyl or ketamine and propofol seemed safe and effective in children undergoing MRI [115-118].

Summary of comparative evidence on safety

Estimate of total patient exposure to date

Midazolam has been used extensively since the mid 80's for short- and long-term sedation in adult and pediatric patients. Registry data from the United States and Canada indicate that midazolam is used in 15-42% of all episodes of procedural sedation [2-4].

Description of adverse effects/reactions

Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam hydrochloride is administered with other medications capable of depressing the central nervous system. The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube (e.g., upper endoscopy and dental procedures) [9].

In a systematic review of the literature Hohl et al. analyzed 28 articles studying more than 3,000 patients exposed to either propofol or midazolam. The total number of patients exposed to midazolam in the studies was 847. The occurrence of minor AEs was too heterogeneous to analyze, owing to varying definitions and reporting among individual studies. A major AE was defined as when one of the following was reported: death, disability, hospital admission, prolonged ED stay, intubation and/or vomiting with aspiration pneumonitis. The overall probabilities of major AEs were 0 in 847 (0%; 95% CI = 0% to 0.45%) for patients treated with midazolam [93].

About 3.4% of children scheduled for elective surgery have been reported to develop paradoxical reactions following premedication with intravenous midazolam. These reactions may occur at variable times after administration and include restlessness, violent behavior, physical assault, acts of self-injury and need for restraints [119].

- Identification of variation in safety due to health systems and patient factors

<u>Geriatric patients</u>

Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam are recommended. Intravenous and intramuscular doses of midazolam should be decreased for elderly and for debilitated patients and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia. Administration of IM and IV midazolam to elderly and/or high risk surgical patients has been associated with rare reports of death under circumstances compatible with cardio-respiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics. Source FDA drug label [9].

<u>Pediatric patients</u>

As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (between 3 months and six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require closer monitoring. In obese pediatric patients, the dose should be calculated based on ideal body weight. When midazolam is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Midazolam hydrochloride should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly, with concomitant use of fentanyl. Source FDA drug label [9].
A large prospective descriptive study by Pitetti et al. evaluated 14386 pediatric patients undergoing procedural sedation. In this cohort midazolam alone did not result in any adverse effects, whereas midazolam-fentanyl was associated with a higher rate of complications: 9,7% [120]. A prospective study including almost 800 children after procedural sedation evaluated post operative complications. Midazolam/fentanyl combinations were associated with a higher rate of post operative vomiting and nausea, whereas the combination of midazolam and ketamine had the least post operative complications [121].

- Summary of comparative safety against comparators

The overall probability of major AEs was 1 in 2,453 for patients treated with propofol (0.04%; 95% CI = 0.01% to 0.23%). No significant difference between midazolam and propofol in the proportion of major AEs was found (p = 0.56). Because of the resulting clinical heterogeneity of the studies in the systematic review, minor AEs could not be pooled into a meaningful summary statistic. Hence, resulting in no clinical or statistical difference in the risk profile between these agents [93].

Propofol, possessing different risks and benefits from traditional sedative agents such as benzodiazepines and opioids, has rapidly gained popularity. The FDA product label for propofol contains a warning that “propofol should be administered only by persons trained in the administration of general anesthesia.” In addition, there have been reports in which failure to use aseptic technique when handling propofol injection emulsion was associated with microbial contamination of the product and with fever, infection, sepsis, other life-threatening illness, and death. Especially in poor resource settings, where hygienic circumstances may not be optimal, the use of propofol may be associated with increased risk of microbial contamination [122].

The adverse event profile of midazolam and diazepam is largely the same, inherent to their mechanism of action and is largely dose-dependent [123]. A safety advantage of benzodiazepines over propofol, alpha 2-adrenoceptor agonists or antihistamines is the availability of an antidote, flumazenil. Flumazenil has been shown to easily and safely antagonize the benzodiazepine effect and related adverse events (such as respiratory depression) [123].

11. **Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group**

- Summary of comparative costs against comparators

Reported prices for the IV injection solution (1 mg/ml) price ranges between 0.05 and 1.1 US$ per unit (1 ml) [124] [125] The unit price (1 ml) is 0.05 US$ in Peru, 0.11 US$ in Honduras, South Africa, the Netherlands and 0.16 US$ in Canada (18211306). Prices for the 5 mg/ml IV injection solution range from 0.15 to 0.94 US$ per unit (1ml).
With an average midazolam dose for sedation ranging from 0.07-0.2 mg/kg, this amounts to a variation in price per procedure between 0.15 US$ and 2.6 US$ for a 70 kg adult, depending on country and solution used.
Oral midazolam (15mg tablet) price is 0.26 US$ in the Netherlands [125].

Diazepam, which is indicated for premedication and sedation for endoscopic procedures, but not for other procedural sedation, is given in doses ranging from 5-15 mg po, IM or IV. The comparable midazolam dose for oral administration is 5-10 mg. Midazolam vs diazepam prices compare as 0.26 US$ vs. 0.014-0.05 US$.
The comparable midazolam dose for IV administration in 5-10 mg. Midazolam vs diazepam prices for IV administration compare as 0.15 US$ and 2 US$ vs. 0.1-0.5 US$.

International propofol prices (2009) range between 0.08 US$ and 0.15 US$ per mL (10mg/mL) for the following countries: South Africa, Honduras, Senegal, Eastern Caribbean States, Costa Rica [124].
The average cost for 20mg/ml ampoule in Canada amounts to 2.9 US$, 2007 price level [126]. For the average procedure 1-3 mg/kg is given, which amounts to 7 to 21 mL for a 70kg adult. As leftover drug

is advised to be discarded, one or two 10 ml ampoules will be used which amounts to 0.80 US$ to 2.90 US$ per procedure.

- comparative cost-effectiveness presented as range of cost per routine outcome

Adult

Hohl et al [126] performed a cost-effectiveness analysis comparing midazolam with propofol for procedural sedation in the emergency room in a community or urban hospital in North America. All costs associated with procedural sedation in this setting were taken into account, including cost of ER visit, labor costs, medication costs and adverse event costs. In addition, mean difference in recovery times, the probabilities of successful procedural sedation (PS) and major AEs, and the drug doses associated with each sedation strategy were incorporated in the analysis. Based on this analysis, the authors showed that due to improved recovery times, PS with propofol was cost-saving in comparison to midazolam. The researches were unable to compare the use of midazolam against other agents such as ketamine, ketafol, etomidate, or methohexital, because insufficient comparative data were available.

Pediatric
A similar cost effectiveness study was performed by Pershad et al. in the pediatric emergency department [117].Total costs were calculated by assessing ED resource utilization associated with uncomplicated PSA (procedural sedation and anesthesia) and with PSA complicated by adverse events in a North American emergency department. When patients experienced emesis, recovery agitation, respiratory depression, lidocaine toxicity, or regional block failure, it was assumed that patients would require 1 additional hour of ED stay.
Under baseline assumptions, the propofol/fentanyl regimen was the most cost-effective choice (expected cost, 84.06 US dollars), followed by axillary block (88.18 US dollars), ketamine/midazolam (105.32 US dollars), and fentanyl/midazolam (159.79 US dollars), respectively. Among PSA regimens during forearm fracture manipulation in the pediatric ED, propofol/fentanyl was the most cost-effective regimen followed by axillary block, ketamine/fentanyl and fentanyl/midazolam.

Maruf et al. compared ketamine-diazepam (A) to midazolam-fentanyl (B). Sedation regimen of group B was five times more costly than group A. Both the regimens were found safe and effective for pediatric sedation during MRI, but ketamine, diazepam combination found more cost effective[118].
Both studies evaluated a combination of drugs making cost evaluations for midazolam alone impossible.

Summary of regulatory status of the medicine

The following midazolam formulations are registered in the Netherlands for procedural sedation and premedication in both adults and children [127]:
RVG 21297 Midazolam 1 mg/ml, solution for injection
RVG 21299 Midazolam 5 mg/ml, solution for injection
RVG 10539 Dormicum 15 mg, tablets
RVG 13027 Dormicum 7,5 mg, tablets

Midazolam is also registered in the US (solution for injection, tablets, oral syrup) for procedural sedation and premedication in both adults and children (Level A evidence) [9].

12. Availability of pharmacopoeial standards

European Pharmacopoeia [128]: standard available
United States Pharmacopeia [129]: standard available
British Pharmacopeia [130]: standard available
WHO International Pharmacopeia [131]: no standard available

13. Proposed (new/adapted) text for the WHO Model Formulary

Advice: follow FDA product label [9]

References

1. Krauss, B. and S.M. Green, *Procedural sedation and analgesia in children.* Lancet, 2006. **367**(9512): p. 766-80.
2. Sacchetti, A., et al., *Procedural sedation in the community emergency department: initial results of the ProSCED registry.* Acad Emerg Med, 2007. **14**(1): p. 41-6.
3. Mensour, M., et al., *Emergency department procedural sedation and analgesia: A Canadian Community Effectiveness and Safety Study (ACCESS).* CJEM, 2006. **8**(2): p. 94-9.
4. Campbell, S.G., et al., *Procedural sedation and analgesia in a Canadian adult tertiary care emergency department: a case series.* CJEM, 2006. **8**(2): p. 85-93.
5. Kain, Z.N., et al., *Premedication in the United States: a status report.* Anesth Analg, 1997. **84**(2): p. 427-32.
6. Kain, Z.N., et al., *Attenuation of the preoperative stress response with midazolam: effects on postoperative outcomes.* Anesthesiology, 2000. **93**(1): p. 141-7.
7. Godwin, S.A., et al., *Clinical policy: procedural sedation and analgesia in the emergency department.* Ann Emerg Med, 2005. **45**(2): p. 177-96.
8. Cohen, L.B., et al., *AGA Institute review of endoscopic sedation.* Gastroenterology, 2007. **133**(2): p. 675-701.
9. *FDA drug label midazolam*. [cited 2010 October 15]; FDA Drug labelling midazolam]. Available from: http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=midazolam.
10. Dahmani, S., et al., *Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies.* Acta Anaesthesiol Scand, 2010. **54**(4): p. 397-402.
11. Walker, K.J. and A.F. Smith, *Premedication for anxiety in adult day surgery.* Cochrane Database Syst Rev, 2009(4): p. CD002192.
12. De Witte, J.L., et al., *Preoperative alprazolam reduces anxiety in ambulatory surgery patients: a comparison with oral midazolam.* Anesth Analg, 2002. **95**(6): p. 1601-6, table of contents.
13. Abdul-Latif, M.S., et al., *Oral midazolam premedication for day case breast surgery, a randomised prospective double-blind placebo-controlled study.* Anaesthesia, 2001. **56**(10): p. 990-4.
14. Ahmed, N. and F.A. Khan, *Evaluation of oral midazolam as pre-medication in day care surgery in adult Pakistani patients.* J Pak Med Assoc, 1995. **45**(9): p. 239-41.
15. Forrest, P., D.C. Galletly, and P. Yee, *Placebo controlled comparison of midazolam, triazolam and diazepam as oral premedicants for outpatient anaesthesia.* Anaesth Intensive Care, 1987. **15**(3): p. 296-304.
16. Raybould, D. and E.G. Bradshaw, *Premedication for day case surgery. A study of oral midazolam.* Anaesthesia, 1987. **42**(6): p. 591-5.
17. Richardson, M.G., C.L. Wu, and A. Hussain, *Midazolam premedication increases sedation but does not prolong discharge times after brief outpatient general anesthesia for laparoscopic tubal sterilization.* Anesth Analg, 1997. **85**(2): p. 301-5.
18. Turner, G.A. and M. Paech, *A comparison of oral midazolam solution with temazepam as a day case premedicant.* Anaesth Intensive Care, 1991. **19**(3): p. 365-8.
19. Acil, M., et al., *Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance.* Eur J Anaesthesiol, 2004. **21**(7): p. 553-7.
20. Fredman, B., et al., *The effect of midazolam premedication on mental and psychomotor recovery in geriatric patients undergoing brief surgical procedures.* Anesth Analg, 1999. **89**(5): p. 1161-6.
21. Naguib, M. and A.H. Samarkandi, *Premedication with melatonin: a double-blind, placebo-controlled comparison with midazolam.* Br J Anaesth, 1999. **82**(6): p. 875-80.
22. Naguib, M. and A.H. Samarkandi, *The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: a double-blinded, placebo-controlled study.* Anesth Analg, 2000. **91**(2): p. 473-9.
23. Paris, A., et al., *Effects of clonidine and midazolam premedication on bispectral index and recovery after elective surgery.* Eur J Anaesthesiol, 2009. **26**(7): p. 603-10.
24. Zalunardo, M.P., et al., *[Quality of premedication and patient satisfaction after premedication with midazolam, clonidine or placebo : Randomized double-blind study with age-adjusted dosage].* Anaesthesist. **59**(5): p. 410-8.
25. van Vlymen, J.M., M.M. Sa Rego, and P.F. White, *Benzodiazepine premedication: can it improve outcome in patients undergoing breast biopsy procedures?* Anesthesiology, 1999. **90**(3): p. 740-7.

26. Hudes, E.T., et al., *A comparison of morphine-perphenazine and midazolam on preoperative sedation and arterial oxygen saturation.* Can J Anaesth, 1991. **38**(2): p. 187-90.
27. Pippingskold, K., et al., *The effect of orally administered diazepam and midazolam on plasma beta-endorphin, ACTH and preoperative anxiety.* Acta Anaesthesiol Scand, 1991. **35**(2): p. 175-80.
28. Praplan-Pahud, J., et al., *Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo.* Br J Anaesth, 1990. **64**(6): p. 670-4.
29. Taittonen, M., et al., *Cardiovascular and metabolic responses to clonidine and midazolam premedication.* Eur J Anaesthesiol, 1997. **14**(2): p. 190-6.
30. Kiefer, R.T., J. Weindler, and K.W. Ruprecht, *The endocrine stress response after oral premedication with low-dose midazolam for intraocular surgery in retrobulbar anaesthesia.* Eur J Ophthalmol, 1998. **8**(4): p. 239-45.
31. Jalbout, N., et al., *Premedication with Midazolam (Dormicum) compared with Promethazine, Droperidol and placebo in relieving anxiety using Beck's anxiety inventory.* J Med Liban, 1994. **42**(2): p. 69-73.
32. Aantaa, R., et al., *A comparison of dexmedetomidine, and alpha 2-adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery.* Br J Anaesth, 1991. **67**(4): p. 402-9.
33. Van de Velde, A., F. Camu, and M.A. Claeys, *Midazolam for intramuscular premedication: dose-effect relationships compared to diazepam, fentanyl and fentanyl-droperidol in a placebo controlled study.* Acta Anaesthesiol Belg, 1986. **37**(2): p. 127-36.
34. Reinhart, K., et al., *Comparison of midazolam, diazepam and placebo i.m. as premedication for regional anaesthesia. A randomized double-blind study.* Br J Anaesth, 1985. **57**(3): p. 294-9.
35. Vinik, H.R., J.G. Reves, and D. Wright, *Premedication with intramuscular midazolam: a prospective randomized double-blind controlled study.* Anesth Analg, 1982. **61**(11): p. 933-7.
36. Cox, R.G., et al., *Evidence-based clinical update: does premedication with oral midazolam lead to improved behavioural outcomes in children?* Can J Anaesth, 2006. **53**(12): p. 1213-9.
37. Hosey, M.T., et al., *The effect of transmucosal 0.2 mg/kg midazolam premedication on dental anxiety, anaesthetic induction and psychological morbidity in children undergoing general anaesthesia for tooth extraction.* Br Dent J, 2009. **207**(1): p. E2; discussion 32-3.
38. Isik, B., O. Baygin, and H. Bodur, *Premedication with melatonin vs midazolam in anxious children.* Paediatr Anaesth, 2008. **18**(7): p. 635-41.
39. Finley, G.A., et al., *High levels of impulsivity may contraindicate midazolam premedication in children.* Can J Anaesth, 2006. **53**(1): p. 73-8.
40. Mishra, L.D., et al., *Injectable midazolam as oral premedicant in pediatric neurosurgery.* J Neurosurg Anesthesiol, 2005. **17**(4): p. 193-8.
41. Samarkandi, A., et al., *Melatonin vs. midazolam premedication in children: a double-blind, placebo-controlled study.* Eur J Anaesthesiol, 2005. **22**(3): p. 189-96.
42. Howell, T.K., et al., *A comparison of oral transmucosal fentanyl and oral midazolam for premedication in children.* Anaesthesia, 2002. **57**(8): p. 798-805.
43. Pandit, U.A., et al., *Oral transmucosal midazolam premedication for preschool children.* Can J Anaesth, 2001. **48**(2): p. 191-5.
44. Fazi, L., et al., *A comparison of oral clonidine and oral midazolam as preanesthetic medications in the pediatric tonsillectomy patient.* Anesth Analg, 2001. **92**(1): p. 56-61.
45. Khalil, S., et al., *Sublingual midazolam premedication in children: a dose response study.* Paediatr Anaesth, 1998. **8**(6): p. 461-5.
46. McGraw, T. and A. Kendrick, *Oral midazolam premedication and postoperative behaviour in children.* Paediatr Anaesth, 1998. **8**(2): p. 117-21.
47. Riva, J., et al., *Oral premedication with midazolam in paediatric anaesthesia. Effects on sedation and gastric contents.* Paediatr Anaesth, 1997. **7**(3): p. 191-6.
48. Gillerman, R.G., et al., *Parental presence plus oral midazolam decreases frequency of 5% halothane inductions in children.* J Clin Anesth, 1996. **8**(6): p. 480-5.
49. Cray, S.H., et al., *Oral midazolam premedication for paediatric day case patients.* Paediatr Anaesth, 1996. **6**(4): p. 265-70.
50. McMillan, C.O., et al., *Premedication of children with oral midazolam.* Can J Anaesth, 1992. **39**(6): p. 545-50.
51. Roelofse, J.A. and P. van der Bijl, *Comparison of rectal midazolam and diazepam for premedication in pediatric dental patients.* J Oral Maxillofac Surg, 1993. **51**(5): p. 525-9.

52. Roelofse, J.A., et al., *Preanesthetic medication with rectal midazolam in children undergoing dental extractions.* J Oral Maxillofac Surg, 1990. **48**(8): p. 791-7; discussion 797.
53. Vetter, T.R., *A comparison of midazolam, diazepam, and placebo as oral anesthetic premedicants in younger children.* J Clin Anesth, 1993. **5**(1): p. 58-61.
54. Gallardo, F., G. Cornejo, and R. Borie, *Oral midazolam as premedication for the apprehensive child before dental treatment.* J Clin Pediatr Dent, 1994. **18**(2): p. 123-7.
55. Liacouras, C.A., et al., *Placebo-controlled trial assessing the use of oral midazolam as a premedication to conscious sedation for pediatric endoscopy.* Gastrointest Endosc, 1998. **47**(6): p. 455-60.
56. Bevan, J.C., et al., *Midazolam premedication delays recovery after propofol without modifying involuntary movements.* Anesth Analg, 1997. **85**(1): p. 50-4.
57. Riad, W., et al., *Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children.* Eur J Anaesthesiol, 2007. **24**(8): p. 697-701.
58. Splinter, W.M., et al., *Midazolam reduces vomiting after tonsillectomy in children.* Can J Anaesth, 1995. **42**(3): p. 201-3.
59. Viitanen, H., et al., *Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children.* Anesth Analg, 1999. **89**(1): p. 75-9.
60. Viitanen, H., et al., *Midazolam premedication delays recovery from propofol-induced sevoflurane anesthesia in children 1-3 yr.* Can J Anaesth, 1999. **46**(8): p. 766-71.
61. Short, T.G. and D.C. Galletly, *Double-blind comparison of midazolam and temazepam as oral premedicants for outpatient anaesthesia.* Anaesth Intensive Care, 1989. **17**(2): p. 151-6.
62. Hargreaves, J., *Benzodiazepine premedication in minor day-case surgery: comparison of oral midazolam and temazepam with placebo.* Br J Anaesth, 1988. **61**(5): p. 611-6.
63. Nightingale, J.J. and J. Norman, *A comparison of midazolam and temazepam for premedication of day case patients.* Anaesthesia, 1988. **43**(2): p. 111-3.
64. Hennessy, M.J., K.C. Kirkby, and I.M. Montgomery, *Comparison of the amnesic effects of midazolam and diazepam.* Psychopharmacology (Berl), 1991. **103**(4): p. 545-50.
65. Levanen, J., M.L. Makela, and H. Scheinin, *Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium.* Anesthesiology, 1995. **82**(5): p. 1117-25.
66. Demiraran, Y., et al., *The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: A prospective, randomized study.* Can J Gastroenterol, 2007. **21**(1): p. 25-9.
67. Kamata, K., et al., *Predominant effects of midazolam for conscious sedation: benefits beyond the early postoperative period.* J Anesth.
68. Eberhart, L.H. and W. Seeling, *Droperidol-supplemented anaesthesia decreases post-operative nausea and vomiting but impairs post-operative mood and well-being.* Eur J Anaesthesiol, 1999. **16**(5): p. 290-7.
69. Jakobsson, J., et al., *Premedication before elective breast surgery, a comparison between ketobemidone and midazolam.* Acta Anaesthesiol Scand, 1991. **35**(6): p. 524-8.
70. Dershwitz, M., et al., *Comparison of the sedative effects of butorphanol and midazolam.* Anesthesiology, 1991. **74**(4): p. 717-24.
71. *Micromedex drug evaluations midazolam*. [cited 2010 Oct 15]; Available from: http://www.micromedex.com/.
72. Sandler, E.S., et al., *Midazolam versus fentanyl as premedication for painful procedures in children with cancer.* Pediatrics, 1992. **89**(4 Pt 1): p. 631-4.
73. Tazeroualti, N., et al., *Oral clonidine vs midazolam in the prevention of sevoflurane-induced agitation in children. a prospective, randomized, controlled trial.* Br J Anaesth, 2007. **98**(5): p. 667-71.
74. Schmidt, A.P., et al., *Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children.* Paediatr Anaesth, 2007. **17**(7): p. 667-74.
75. Bergendahl, H.T., et al., *Clonidine vs. midazolam as premedication in children undergoing adeno-tonsillectomy: a prospective, randomized, controlled clinical trial.* Acta Anaesthesiol Scand, 2004. **48**(10): p. 1292-300.
76. Almenrader, N., et al., *Premedication in children: a comparison of oral midazolam and oral clonidine.* Paediatr Anaesth, 2007. **17**(12): p. 1143-9.
77. Cao, J., et al., *Effects of premedication of midazolam or clonidine on perioperative anxiety and pain in children.* Biosci Trends, 2009. **3**(3): p. 115-8.

78. Ghai, B., et al., *Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication.* Paediatr Anaesth, 2005. **15**(7): p. 554-9.
79. Weber, F., H. Wulf, and G. el Saeidi, *Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children.* Can J Anaesth, 2003. **50**(5): p. 470-5.
80. Trabold, B., et al., *A comparison of two different doses of ketamine with midazolam and midazolam alone as oral preanaesthetic medication on recovery after sevoflurane anaesthesia in children.* Paediatr Anaesth, 2002. **12**(8): p. 690-3.
81. Astuto, M., N. Disma, and E. Crimi, *Two doses of oral ketamine, given with midazolam, for premedication in children.* Minerva Anestesiol, 2002. **68**(7-8): p. 593-8.
82. Funk, W., et al., *Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone.* Br J Anaesth, 2000. **84**(3): p. 335-40.
83. Kentrup, H., et al., *Midazolam and ketamine as premedication in colonoscopies: a pharmacodynamic study.* Int J Clin Pharmacol Ther, 1994. **32**(2): p. 82-7.
84. Tanaka, M., et al., *Reevaluation of rectal ketamine premedication in children: comparison with rectal midazolam.* Anesthesiology, 2000. **93**(5): p. 1217-24.
85. van der Bijl, P., J.A. Roelofse, and I.A. Stander, *Rectal ketamine and midazolam for premedication in pediatric dentistry.* J Oral Maxillofac Surg, 1991. **49**(10): p. 1050-4.
86. Alderson, P.J. and J. Lerman, *Oral premedication for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine.* Can J Anaesth, 1994. **41**(3): p. 221-6.
87. Marhofer, P., et al., *S(+)-ketamine for rectal premedication in children.* Anesth Analg, 2001. **92**(1): p. 62-5.
88. Martinez, J.L., et al., *A comparison of oral diazepam versus midazolam, administered with intravenous meperidine, as premedication to sedation for pediatric endoscopy.* J Pediatr Gastroenterol Nutr, 2002. **35**(1): p. 51-8.
89. Haas, D.A., et al., *A pilot study of the efficacy of oral midazolam for sedation in pediatric dental patients.* Anesth Prog, 1996. **43**(1): p. 1-8.
90. Saarnivaara, L., L. Lindgren, and U.M. Klemola, *Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery.* Br J Anaesth, 1988. **61**(4): p. 390-6.
91. Yuen, V.M., et al., *A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial.* Anesth Analg, 2008. **106**(6): p. 1715-21.
92. Pywell, C.A., Y.J. Hung, and J. Nagelhout, *Oral midazolam versus meperidine, atropine, and diazepam: a comparison of premedicants in pediatric outpatients.* AANA J, 1995. **63**(2): p. 124-30.
93. Hohl, C.M., et al., *Safety and clinical effectiveness of midazolam versus propofol for procedural sedation in the emergency department: a systematic review.* Acad Emerg Med, 2008. **15**(1): p. 1-8.
94. McQuaid, K.R. and L. Laine, *A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures.* Gastrointest Endosc, 2008. **67**(6): p. 910-23.
95. Munro, A. and I. Machonochie, *Midazolam or ketamine for procedural sedation of children in the emergency department.* Emerg Med J, 2007. **24**(8): p. 579-80.
96. Migita, R.T., E.J. Klein, and M.M. Garrison, *Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review.* Arch Pediatr Adolesc Med, 2006. **160**(1): p. 46-51.
97. Mace, S.E., et al., *Clinical policy: evidence-based approach to pharmacologic agents used in pediatric sedation and analgesia in the emergency department.* J Pediatr Surg, 2004. **39**(10): p. 1472-84.
98. Kwan, I., et al., *Conscious sedation and analgesia for oocyte retrieval during in vitro fertilisation procedures.* Cochrane Database Syst Rev, 2005(3): p. CD004829.
99. Ashley, P.F., et al., *Sedation versus general anaesthesia for provision of dental treatment in under 18 year olds.* Cochrane Database Syst Rev, 2009(1): p. CD006334.
100. Matharu, L. and P.F. Ashley, *Sedation of anxious children undergoing dental treatment.* Cochrane Database Syst Rev, 2006(1): p. CD003877.
101. Stewart, S.H., et al., *Effects of midazolam on explicit vs implicit memory in a pediatric surgery setting.* Psychopharmacology (Berl), 2006. **188**(4): p. 489-97.

102. Wan, K., Q. Jing, and J.Z. Zhao, *Evaluation of oral midazolam as conscious sedation for pediatric patients in oral restoration.* Chin Med Sci J, 2006. **21**(3): p. 163-6.
103. Herd, D.W., et al., *Conscious sedation reduces distress in children undergoing voiding cystourethrography and does not interfere with the diagnosis of vesicoureteric reflux: a randomized controlled study.* AJR Am J Roentgenol, 2006. **187**(6): p. 1621-6.
104. Stokland, E., et al., *Sedation with midazolam for voiding cystourethrography in children: a randomised double-blind study.* Pediatr Radiol, 2003. **33**(4): p. 247-9.
105. Shane, S.A., S.M. Fuchs, and H. Khine, *Efficacy of rectal midazolam for the sedation of preschool children undergoing laceration repair.* Ann Emerg Med, 1994. **24**(6): p. 1065-73.
106. Theroux, M.C., et al., *Efficacy of intranasal midazolam in facilitating suturing of lacerations in preschool children in the emergency department.* Pediatrics, 1993. **91**(3): p. 624-7.
107. Hennes, H.M., et al., *The effect of oral midazolam on anxiety of preschool children during laceration repair.* Ann Emerg Med, 1990. **19**(9): p. 1006-9.
108. Cohen, L.B., et al., *Endoscopic sedation in the United States: results from a nationwide survey.* Am J Gastroenterol, 2006. **101**(5): p. 967-74.
109. Di Liddo, L., et al., *Etomidate versus midazolam for procedural sedation in pediatric outpatients: a randomized controlled trial.* Ann Emerg Med, 2006. **48**(4): p. 433-40, 440 e1.
110. Lundy, J.B., M.L. Slane, and J.D. Frizzi, *Acute adrenal insufficiency after a single dose of etomidate.* J Intensive Care Med, 2007. **22**(2): p. 111-7.
111. Micromedex® Healthcare Series [Internet database]. Greenwood Village, C.T.R.H.I.U.p.
112. Padmanabhan, M.Y., et al., *A comparative evaluation of agents producing analgo-sedation in pediatric dental patients.* J Clin Pediatr Dent, 2009. **34**(2): p. 183-8.
113. Erk, G., et al., *The use of ketamine or ketamine-midazolam for adenotonsillectomy.* Int J Pediatr Otorhinolaryngol, 2007. **71**(6): p. 937-41.
114. Lucas da Silva, P.S., et al., *Procedural sedation for insertion of central venous catheters in children: comparison of midazolam/fentanyl with midazolam/ketamine.* Paediatr Anaesth, 2007. **17**(4): p. 358-63.
115. Heard, C.M., P. Joshi, and K. Johnson, *Dexmedetomidine for pediatric MRI sedation: a review of a series of cases.* Paediatr Anaesth, 2007. **17**(9): p. 888-92.
116. Shorrab, A.A., A.D. Demian, and M.M. Atallah, *Multidrug intravenous anesthesia for children undergoing MRI: a comparison with general anesthesia.* Paediatr Anaesth, 2007. **17**(12): p. 1187-93.
117. Pershad, J., J. Wan, and D.L. Anghelescu, *Comparison of propofol with pentobarbital/midazolam/fentanyl sedation for magnetic resonance imaging of the brain in children.* Pediatrics, 2007. **120**(3): p. e629-36.
118. Maruf, A.A., et al., *Procedural sedation in children for magnetic resonance imaging--comparison between ketamine diazepam combination with midazolam fentanyl combination.* Mymensingh Med J, 2010. **19**(1): p. 60-5.
119. Golparvar, M., et al., *Paradoxical reaction following intravenous midazolam premedication in pediatric patients - a randomized placebo controlled trial of ketamine for rapid tranquilization.* Paediatr Anaesth, 2004. **14**(11): p. 924-30.
120. Pitetti, R., et al., *Effect on hospital-wide sedation practices after implementation of the 2001 JCAHO procedural sedation and analgesia guidelines.* Arch Pediatr Adolesc Med, 2006. **160**(2): p. 211-6.
121. McQueen, A., et al., *Procedural sedation and analgesia outcomes in children after discharge from the emergency department: ketamine versus fentanyl/midazolam.* Ann Emerg Med, 2009. **54**(2): p. 191-97 e1-4.
122. *FDA drug label propofol*. [cited 2010 Oct 15]; Available from: http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=propofol.
123. Jensen, S., L. Knudsen, and L. Kirkegaard, *Flumazenil used in the antagonizing of diazepam and midazolam sedation in out-patients undergoing gastroscopy.* Eur J Anaesthesiol Suppl, 1988. **2**: p. 161-6.
124. *International Drug Price Indicator Guide* [cited 2010 Oct 15]; Available from: http://erc.msh.org.
125. *Dutch Formulary 'Farmacotherapeutisch Kompas'*. [cited 2010 Oct 15]; Available from: www.fk.cvz.nl.
126. Hohl, C.M., et al., *A cost-effectiveness analysis of propofol versus midazolam for procedural sedation in the emergency department.* Acad Emerg Med, 2008. **15**(1): p. 32-9.
127. *Medicines Evaluation Board, the Netherlands*.
128. *European Pharmacopoeia: midazolam*. [cited 2010 Oct 15]; Available from: http://extranet.pheur.org/4DLink1/4DCGI/Web_View/mono/936.

129. *United States Pharmacopeia*. [cited 2010 Oct 15]; Available from: http://www.usp.org/USPNF/.
130. *British Pharmacopeia*. [cited 2010 Oct 15]; Available from: http://www.pharmacopoeia.co.uk/bp2011/ixbin/bp.cgi.
131. *WHO International Pharmacopeia: midazolam*. [cited 2010 Oct 15]; Available from: http://apps.who.int/phint/en/p/docf/.

Addendum 1

Tradenames and manufacturers. Source:Micromedex®, accessed Nov 2010.

Tradename List for midazolam:	
Name, Form & Strength	Contact
Anesfar	Fahrenheit, Indon.
Apo-Midazolam - 1 MG/ML - Injectable	Apotex
Apo-Midazolam - 5 MG/ML - Injectable	Apotex
Benzosed	Troika, Venez.
Damizol	Specifar, Gr.
Demizolam	Dem, Turk.
Doricum (DI)	Roche, Venez.
Dormicum (FM)	Roche, Israel
Dormicum	EGIS, Hung.
Dormicum	Roche, Austria
Dormicum	Roche, Belg.
Dormicum	Roche, Cz.
Dormicum	Roche, Denm.
Dormicum	Roche, Fin.
Dormicum	Roche, Ger.
Dormicum	Roche, Gr.
Dormicum	Roche, Hong Kong
Dormicum	Roche, Indon.
Dormicum	Roche, Malaysia
Dormicum	Roche, Mex.
Dormicum	Roche, Neth.
Dormicum	Roche, Norw.
Dormicum	Roche, Philipp.
Dormicum	Roche, Pol.
Dormicum	Roche, Port.
Dormicum	Roche, S.Afr.
Dormicum	Roche, Singapore
Dormicum	Roche, Spain
Dormicum	Roche, Swed.
Dormicum	Roche, Switz.
Dormicum	Roche, Thai.
Dormicum	Roche, Turk.
Dormire	Cristalia, Braz.
Dormium	Uniao Quimica, Braz.
Dormixal	Demo, Gr.
Dormizol (DI)	Duopharma, Philipp.
Dormonid	Roche, Braz.
Dormonid	Roche, Chile

Fortanest	Kalbe, Indon.
Fulsed (FM)	Ranbaxy, Cz.
Fulsed	Ranbaxy, Malaysia
Fulsed	Ranbaxy, Singapore
Fulsed	Ranbaxy, Ukr.
Hipnazolam (FM)	Sigma, Braz.
Hipnoz	Pharos, Indon.
Hypnovel - 5 MG/ML - Injectable	Roche
Hypnovel	Roche, Austral.
Hypnovel	Roche, Fr.
Hypnovel	Roche, Irl.
Hypnovel	Roche, NZ
Hypnovel	Roche, UK
Ipnovel	Roche, Ital.
Midacum	Hexal, S.Afr.
Midanium	Cipla-Medpro, S.Afr.
Midanium	Polfa Warszawa, Pol.
Midaselect (FM)	Curasan, Ger.
Midazepin	Behrens, Venez.
Midazolam - 1 MG/ML - Injectable	Faulding Laboratories
Midazolam - 1 MG/ML - Injection Liquid	Novopharm
Midazolam - 1 MG/ML - Injection Solution	Hospira
Midazolam - 5 MG/ML - Injectable	Faulding Laboratories
Midazolam - 5 MG/ML - Injection Liquid	Novopharm
Midazolam - 5 MG/ML - Injection Solution	Hospira
Midazolam Hydrochloride - 1 MG/ML - Injectable	Apotex
Midazolam Hydrochloride - 1 MG/ML - Injection Solution	Abbott Laboratories
Midazolam Hydrochloride - 1 MG/ML - Injection Solution	APP Pharmaceuticals
Midazolam Hydrochloride - 1 MG/ML - Injection Solution	Baxter Healthcare
Midazolam Hydrochloride - 1 MG/ML - Injection Solution	Cura Pharmaceuticals
Midazolam Hydrochloride - 1 MG/ML - Injection Solution	Hospira
Midazolam Hydrochloride - 1 MG/ML - Injection Solution	Hospira
Midazolam Hydrochloride - 1 MG/ML - Injection Solution	Wockhardt USA
Midazolam Hydrochloride - 2 MG/ML - Oral Syrup	Precision Dose
Midazolam Hydrochloride - 2 MG/ML - Oral Syrup	Ranbaxy Pharmaceuticals
Midazolam Hydrochloride - 2 MG/ML -	Roxane Laboratories

Oral Syrup	
Midazolam Hydrochloride - 5 MG/ML - Injectable	Apotex
Midazolam Hydrochloride - 5 MG/ML - Injection Solution	Abbott Laboratories
Midazolam Hydrochloride - 5 MG/ML - Injection Solution	Baxter Healthcare
Midazolam Hydrochloride - 5 MG/ML - Injection Solution	Cura Pharmaceuticals
Midazolam Hydrochloride - 5 MG/ML - Injection Solution	Hospira
Midazolam Hydrochloride - 5 MG/ML - Injection Solution	Hospira
Midazolam Hydrochloride - 5 MG/ML - Injection Solution	Wockhardt USA
Midazolam Hydrochloride - Preservative-Free - 1 MG/ML - Injection Solution	Cura Pharmaceuticals
Midazolam Hydrochloride - Preservative-Free - 5 MG/ML - Injection Solution	Cura Pharmaceuticals
Midazolam Hydrochloride-Sodium Chloride - 1 MG/ML - Injection Solution	Pharmedium Services
Midazolam Injection Bp - 1 MG/ML - Injectable	Baxter
Midazolam Injection Bp - 5 MG/ML - Injectable	Baxter
Midazolam Injection BP 2010	
Midazolam Injection USP 32	
Midazolam Oral Solution BP 2010	
Midazol (DI)	Taro, Israel
Midazol (FM)	Hameln, Thai.
Midolam	Rafa, Israel
Miloz	Novell, Indon.
Mizolam	CCM, Malaysia
Noctura (DI)	Recalcine, Chile
Novaplus Midazolam - 1 MG/ML - Injection Solution	Hospira
Novaplus Midazolam - 5 MG/ML - Injection Solution	Hospira
Pms-Midazolam - 1 MG/ML - Injectable	Pharmascience
Pms-Midazolam - 5 MG/ML - Injectable	Pharmascience
Relacum	Pisa, Mex.
Sedacum	Dexa, Indon.
Sedoz	Claris, Philipp.
Sopodorm	ICN, Pol.
Terap	Sanitas, Chile
Versed - 1 MG/ML - Injectable	Hoffmann-La Roche
Versed - 1 MG/ML - solution for injection	Roche Pharmaceuticals

Versed - 2 MG/ML - Oral Syrup	Roche Pharmaceuticals
Versed - 5 MG/ML - Injectable	Hoffmann-La Roche
Versed - 5 MG/ML - solution for injection	Roche Pharmaceuticals
Versed (FM)	Roche, Canad.
Versed (FM)	Roche, USA
Versed	Roche, Fr.
Zolamid	Mayne, Port.
Zolidan (FM)	BPL-Meizler, Braz.
Zolmid	Laboratorios Chile, Chile
Zomsol	Solara, Mex

Addendum 2. Disclosures

Dr. de Wildt received an unrestricted travel grant from Roche the Netherlands to present study results at an international conference (1998). Dr de Wildt's PhD research (thesis 2001) was partially funded by unrestricted financial support from Roche, USA (to pay for drug analysis costs). Dr de Wildt is a paid consultant to Daichii Sankyo.