

March 10, 2011

Oral anxiolytic medication prior to ambulatory healthcare encounters for individuals with special developmental and behavioral challenges

Clinical Question

- P (population/problem): In children with special developmental and behavioral challenges, who present for an ambulatory healthcare encounter and have significant anxiety that may disrupt their visit,
- I (intervention): does the use of an oral anxiolytic medication before the healthcare encounter,
- C (comparison): in comparison to either forced compliance, an incomplete healthcare visit, sedation, or general anesthesia,
- O (outcome): allow for improved experience and completion of care with acceptable side effects?

Target Population

Inclusion criteria:

- age 3 years and older
- patients with special developmental and behavioral challenges who have difficulty tolerating ambulatory healthcare encounters
- able to take oral medications
- unable to tolerate healthcare encounters even with non-pharmacological support interventions

Exclusion criteria:

- patients with contraindications based on history and physical examination, including:
 - major craniofacial airway abnormalities
 - obstructive sleep apnea
 - major cardiac anomalies

Recommendations (See Table of Recommendation Strength following references)

1. It is recommended that the following parameters be taken into account when selecting the specific anxiolytic medication.
 - patient's current medications (with specific attention to drug-drug interactions)
 - contraindications in the medical and behavioral history, and individual patient challenges
 - specific procedure/visit considerations (e.g. invasiveness, duration)

(*Local Consensus 2011 [5]*).
2. It is recommended that the selected anxiolytic medication be trialed by the family prior to the day of the healthcare encounter, when possible, to assess appropriate timing of dose and to observe for possible side effects. The lowest possible therapeutic dose of the anxiolytic medication used is preferred to avoid adverse effects (*Local Consensus 2011 [5]*). See Appendix 3 (section D).
3. It is recommended that the pharmacological intervention be:
 - first line: clonazepam (*Local Consensus 2011 [5]*)
Note: If a patient takes a different medication for maintenance which would also be effective for anxiety, an alternate for first line pharmacological intervention would be to increase dosage of maintenance medication (*Local Consensus 2011 [5]*).
 - second line: risperidone (*Veser 2006 [2b]*, *Crosland 2003 [4b]*)
 - third line: lorazepam (adolescents age 13 and older) (*Veser 2006 [2b]*, *Battaglia 1997 [2b]*).See table for dosages. The lowest possible therapeutic dose of the anxiolytic medication used is preferred to avoid adverse effects.

Table: Oral Anxiolytic Medications for Healthcare Encounters for Patients with Special Developmental and Behavioral Challenges

Name/Formulations	Dose <i>The lowest possible therapeutic dose of the anxiolytic medication used is preferred to avoid adverse effects.</i>	Onset of Action	Duration of Action	When to redose (by Healthcare Personnel)	Possible Adverse Effects
Benzodiazepines					
Clonazepam (Klonopin) Tablet: 0.5 mg, 1 mg Orally disintegrating tablet: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg Liquid (Compound): 0.1 mg/ml	< 10 yrs: 0.125 mg to 0.5 mg ≥ 10 yrs: 0.5 mg to 1 mg	20 to 60 minutes	6 to 12 hours	45 to 60 minutes	Ataxia, somnolence, abnormal movements
Lorazepam (Ativan) (adolescents) Tablet: 0.5 mg, 1 mg, 2 mg Liquid: 2 mg/ml	≥ 13 years of age 0.02 to 0.05 mg/kg (max dose 2 mg)	20 to 30 minutes	6 to 8 hours	45 to 60 minutes	Asthenia, dizziness, vertigo, blurred vision
Atypical Antipsychotics					
Risperidone M-tab (Risperdal M-tab) Orally disintegrating tablet: 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg	≥ 5 years of age: 15 to 20 kg: 0.25 mg ≥ 20 kg: 0.5 mg <5 years of age: No dosing recommendations available, use with caution	60 minutes	Up to 24 hours	1.5 to 2 hours	QTc prolongation, weight gain, constipation, dry mouth, dizziness, EPS

(Micromedex Inc. Updated periodically [5], Local Consensus 2011 [5], Taketomo 2008 [5])

Abbreviations: EPS = extrapyramidal system symptoms, kg = kilograms, mg = milligrams, ml = milliliter, QTc = a parameter of an electrocardiograph; yrs = years

Discussion/summary of evidence

There is little direct evidence published on the use of oral anxiolytics for pre-procedural dosing in children with special needs. The populations studied in the published articles evaluated for this review most often were typically-developing children or adults, and the studies often specifically excluded children with developmental disabilities and behavioral issues. Therefore, these recommendations were developed from a combination of extrapolation from the sparse and indirect evidence and the more than 10 years' of local clinical experience, by several clinicians, with pre-procedural anxiolytic medication in this population.

Oral medications with effective anxiolytic, not sedative, properties were the object of this review. No published literature on the use of clonazepam was identified in the literature search; lack of published evidence does not imply lack of efficacy, and therefore the best available evidence was extensive local clinical experience. The selection of clonazepam for first line medication was based on the following factors:

- over the past 10 years: successful, local clinical experience by several clinicians with this population for this indication
- ease of administration (orally disintegrating tablet),
- duration of action (long enough to complete procedure without redosing), and
- delayed onset (appropriate for transport of patient from home).

The most direct evidence identified to answer the clinical question was a small prospective trial of oral clonidine in a pediatric population with autism undergoing EEG. Pre-procedural anxiolytic medication for EEG is particularly problematic due to the interference of some drugs with brain wave activity; clonidine does not exhibit this disadvantage. Ninety-three percent of the participants completed the test with a satisfactory EEG reading (*Mehta 2004 [3b]*). Due to the local consensus for concern with risk for hypotension in the non-monitored setting, this medication was not selected to be included in the recommendations.

Two small randomized controlled studies on lorazepam were conducted in agitated adult populations and may be best generalizable to adolescents, rather than to younger children. Lorazepam alone was as effective as when combined with antipsychotic agents, and more side effects were exhibited with haloperidol alone than with lorazepam alone (*Veser 2006 [2b]*, *Battaglia 1997 [2b]*).

All reviewed articles from the literature search for the recommended medications are summarized in Appendix 1.

Additional articles from the literature search for medications not included in these recommendations are summarized in Appendix 2. Considerations that eliminated medications from the recommendations include:

- sedative properties [midazolam (*Almenrader 2007 [2b]*, *Schmidt 2007 [2b]*), diazepam (*Wilner 2002 [2b]*)]
- paradoxical behaviors in this population (opposite than intended effect) [midazolam (*Almenrader 2007 [2b]*, *Schmidt 2007 [2b]*, *Finley 2006 [2b]*)]
- emergent behaviors (agitation when the drug effect is wearing off) [midazolam (*Kanegaye 2003 [2a]*, *McGraw 1998 [2a]*, *Almenrader 2007 [2b]*, *Tazeroualti 2007 [2b]*), diazepam (*Kalachnik 2002 [1b]*, *Marrosu 1987 [2b]*)],
- short duration of action [diazepam (*Marrosu 1987 [2b]*)],
- safety concerns in the non-monitored setting [clonidine (*Mehta 2004 [3b]*)], and
- lack of local experience in combination with lack of published evidence of efficacy [other antipsychotic agents (*Wilner 2002 [2b]*)].

Health Benefits and Safety Concerns

Safety concerns are a key driver in the selection of medications for pre-procedural anxiolytic medications for this population. Side effects and potential adverse effects of medication administration are always balanced against the benefits of their use and alternatives to their use. See the Table for potential side effects and adverse effects for recommended medications, and see the discussion above for safety concerns for specific medications not included in these recommendations. See Appendix 3 for safety guidance for use of oral anxiolytic medication prior to healthcare encounters.

The following benefits from implementation of these recommendations are predicted:

- a more productive and thorough appointment

- decreased distress during appointment
- improved experience of care
- improved reliability for completion of follow-up appointments.

Alternatives to use of these oral anxiolytic drugs include:

- non-pharmacological methods (i.e.: preparation, distraction, relaxation techniques, and other psychosocial methods used to support children through stressful healthcare encounters)
- non-oral medications
- sedatives
- general anesthesia.

Non-pharmacological methods are safest and patients are not considered eligible for anxiolytic recommendations unless it has been observed that the patient is unable to tolerate healthcare encounters even with non-pharmacological support interventions. The potential benefit of preprocedural anxiolytic medications required to accomplish medical encounters in this population is revealed both in terms of improved patient safety and in minimization of resource expenditure when compared to the alternatives of non-oral, sedative, or general anesthetic medications. Use of those alternatives requires higher acuity medical resources such as the use of the operating room environment and/or the need for more intensive monitoring. Safety risks of those alternatives may include oversedation leading to depression of respiratory effort, malignant hyperthermia, and cardiac dysrhythmias.

A separate search of the literature was conducted to specifically address safety concerns with use of the three recommended medications: clonazepam, risperidone and lorazepam. The appraisal of this literature confirmed that the use of these medications as recommended in this BEST is safe regarding heart rate, blood pressure, other cardiovascular events, and airway compromise (*Antia 2005 [1b]*, *Miral 2008 [2b]*, *Luby 2006 [2b]*, *Aman 2005 [2b]*, *Shea 2004 [2b]*, *Graae 1994 [2b]*, *Findling 2004 [4a]*, *Alacqua 2008 [4b]*, *Nahshoni 2007 [4b]*, *Malone 2002 [4b]*).

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Note: When using the electronic version of this document,  indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the Cincinnati Children's Hospital Medical Center (CCHMC) network.

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Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.
<p>Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.</p> <ol style="list-style-type: none"> 1. Grade of the Body of Evidence (see note above) 2. Safety / Harm 3. Health benefit to patient (<i>direct benefit</i>) 4. Burden to patient of adherence to recommendation (<i>cost, hassle, discomfort, pain, motivation, ability to adhere, time</i>) 5. Cost-effectiveness to healthcare system (<i>balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis</i>) 6. Directness (<i>the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]</i>) 7. Impact on morbidity/mortality or quality of life 	

Supporting information

Introductory/background information

The Adaptive Care Team (ACT) was developed to focus on the ability for individuals with developmental and behavioral needs to tolerate healthcare procedures/visits. Preparation and various support interventions are first line strategies to assist all patients’ coping and cooperation with healthcare encounters. When these strategies are not effective, additional staff, restraining, and general anesthesia have been some of the next line options. These options and the patient’s nonadherence, have a negative impact on:

- patient/family stress level and satisfaction
- patient return visits
- clinic flow and schedules
- staff productivity
- efficiency, efficacy and safety of healthcare procedures/visits.

As part of a mission to provide patient/family-centered care for all patients and as a response to staff requesting more strategies to use with this population, this subcommittee was formed to evaluate the use of pre-procedural anxiolytic medication when non-pharmacological support interventions have been unsuccessful or when the patient has been assessed as having very high anxiety using a distress assessment tool or clinical judgment.

Appendix 1: Studies of use of recommended medications for decreasing anxiety during healthcare encounters

Study	Drug	Comparison	Dose	Study Design	Sample size	Population	Results	Comments/ Side Effects
Clonazepam (Klonopin) – no studies								
Risperidone (Risperdal M-tab) – 2 studies								
<i>(Veser 2006 [2b])</i>	risperidone w/ lorazepam or haloperidone w/ lorazepam	placebo w/ lorazepam	2 mg oral risperidone, or 5 mg IM haloperidol w/ 2 mg IM lorazepam	pilot/ RCT/ double blind/ placebo	30	adults: 18 to 65 years old • agitated or psychotic • presenting to the emergency department	No significant difference between groups. Lorazepam alone was as effective as either antipsychotic with lorazepam	12 patients returned for 24 hour follow up. No deleterious effects were observed
<i>(Crosland 2003 [4b])</i>	risperidone	placebo	• initial placebo phase • low dose (1 mg per day for children) phase • high dose (0.5 mg/kg per day) phase • second placebo phase	N of 1 case studies 4 phases	2	6 and 24 years old with autism	For both individuals, • destructive behavior during the demand condition was significantly reduced during the medication phases, • destructive behavior to obtain tangible items (Reggie) and attention (Sean) was not reduced In addition, there appeared to be a differential effect of the medication on self-injurious behavior versus aggression for Sean.	weight gain in Sean led to discontinuation of the medication
Lorazepam (Ativan) – 2 studies								
<i>(Veser 2006 [2b])</i>	risperidone w/lorazepam or haloperidone w/lorazepam	placebo w/lorazepam	• oral risperidone 2 mg and • IM lorazepam 2 mg or • IM haloperidol 5 mg and • IM lorazepam 2 mg	pilot/ RCT/ double blind/ placebo	30	adults: 18 to 65 years old • agitated or psychotic • presenting to the emergency department	No significant difference between groups. Lorazepam alone was as effective as either antipsychotic with lorazepam	12 patients returned for 24 hour follow up. No deleterious effects were observed

Study	Drug	Comparison	Dose	Study Design	Sample size	Population	Results	Comments/ Side Effects
<i>(Battaglia 1997 [2b])</i>	haloperidone	lorazepam	<ul style="list-style-type: none"> • IM 5 mg haloperidol or • IM 2 mg lorazepam, or • both 	RCT/ double blind	98	adults: 18 to 57 years old <ul style="list-style-type: none"> • psychotic, agitated or aggressive • presenting to emergency department 	all groups <ul style="list-style-type: none"> • significant reduction on the Agitated Behavioral Scale (ABS). combination group <ul style="list-style-type: none"> • significantly greater reduction in ABS score 1 hour after injection. 	side effects did not differ significantly between treatment groups, although patients receiving haloperidol alone tended to have more extrapyramidal system symptoms.

Appendix 2: Relevant studies of medications not included in the recommended anxiolytics (in alphabetic order by drug name)

Study	Drug	Comparison	Dose	Study Design	Sample size	Population	Results	Comments/ Side Effects
Clonidine (Catapres) – 9 studies								
<i>(Almenrader 2007 [2b])</i>	midazolam	clonidine	oral midazolam 0.5 mg/kg oral clonidine 4 µg/kg	RCT	64	1 to 6 years old scheduled for surgery. <u>exclusion criteria:</u> • children who spat out the medicine	14% of children rejected oral midazolam. Onset of sedation was significantly faster after premedication with midazolam (30 ± 13.1 min) than with clonidine (38.5 ± 14.6 min), but level of sedation was significantly better after premedication with clonidine. Quality of mask induction was equally successful in both groups. A steal-induction was performed in 66% of patients in the clonidine group, but none in the midazolam group	They observed a trend towards an increased incidence of emergence agitation after premedication with midazolam. Parental satisfaction was significantly higher in the clonidine group.
<i>(Schmidt 2007 [2b])</i>	midazolam	clonidine dexmedetomidine	• oral midazolam 0.5 mg/kg or • oral clonidine 4 µg/kg or • transmucosal dexmedetomidine (DEX) 1 µg/kg	RCT/ double blind	60	7 to 12 years old undergoing elective ambulatory surgery <u>exclusion criteria:</u> children with • autism • cerebral palsy • difficulty in understanding verbal commands from study. • chronic pain children taking analgesics or anticonvulsants	Dexmedetomidine and clonidine were related to lower scores of pain than midazolam. α ₂ -agonists produced lower scores of preoperative mean arterial pressure and heart rate than midazolam. Both groups had similar levels of postoperative state-anxiety in children. There was no difference in preanesthesia levels of sedation and response to separation from parents between groups.	There were no differences between groups in adverse effects of studied drugs during emergence from anesthesia or follow-up in PACU.
<i>(Tazeroualti 2007 [2b])</i>	clonidine (2 doses)	midazolam	• oral midazolam 0.5 mg/kg or • oral clonidine 2 µg/kg or • oral clonidine 4 µg/kg	RCT/ double blind	68	1 to 6 years old healthy undergoing circumcision <u>exclusion criteria:</u> • family history of malignant hyperthermia • mental retardation • neurological disease potentially associated with symptoms of agitation.	Only the 4 µg/kg dose of clonidine was associated with a significant reduction in emergence agitation. Fewer children in the clonidine 4 µg/kg group displayed agitation (25%) than in the midazolam group (60%) (P < 0.025).	Incidence of hypotension and bradycardia, time to first micturition and first drink did not differ among groups.

Study	Drug	Comparison	Dose	Study Design	Sample size	Population	Results	Comments/ Side Effects
(Sumiya 2003 [2b])	clonidine (2 doses)	doses	oral clonidine 2 µg/kg, or oral clonidine 4 µg/kg	RCT	16	1 to 11 years old	The patients with satisfactory sedation had higher plasma clonidine concentration than that of the patients with unsatisfactory sedation (0.45+/- 0.16 µg/ml vs. 0.26+/- 0.16 µg/ml, $p < 0.05$). The clonidine concentrations in the satisfactory group ranged from 0.28 to 0.81 µg/ml.	There was no significant difference in hemodynamic parameters (SBP, DBP and HR) before and after administration of clonidine lollipop in both satisfactory and unsatisfactory sedation groups.
(Fazi 2001 [2b])	clonidine	midazolam	oral <ul style="list-style-type: none"> midazolam 0.5 mg/kg clonidine 4 µg/kg 	RCT/ double blind	134	4 to 12 years old without central nervous system disorders	<ul style="list-style-type: none"> anxiety scores were higher at separation from parents in the clonidine group. anxiety scale scores at baseline and ten minutes before patient separation from parents were similar between the two groups. 	time from administration to separation from parents <ul style="list-style-type: none"> clonidine 75+/- 25 min midazolam 35 min +/- 13min.
(Reimer 1998 [2b])	clonidine / placebo	placebo / fentanyl	<ul style="list-style-type: none"> oral clonidine 4 µg/kg and IV placebo intraoperatively or <ul style="list-style-type: none"> oral placebo and IV 3 µg/kg fentanyl intraoperatively 	RCT/ double blind/ placebo	36	7 to 12 years old presenting for elective adenotonsillectomy <u>exclusion criteria:</u> <ul style="list-style-type: none"> inability to understand English obesity inability to use a visual analogue scale. 	<ul style="list-style-type: none"> children in clonidine group had a higher incidence of preoperative sedation (63%) than those receiving fentanyl (6%). VAS scores were similar throughout the observation period. 	<ul style="list-style-type: none"> no difference either in the number of morphine or codeine rescue doses administered or in the incidence of side effects. preinduction mean arterial pressure was lower in the clonidine group but required no intervention.
(Mikawa 1996 [2b])	clonidine (2 doses)	placebo	oral <ul style="list-style-type: none"> 2 µg/kg 4 µg/kg placebo 	RCT/ placebo/ double blind/ placebo	90	5 to 12 years old undergoing minor elective surgery	clonidine 4 µg/kg group <ul style="list-style-type: none"> lowest top scores (Objective Pain Scale) during 12 hrs after surgery reduced requirement for postoperative supplementary analgesic (diclofenac suppository) compared with <ul style="list-style-type: none"> the other two groups 	<ul style="list-style-type: none"> no clinically significant differences in postoperative vital signs between groups clonidine is inexpensive
(Mikawa 1993 [2b])	clonidine (2 doses)	diazepam	oral clonidine <ul style="list-style-type: none"> 2 µg/kg 4 µg/kg or <ul style="list-style-type: none"> oral diazepam <ul style="list-style-type: none"> 0.4 mg/kg 	RCT/ placebo/ double blind	105	4 to 12 years old undergoing elective ophthalmologic surgery	clonidine 4 µg/kg group <ul style="list-style-type: none"> better preoperative sedation than placebo or clonidine 2 µg/kg lowest top scores (Objective Pain Scale) during 12 hrs after surgery reduced requirement for postoperative supplementary analgesic (diclofenac suppository) than the other groups 66% of parents satisfied compared to 11% of diazepam group 60% of patients satisfied compared to 20 to 23% of other two groups 	<ul style="list-style-type: none"> postoperative vital signs lower in clonidine groups, resolving in 10 hrs for high-dose and 8 hrs for low-dose groups no intervention was required for any low vital signs

Study	Drug	Comparison	Dose	Study Design	Sample size	Population	Results	Comments/ Side Effects
(Mehta 2004 [3b])	clonidine	none	oral clonidine 0.05 mg to 0.2 mg	prospective study	27	2 to 17 years old with autism undergoing EEG	93% completed the test with a satisfactory EEG reading. 85% achieved a sedation score of 2 or less. Mean time to sedation was 58 minutes with a range of 15 to 135 minutes (SD 32.7). Mean time to recovery was 105 ranging from 20 to 195 (SD 40.9)	Mild and asymptomatic reduction in blood pressure and pulse rate occurred in 4 of the 23 successfully sedated patients
Diazepam (Valium) – 3 studies, plus 1 above in comparison to clonidine								
(Wilner 2002 [2b])	ziprasidone	diazepam placebo	single oral dose • 20 mg ziprasidone or • 10 mg diazepam or • placebo	RCT/ placebo/ double blind	90	adults: 18 to 50 years undergoing dental procedures	anxiolytic effect: ziprasidone at 3 hours postdose, • was significantly greater than that of placebo ($p < 0.05$) • somewhat greater than that of diazepam diazepam at 3 hour postdose • was not significantly different from that of placebo diazepam at 1 hour postdose • was significantly greater than that of placebo ($p < 0.05$) sedative effect: ziprasidone at all times • never greater than that of placebo diazepam at 1 to 1.5 hours postdose • significantly greater than that of placebo	<ul style="list-style-type: none"> no serious adverse events were reported seven subjects reported adverse events that were considered to be related to the study drugs, including <ul style="list-style-type: none"> one patient in the ziprasidone group experienced moderate nausea and severe vomiting three patients in the diazepam group reported mild headache one patient in the diazepam group reported moderate somnolence one patient in the placebo group reported mild headache, myalgia, and dizziness
(Mikawa 1993 [2b])	clonidine (2 doses)	diazepam	oral clonidine • 2 µg/kg or • 4 µg/kg or oral diazepam • 0.4 mg/kg	RCT/ placebo/ double blind	105	4 to 12 years old undergoing elective ophthalmologic surgery	clonidine 4 µg/kg group • better preoperative sedation than placebo or clonidine 2 µg/kg • lowest top scores (Objective Pain Scale) during 12 hrs after surgery • reduced requirement for postoperative supplementary analgesic (diclofenac suppository) than the other groups • 66% of parents satisfied compared to 11% of diazepam group • 60% of patients satisfied compared to 20 to 23% of other two groups	<ul style="list-style-type: none"> postoperative vital signs lower in clonidine groups, resolving in 10 hrs for high-dose and 8 hrs for low-dose groups no intervention was required for any low vital signs
(Marrosu 1987 [2b])	diazepam	none	IM 10 mg	prospective	7	7 to 11 years old with autism	global worsening compared to basal condition: • observed behavior • mood • anxiety	<ul style="list-style-type: none"> behavioral effects present 10 to 15 min after treatment max effect at 15 to 25 min effects lasted about 60 min basal condition recorded at 3 hours after administration

Study	Drug	Comparison	Dose	Study Design	Sample size	Population	Results	Comments/ Side Effects
Midazolam – 3 studies, plus 4 more above in comparison to clonidine								
<i>(Finley 2006 [2b])</i>	midazolam	placebo	oral midazolam 0.5 mg/kg mixed with acetaminophen suspension or acetaminophen alone	RCT/ placebo	40	4 to 6 years old undergoing myringotomy <u>exclusion criteria:</u> <ul style="list-style-type: none"> • history of neurological or cognitive impairment or disease • previous adverse reaction to a benzodiazepine • taking medication other than antibiotics 	Children who received midazolam reacted significantly less to induction of anesthesia than did children in the placebo control group, $F(1, 38) = 7.46, P = 0.01$. Baseline level of impulsivity was positively associated with adverse reactions to anesthesia induction in the drug group, but not in the placebo group, suggesting that high levels of trait impulsivity may contraindicate the use of midazolam as a preoperative medication.	Children were excluded if they had a history of neurological or cognitive impairment or disease, previous adverse reaction to a benzodiazepine, or were taking medication other than antibiotics.
<i>(Kanegaye 2003 [2a])</i>	midazolam	standard dose (SDM) high dose (HDM)	0.5 mg/kg (SDM) 1 mg/kg (HDM)	RCT, double blind	65	6 to 48 months old undergoing cutaneous procedures	Behavior scores improved for both groups following medication administration and at best sedation during procedure. HDM produced better sedation at time of first suture (successful sedation: 70%, SDM vs. 91%, HDM; intergroup difference = 21%; 95% confidence interval [CI] = 2, 41) and at best point during the procedure (72%, SDM vs. 97%, HDM; D = 25%; 95% CI = 8, 43). However, sedative efficacy declined such that only 50% and 73% of the SDM and HDM groups, respectively, had successful sedation at the worst point during the procedures. Postprocedure agitation occurred in 17% of patients (6%, SDM vs. 27%, HDM; D = 21%; 95% CI = 3, 39).	
<i>(McGraw 1998 [2a])</i>	midazolam	placebo	<ul style="list-style-type: none"> • oral 0.5 mg/kg or • placebo 	RCT, double blind/ placebo	70	1 to 10 years old undergoing outpatient sedation procedures	<ul style="list-style-type: none"> • no difference on behavioral evaluation scores • children in midazolam group cried significantly less during induction than children in placebo group ($p < .02$) • at one week follow up children in midazolam group had significantly more adverse postoperative behavioral changes than children in placebo group ($p < .02$) 	Negative postoperative behavior included <ul style="list-style-type: none"> • increased anxiety • nightmares • night terrors • food rejection • negativism.

Appendix 3: Safety Guide for use of oral anxiolytic medication prior to healthcare encounters

- A. Patient indications for use:
 - unable to tolerate ambulatory procedures/visits even with non-pharmacological support interventions
 - special developmental or behavioral challenges
 - age over 3 years
 - able to take oral medication

- B. Patient contraindications for use (include but are not limited to):
 - major craniofacial airway abnormalities
 - obstructive sleep apnea
 - major cardiac anomalies

- C. Selection of medication (see also recommendations)
 - consider current/concomitant medications
 - consider onset and duration of action of selected medication (see Table)
 - consider potential medication tolerance issues when used frequently (becomes less effective with frequent use)
 - the lowest possible therapeutic dose of the medication used is preferred to avoid adverse effects

- D. Trial at home on a day prior to the healthcare encounter (if feasible)
 - to observe the effects of the medication and report to provider (desired and adverse effects such as more subdued or more agitated)
 - to determine the time interval from administration to peak effect time (when child is most subdued)
 - desire peak anxiolysis to occur just before patient arrives for appointment/treatment
 - provider may adjust dose or selection of medication based on parent report of desired and adverse effects

- E. Parent/family able to safely administer anxiolytic medication (prior trial by family recommended)
 - understands relationship of time-of-dose to time-of-arrival for appointment/treatment
 - understands concern for compromised airway while medicated
 - has considered appropriate monitoring and reporting measures such as:
 - additional person to assist
 - continuous observation when possible
 - accurate medication details (medication, dose, time-of-dose) communicated to clinical staff upon arrival at appointment

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Search strategy

1. Initial Searches

Databases: CINAHL, MEDLINE, PSYCHINFO

All dates through December, 2008

Keywords: autism, developmental disabilities, pervasive developmental disability, patient compliance, preoperative, anxiety, medication, pre-medication, clonidine, anti-psychotic, benzodiazepine, anxiolytics, side effects

Database: MEDLINE

All dates through April 20, 2009

*Antipsychotic Agents/ or atypical antipsychotics.mp AND
(premedication.mp OR anxiolytic.mp OR Anti-Anxiety Agents/ OR chemical restraint.mp)
Filtered for child age 0 to 18 years and English language

2. Additional Searches

Databases: CINAHL, MEDLINE, PSYCHINFO

All Dates through April 20, 2009

Keywords: busparone, chloral hydrate, clonidine, haliperidone

Database: MEDLINE

All Dates through May, 2010

a. clonazepam OR risperidone OR lorazepam

b. filtered for English language only and children age 0 to 18 years

c. AND (airway OR cardiov\$ OR blood pressure OR tachycardia OR safety)

- filtered for (autism OR ex Autism Disorder/ OR exp Disabled Children)

- filtered for (anx\$ or exp Anxiety/ OR Anti-Anxiety Agents/ OR Dental Anxiety)
- d. separate search for a AND b above AND (overdose\$ or accidental ingestion or poison control center\$)

3. Additional articles identified from reference lists and clinicians

Applicability issues

- In order for these recommendations to be useful, patients must be identified as having difficulty tolerating healthcare encounters.
- These recommendations are made as pre-appointment measures.
- A process for identification of prescribing clinician must be developed.
- CCHMC policy is in agreement with these recommendations: Policy V-114 Procedural Sedation/Analgesia/Anesthesia Monitoring Guidelines (policy dated October 13, 2010).
- Safety guidance for clinicians and parents in the use of these recommendations is provided (Appendix 3).

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This Best Evidence Statement has been reviewed against quality criteria by 2 independent reviewers from the Cincinnati Children's Hospital Medical Center (CCHMC) Evidence Collaboration.

Additionally for more information about this CCHMC Best Evidence Statement, contact: 513-636-4799

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.