Useful Research Abstracts About Benzos:
the increased risk for delirium and medical trauma

Briefly, **benzos have now been shown to quadruple rates of delirium, increase rates of medical trauma (which is associated with medical nonadherence among solid transplant pts), and increase length of stay in the PICU and hospital. There are also long-term cognitive impacts on IQ.** I highlighted the findings below in case you want to quickly skim.

Precedex appears to be protective against delirium, as is melatonin.

Hope this is helpful!

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Am J Respir Crit Care Med. 2008 May 1;177(9):976-82. doi: 10.1164/rccm.200706-857OC. Epub 2008 Jan 31.

Children's factual and delusional memories of intensive care.

Colville G1, Kerry S, Pierce C.

OBJECTIVES: Delusional memories are significantly associated with post-traumatic stress in adult patients after intensive care. In this study, we attempted to establish whether this relationship was found in children. We also examined the association between factual memory and distress.

METHODS: One hundred two consecutive children, aged between 7 and 17 years, were interviewed about their pediatric intensive care unit (PICU) experience 3 months after discharge from a PICU. Principal measures were the ICU Memory Tool (a checklist of intensive care memories) and an abbreviated version of the Impact of Event Scale (a screen for post-traumatic stress disorder).

MEASUREMENTS AND MAIN RESULTS: In total, 64 of 102 (63%) children reported at least one factual memory of their admission and 33 of 102 (32%) reported delusional memories, including disturbing hallucinations. Traumatic brain injury was negatively associated with factual memory (odds ratio, 0.23; 95% confidence interval [CI], 0.09-0.58; P = 0.002). Longer duration of opiates/benzodiazepines was associated with delusional memory (odds ratio, 4.98; 95% CI, 1.3-20.0; P = 0.023). Post-traumatic stress scores were higher in children reporting delusional memories (adjusted difference, 3.0; 95% CI, 0.06-5.9; P = 0.045) when illness severity and emergency status were controlled for. Factual memory was not significantly associated with post-traumatic stress.

CONCLUSIONS: This study indicates that delusional memories are reported by almost one-third of children and are associated both with the duration of opiates/benzodiazepines and risk of post-

traumatic stress. More research is needed on the presence of delusional memories and associated risk factors in children receiving intensive care treatment.

Posttraumatic stress disorder in critical illness survivors: a meta-analysis. Crit Care Med. 2015 May;43(5):1121-9

Parker AM[1], Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM.

OBJECTIVE: To conduct a systematic review and metaanalysis of the prevalence, risk factors, and prevention/treatment strategies for posttraumatic stress disorder symptoms in critical illness survivors.

STUDY SELECTION: Eligible studies met the following criteria: 1) adult general/nonspecialty ICU, 2) validated posttraumatic stress disorder instrument greater than or equal to 1 month post-ICU, and 3) sample size greater than or equal to 10 patients.

DATA SYNTHESIS: The search identified 2,817 titles/abstracts, with 40 eligible articles on 36 unique cohorts (n = 4,260 patients). The Impact of Event Scale was the most common posttraumatic stress disorder instrument. Between 1 and 6 months post-ICU (six studies; n = 456), the pooled mean (95% CI) Impact of Event Scale score was 20 (17-24), and the pooled prevalences of clinically important posttraumatic stress disorder symptoms (95% CI) were 25% (18-34%) and 44% (36-52%) using Impact of Event Scale thresholds greater than or equal to 35 and greater than or equal to 20, respectively. Between 7 and 12 months post-ICU (five studies; n = 698), the pooled mean Impact of Event Scale score was 17 (9-24), and pooled prevalences of posttraumatic stress disorder symptoms were 17% (10-26%) and 34% (22-50%), respectively.ICU risk factors for posttraumatic stress disorder symptoms included benzodiazepine administration and post-ICU memories of frightening ICU experiences. Posttraumatic stress disorder symptoms were associated with worse quality of life. In European-based studies: 1) an ICU diary was associated with a significant reduction in posttraumatic stress disorder symptoms, 2) a self-help rehabilitation manual was associated with significant posttraumatic stress disorder symptom reduction at 2 months, but not 6 months; and 3) a nurse-led ICU follow-up clinic did not reduce posttraumatic stress disorder symptoms.

CONCLUSIONS: Clinically important posttraumatic stress disorder symptoms occurred in one fifth of critical illness survivors at 1-year follow-up, with higher prevalence in those who had comorbid psychopathology, received benzodiazepines, and had early memories of frightening ICU experiences. In European studies, ICU diaries reduced posttraumatic stress disorder symptoms.

Acta Anaesthesiol Scand. 2010 Apr;54(4):397-402. doi: 10.1111/j.1399-6576.2009.02207.x. Epub 2010 Jan 18.

Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies.

Dahmani S[1], Brasher C, Stany I, Golmard J, Skhiri A, Bruneau B, Nivoche Y, Constant I, Murat I.

Abstract

BACKGROUND: Premedication is considered important in pediatric anesthesia. Benzodiazepines are the most commonly used premedication agents. Clonidine, an alpha2 adrenoceptor agonist, is gaining popularity among anesthesiologists. The goal of the present study was to perform a meta-analysis of studies comparing premedication with clonidine to Benzodiazepines.

METHODS: A comprehensive literature search was conducted to identify clinical trials focusing on the comparison of clonidine and Benzodiazepines for premedication in children. Six reviewers independently assessed each study to meet the inclusion criteria and extracted data. Original data from each trial were combined to calculate the pooled odds ratio (OR) or the mean differences (MD), 95% confidence intervals [95% CI] and statistical heterogeneity were accessed.

RESULTS: Ten publications fulfilling the inclusion criteria were found. Premedication with clonidine, in comparison with midazolam, exhibited a superior effect on sedation at induction (OR=0.49 [0.27, 0.89]), decreased the incidence of emergence agitation (OR=0.25 [0.11, 0.58]) and produced a more effective early post-operative analgesia (OR=0.33 [0.21, 0.58]). Compared with diazepam, clonidine was superior in preventing post-operative nausea and vomiting (PONV).

DISCUSSION: Premedication with clonidine is superior to midazolam in producing sedation, decreasing post-operative pain and emergence agitation. However, the superiority of clonidine for PONV prevention remains unclear while other factors such as nausea prevention might interfere with this result.

Mody K1, Kaur S2, Mauer EA3, Gerber LM3, Greenwald BM2, Silver G4, Traube C2.**Benzodiazepines and Development of Delirium in Critically Ill Children: Estimating the Causal Effect.** Crit Care Med. 2018 Sep;46(9):1486-1491. doi: 10.1097/CCM.0000000000003194.

OBJECTIVES: Benzodiazepine use may be associated with delirium in critically ill children. However, benzodiazepines remain the first-line sedative choice in PICUs. Objectives were to determine the temporal relationship between administration of benzodiazepines and delirium development, control for time-varying covariates such as mechanical ventilation and opiates, and evaluate the association between dosage of benzodiazepines and subsequent delirium.

DESIGN: Retrospective observational study.

SETTING: Academic tertiary care PICU.

PATIENTS: All consecutive admissions from January 2015 to June 2015.

INTERVENTIONS: Retrospective assessment of benzodiazepine exposure in a population that had been prospectively screened for delirium.

MEASUREMENTS AND MAIN RESULTS: All subjects were prospectively screened for delirium throughout their stay, using the Cornell Assessment for Pediatric Delirium, with daily cognitive status assigned as follows: delirium, coma, or normal. Multivariable mixed effects modeling determined predictors of delirium overall, followed by subgroup analysis to assess effect of benzodiazepines on subsequent development of delirium. Marginal structural modeling was used to create a pseudorandomized sample and control for time-dependent variables, obtaining an unbiased estimate of the relationship between benzodiazepines and next day delirium. The cumulative daily dosage of benzodiazepines was calculated to test for a dose-response relationship. Benzodiazepines were strongly associated with transition from normal cognitive status to delirium, more than**quadrupling delirium rates** (odds ratio, 4.4; CI, 1.7-11.1; $p < 0.002$). Marginal structural modeling demonstrated odds ratio 3.3 (CI, 1.4-7.8), after controlling for time-dependent confounding of cognitive status, mechanical ventilation, and opiates. With every one log increase in benzodiazepine dosage administered, there was a 43% increase in risk for delirium development.

CONCLUSIONS: Benzodiazepines are an independent and modifiable risk factor for development of delirium in critically ill children, even after carefully controlling for time-dependent covariates, with a dose-response effect. This temporal relationship suggests causality between benzodiazepine exposure and pediatric delirium and supports limiting the use of benzodiazepines in critically ill children.

Smith HAB1, Gangopadhyay M, Goben CM, Jacobowski NL, Chestnut MH, Thompson JL, Chandrasekhar R, Williams SR, Griffith K, Ely EW, Fuchs DC, Pandharipande PP**. Delirium and Benzodiazepines Associated With Prolonged ICU Stay in Critically Ill Infants and Young Children**. Crit Care Med. 2017 Sep;45(9):1427-1435. doi: 10.1097/CCM.0000000000002515.

OBJECTIVES: Delirium is prevalent among critically ill children, yet associated outcomes and modifiable risk factors are not well defined. The objective of this study was to determine associations between pediatric delirium and modifiable risk factors such as benzodiazepine exposure and short-term outcomes.

DESIGN: Secondary analysis of collected data from the prospective validation study of the Preschool Confusion Assessment Method for the ICU.

SETTING: Tertiary-level PICU.

PATIENTS: Critically ill patients 6 months to 5 years old.

MEASUREMENTS AND MAIN RESULTS: Daily delirium assessments were completed using the Preschool Confusion Assessment Method for the ICU. Associations between baseline and in-hospital risk factors were analyzed for likelihood of ICU discharge using Cox proportional hazards regression and delirium duration using negative binomial regression. Multinomial logistic regression was used to determine associations between daily risk factors and delirium presence the following day. Our 300-patient cohort had a median (interquartile range) age of 20 months (11-37 mo), and 44% had delirium for at least 1 day (1-2 d). Delirium was significantly associated with a decreased likelihood of ICU discharge in preschool-aged children (age-specific hazard ratios at 60, 36, and 12 mo old were 0.17

[95% CI, 0.05-0.61], 0.50 [0.32-0.80], and 0.98 [0.68-1.41], respectively). Greater benzodiazepine exposure (75-25th percentile) was significantly associated with a lower likelihood of ICU discharge (hazard ratio, 0.65 [0.42-1.00]; p = 0.01), longer delirium duration (incidence rate ratio, 2.47 [1.36-4.49]; p = 0.005), and increased risk for delirium the following day (odds ratio, 2.83 [1.27-6.59]; p = 0.02).

CONCLUSIONS: Delirium is associated with a lower likelihood of ICU discharge in preschool-aged children. Benzodiazepine exposure is associated with the development and longer duration of delirium, and lower likelihood of ICU discharge. These findings advocate for future studies targeting modifiable risk factors, such as reduction in benzodiazepine exposure, to mitigate iatrogenic harm in pediatric patients.

Below are a couple more references on the **long-term cognitive effects** of benzo use among medically ill children. Also, below, is a description of a new study, recently presented at the annual meeting of the International Anesthesia Research Society on the **independent risk of benzos for development of delirium in medically ill children**. They reportedly "demonstrated that younger age, higher severity of illness and, more importantly, benzodiazepine exposure are independent risk factors for increased delirium duration. Benzodiazepine administration was also significantly associated with the transition to delirium the day following drug exposure."

Chen X, Wan Y, Wen K, Liang T, Lin T, Li P. **Effect of neonatal perioperative anesthetic exposure in cardiac surgery on neuro- developmental outcomes in preschool children**. Nan Fang Yi Ke Da Xue Xue Bao. 2015 Aug;35(9):1331-4.

OBJECTIVE: To evaluate the effect of neonatal perioperative anesthetic exposure in complex cardiac surgery on neurodevelopmental outcomes in preschool children.

METHODS: General clinical data and data concerning anesthetic exposure were collected from 89 infants undergoing complex cardiac surgery at Sichuan People' Hospital. The cohort was followed for neurodevelopment till preschool age (48-72 months) and assessed with Wechsler Preschool and Primary Scale of Intelligence-III, Beery-Buktenica Developmental Test of Visual Motor Integration (VMI-V), and General Adaptive Composite (GAC) of the Adaptive Behavior Assessment System-II.

RESULTS: Seventy-one children were enrolled into the final analysis. Multiple linear regression found days on benzodiazepines (beta;=-0.49, P=0.005) and cumulative dose of benzodiazepines (β=-0.10, P=0.023) were associated with the full-scale IQ in these preschool children. Days on benzodiazepines (beta;=-0.39, P=0.009) and on chloral hydrate (beta;=-1.19, P=0.020) were associated with lower performance intelligence quotient (PIQ) at the preschool age. Cumulative dose of benzodiazepine exposure (beta;=-0.008, P=0.012) was associated with lower VMI scores. No correlations of other sedation/analgesia variables were found with the full-scale IQ, PIQ, Verbal IQ, VMI, or GAC scores.

CONCLUSION: We found a significant association of days on benzodiazepines, cumulative dose of benzodiazepines, and days on chloral hydrate in neonatal cardiac surgery with neurodevelopmental outcomes at the preschool age, suggesting the need

of minimizing anesthetic exposure during a neonatal cardiac surgery to improve the children's neurodevelopmental outcomes.

Garcia Guerra G1, Robertson CM, Alton GY, Joffe AR, Cave DA, Yasmin F, Dinu IA, Creighton DE, Ross DB, Rebeyka IM; Western Canadian **Complex Pediatric Therapies Follow-up Group. Neurotoxicity of sedative and analgesia drugs in young infants with congenital heart disease: 4-year follow-up.** Paediatr Anaesth. 2014 Mar;24(3):257-65. doi: 10.1111/pan.12257. Epub 2013 Sep 19.

OBJECTIVES/AIM: To determine whether sedation/analgesia drugs used before, during, and after infant cardiac surgery are associated with neurocognitive and functional outcomes.

BACKGROUND: Some animal models suggest neurotoxic effects of anesthetic drugs on the developing brain; however, potential human effects are unknown. Whether these results can be extrapolated to humans is unknown.

METHODS/MATERIALS: Prospective follow-up project of all infants ≤6 weeks old having surgery for congenital heart disease between 04/03 and 12/06. Demographic, perioperative, and sedation/analgesia variables were collected. Outcomes at kindergarten age were Wechsler Preschool and Primary Scale of Intelligence-III, Beery-Buktenica Developmental Test of Visual Motor Integration (VMI-V), and General Adaptive Composite (GAC) of the Adaptive Behavior Assessment System-II. Multivariable linear regression was used to identify predictor variables.

RESULTS: From 135 infants who underwent heart surgery, 19 died, 17 were excluded, 8 were lost to follow-up, leaving 91 children for analysis. Multiple linear regression found days on chloral hydrate [3.5 (3.7) days] was associated with lower performance intelligence quotient (PIQ) (Effect size -1.03; 95% CI -1.96, -0.10; P = 0.03), and cumulative dose [54.2 (60.3) mg·kg(-1)] of benzodiazepines was associated with lower Visual Motor Integration scores (Effect size -0.07; 95% CI -0.12, -0.01; P = 0.026). No other associations were found between sedation/analgesia variables and full-scale IQ, PIQ, Verbal IQ, VMI, or GAC.

CONCLUSION: Assessment of this cohort at kindergarten age found a small statistically significant association between days on chloral hydrate and PIQ, and benzodiazepine cumulative dose and lower VMI. No other association between sedation/analgesia drugs and outcomes was found.

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http://www.anesthesiologynews.com/Clinical-Anesthesiology/Article/10-16/Benzodiazepine-Exposure-Can-Predict-Delirium-in-Critically-Ill-Children/38055/ses=ogst?enl=true

Benzodiazepine Exposure Can Predict Delirium in Critically Ill Children

San Francisco—Age, severity of illness and benzodiazepine exposure are the strongest predictors of delirium in critically ill children. According to a new study, given the prevalence of delirium in this vulnerable population, studies targeting benzodiazepine exposure as a potentially modifiable target are warranted to reduce the burden of cognitive impairment. “Unfortunately, delirium is extremely prevalent among critically ill children,” said Heidi Smith, MD, MSCI, a pediatric anesthesiologist at Vanderbilt University Medical Center, in Nashville, Tenn. “Our study has demonstrated that younger age, higher severity of illness and, more importantly, benzodiazepine exposure are independent risk factors for increased delirium duration. Benzodiazepine administration was also significantly associated with the transition to delirium the day following drug exposure.” As Dr. Smith reported at the 2016 annual meeting of the International Anesthesia Research Society (abstract S-95), the recently validated test, the PreSchool Confusion Assessment Method for the ICU (psCAM-ICU), designed for use in children 6 months to 5 years of age, has demonstrated an alarming prevalence of delirium. Approximately 44% of critically ill children in this population and over 50% of children younger than 2 years of age experience delirium during their ICU stay (Crit Care Med 2016;44:592-600).

Long-Term Cognitive Impairment

Studies also have shown that benzodiazepine exposure is a key risk factor for not only delirium in adults, but also long-term cognitive impairment in survivors of critical illness (N Engl J Med 2013;369:1306-1316; Anesthesiology 2006;104:21-26). “This is a poignant realization,” Dr. Smith said, “because currently the foundation of sedation in the pediatric ICU setting is benzodiazepine administration. Understanding the relationship between benzodiazepine exposure with delirium and long-term cognitive outcomes in children is paramount.” For this prospective cohort study, Dr. Smith and her colleagues enrolled critically ill patients aged 6 months to 5 years who were admitted to the pediatric medical ICU (PICU) and pediatric cardiac ICU (PCICU) of a tertiary medical center.

Patients were evaluated for delirium using the psCAM-ICU for up to 14 daily assessments while in the ICU. Of the 300 patients enrolled (median age, 20 months), 43% required mechanical ventilation, and 44% had at least one positive delirium assessment. Age, severity of illness and higher benzodiazepine exposure were all significantly associated with longer duration of delirium, Dr. Smith reported. Benzodiazepine use also was the strongest risk factor for transitioning to delirium. In multinomial models, increased benzodiazepine exposure was significantly associated with a higher likelihood of being delirious the day after compared with having normal mental status, the researchers noted.

Long-Term Effects of Delirium

According to Dr. Smith, these results could help change practices regarding the use of benzodiazepines. “Our study demonstrates that benzodiazepine exposure is associated with an increased ICU length of stay, and there have been other, smaller studies that

suggest delirium is associated with both longer ICU and hospital length of stay in children," she explained. "But, even more important is the relationships between critical illness, delirium and sedation on the development of long-term cognitive impairment for arguably the most fragile population—our children." For Dr. Smith, the next phase of research for pediatric providers should involve further delineation of these relationships as well as advocating the benefits of avoiding the onset of delirium in the first place. "Some of this may be attributable to critical illness," she said, "but there are definitely cases of delirium that are associated with iatrogenic risk factors; those are the things that we really need to focus on as clinicians." Dr. Smith explained that delirium management is directed at treating the behaviors reflected by a sick brain. Although there is not "one" drug that can reverse the presence of delirium acutely, she asserted that providers can still take steps in the ICU to decrease the development or severity of delirium while effectively treating critical illness. "We have to become really inventive about the way that we manage pain and anxiety in children rather than solely relying on sedation when in the ICU," she said, "especially when they are on mechanical ventilation. We need better strategies for liberating them from the ventilator as quickly as possible."

Intensivists Must Alter Goals

The proven relationship between delirium and long-term cognitive impairment in adults leaves obvious concern for a population whose brains are still maturing. "What happens to children, who are on a steep curve of neurodevelopment, when they have a critical illness and develop delirium?" Dr. Smith asked. In a study of delusional memory after ICU or critical illness, Gillian Colville, BSc, MPhil, CPsychol, a psychologist from London, showed that approximately one-third of children who survive critical illness have delusional memories of their ICU experience (Am J Respir Crit Care Med 2008;177:976-982). According to this study, children with delusional memories are more likely to have been exposed to high levels of benzodiazepines and opioids, and to later demonstrate higher post-traumatic stress disorder scores. "A better understanding of the long-term effects of both critical illness and delirium on children will push us all to become more vigilant in changing practice to improve care," Dr. Smith said. "As intensivists, we may think that we have done a good job if we can get the child out of the ICU breathing on their own … but, for a long time, we have failed to see that 'A' students now go home to become 'C' students, younger children have delay in normal development and still others continue to suffer psychologically. "The goal must shift to not only treat critical illness, but consider and protect the brain as much as possible during this battle. Illustrating the prevalence of delirium and associated risk factors such as benzodiazepine exposure is the beginning. Now we go back to work to determine those strategies to change the status quo," she concluded.

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