CRITICAL REVIEW FORM FOR HARM – Example #2 - Case Control Study

Citation: *The relationship of postoperative delirium with psychoactive medications.* JAMA. 1994; 272:1518-1522.

Guide	Comments
I) Are the Results Valid?	
Did experimental and control groups begin the study with a similar prognosis	
Did the investigators demonstrate similarity with respect to all known determinants of outcome; did they adjust for differences in the analysis.	Yes. This study is a case-control study that was nested within a prospective cohort. The cohort study was designed to derive a clinical prediction model for postoperative delirium. 1341 patients were identified at the time of admission and all patients underwent an extensive preoperative assessment including review of medical history, physical examination, functional and cognitive testing and laboratory tests. Cases were patients who developed delirium on post-operative day 2→5. (Post op day #1 was excluded due to concern that anesthesia effect might mimic delirium). Controls were matched to each case from the population of patients in the prospective cohort who did NOT develop delirium. Controls did not develop delirium, but had the same preoperative risk for delirium as the case patient based on the seven criteria (listed below). Controls had to still be in the hospital on the day the delirium developed in the case patient. Up to 2 matched controls were identified for each case. If no control patient met the criteria for perfect match, a control was selected with the closest pre-operative risk for delirium. No control was matched to a case with >10% difference in calculated risk. All controls were used only once. 2 matched controls were used for 63 of the 91 patients who developed delirium (69%). 1 matched control was used for the remaining. Thus, total number of matched controls was 154. Delirium risk assessment: All patients in the cohort were interviewed with respect to seven criteria pertaining to risk for delirium: age, poor cognitive function, poor physical function, self-reported alcohol abuse, markedly abnormal preoperative serum sodium, potassium or glucose levels, aortic aneurysm surgery and non-cardiac thoracic surgery.

For case-control studies: Were exposed patients equally likely to be identified in the two groups?	Yes. All 1341 study patients in the prospective cohort underwent identical daily structured interviews on postoperative days 2→ 5, or until the day before discharge if discharge occurred prior to day 6. Within this cohort, patients with delirium were identified if they met criteria for delirium using the *Confusion Assessment Method (CAM) diagnostic algorithm.*
Did experimental and control groups retain a similar prognosis after the study started?	
Were the outcomes and exposures measured in the same way in the groups being compared?	All risk and pre-operative data was collected prospectively on all patients, regardless of the ultimate development of delirium. Data on medication exposure was obtained by review of the nurses' medication flow sheet for those medications given (not simply those ordered) as well as from the pain service orders (which controlled the administration of epidural and patient-controlled analgesia). A reviewer blinded to the study hypothesis collected chart review data. For both cases and controls, medication exposures were recorded for the 24-hour period before the delirium developed. Care was taken to record medications given in the period prior to delirium to exclude medications given after signs of delirium developed. Possible confounders, specifically with respect to the use of benzodiazepines might be that the early signs of delirium (e.g. sleeplessness and agitation) might be treated with benzo's. Therefore, it is possible that cases might be 'exposed' to these drugs as a sign of early delirium that was not yet diagnosed, as opposed to benzodiazepines *causing* the delirium. Other confounders relate to the possibility that other coincident factors may have been related to the use of these medications (e.g. sleep deprivation, agitation, pain control).
Was follow-up sufficiently complete?	As this was a nested case control study in the context of prospective data collection. Follow up was complete for those who remained hospitalized for the 5 days of the data collection period. Those who were discharge early were not followed outside the hospital.

What are the Results? How strong is the association between exposure and outcome? How precise is the estimate of risk?	Three medication classes were selected for study: narcotics, benzodiazepines and anticholinergics. **Narcotic Agents**: Only Meperidine was associated with Delirium (OR 2.7; 95% CI, 1.3 to 5.5). Of note, narcotic medications were commonly used with roughly 95% of all patients (cases and controls) receiving narcotics during the 24-hour period of analysis. Epidural anesthesia was associated with delirium (OR 2.3; CI, 1.2 to 4.4). {This may be related to the high proportion of patients who had epidural anesthesia with meperidine as the agent used.} Patient-controlled anesthesia was not associated with delirium (OR 1.1; CI 0.5 to 2.2) **Benzodiazepines** These drugs were used less frequently with 21% of cases and 8% of controls receiving benzodiazepines during the 24-hour period of analysis. Overall, benzodiazepines were associated with delirium (OR 3.0; CI 1.3 to 6.8). Long acting benzo (OR 5.4 CI, 1.0 to 29.2) > short acting (OR 2.6, CI 1.1 to 6.5) High-dose benzo (OR 3.3 CI 1.0 to 11) > low dose (OR 2.6 CI 0.8 TO 9.1) **Anticholinergic agents** were not associated with delirium (OR 1.5 CI 0.6 to 3.4). {The relatively small proportion of patients receiving these drugs during the 24-hour period of analysis (9%) may have limited power to detect a difference in this category.}

How can I apply the results to my patient care?	
Were the study patients similar to my patient?	These patients were all surgical patients admitted to Brigham and Women's Hospital in Boston for major elective non-cardiac procedures. Average age of patient was 73 years. Roughly half of the patients in the study underwent an orthopedic procedure. 50% were women and the participant's race is not reported. Thus, for those characteristics described, the patients in the study are quite similar to my own patient.
Was the duration of follow-up adequate?	Follow up was 5 days postoperative or to discharge. This length of time is likely sufficient for this question, but you might miss cases who were discharged early or events that were late occuring.
Should I attempt to stop the exposure?	We really considered two questions as a result of the orthopedic consult: Are benzodiazepines associated with postoperative delirium, and are narcotics, specifically PCA morphine associated with postoperative delirium. In this study, the answers should be looked at separately. Question 1: Are benzodiazepines associated with postoperative delirium? Yes. The odds ratio for development of delirium when exposed to benzodiazepines was 3.0. In addition, this paper gives evidence that the association may be stronger for longer acting medications as well as for higher dose of medications. In fact, for our patient, she is on a long acting drug (lorazepam) with potential for "high doses" (anything greater than 1 mg). It would be prudent to stop this exposure in this patient. Question 2: Are narcotics, specifically PCA morphine, associated with postoperative delirium? In this study, only meperidine was associated with delirium (OR 2.7). Morphine, by PCA (the regimen our patient was on), was not associated with delirium (OR 0.9; CI 0.4-1.9). However, one should maintain some caution and consider that it is possible that the lack of association was related to insufficient power to detect a statistical difference. In this setting, it might be reasonable to cautiously continue our patient's PCA morphine pain management at the lowest possible dose, including a strategy to augment pain management with non-narcotic medications (e.g. NSAIDS) and switch to these medications when pain control allows.