Critical Review Form
Therapy

PGY-2

Timing of opioid administration as a quality indicator for pain crises in sickle cell disease, Pediatrics 2015; 135: 475-482.

Objective: **"…to study a single center's SCD [sickle cell disease] population with VOC [vaso-occlusive crisis] to determine whether the time to opioid administration (TTO) was associated with outcomes of care in the ED [emergency department]." (p. 476)**

Methods: **Retrospective cohort study of pediatric patients with VOC who received parenteral opioids in the ED of Children's Medical Center Dallas between Jan 2008 and Dec 2010. Although no chart review methods are cited, the investigators report identification of cases using ICD-9 codes. Inclusion criteria included previously established SDC of any genotype, VOC defined by new onset of pain without an alternative explanation, age range 5-18, and treatment with parenteral opioids. Exclusion criteria included confounding sources of pain (examples: headache, cholelithiasis), transfer to Children's Medical Center from another medical center, surgical procedure in preceding 2-weeks, transfusion in preceding 30-days, or participation in a chronic transfusion program.**

The primary outcome was hospital admission. Secondary outcomes included: change in first 2 recorded pain scores, area under the curve for all pain scores at 4 hours, total ED length of stay in minutes, and total IV opioid dose in milligrams per kilogram of morphine equivalent. Pain was assessed using either 5-point patient-reported numeric pain scale or the 5-point Faces pain scale. TTO was defined as "time in minutes from presentation to ED to receipt of first dose of parenteral opioids" (p. 476) Additional co-variates assessed included patient age, initial and total opioid doses, gender, fever presence, baseline hemoglobin and reticulocyte count, hemoglobin and reticulocyte counts at presentation, primary payer, ambulance arrival, previous admissions for VOC in last 12-months, number of missed clinic appointments in last 12-months, pain location, number of pain locations, weekend presentation, and year of presentation. A significant confounder was the introduction of an electronic medical record in mid-2009. (p. 477)

Again, no chart review methods are cited but the authors do report senior author review of 20 charts independently, as well as senior authors who "examined the data for extreme or missing values and inconsistencies in static variables" (p. 477) Univariate mixed regression models tested associations between measured covariates and primary/secondary outcomes. Covariates that were statistically significant in univariate analysis ("statistically significant" was never defined by the authors with no discussion about alpha-inflation or Bonferroni corrections), "were subsequently evaluated in a multivariate mixed model" (p. 477)

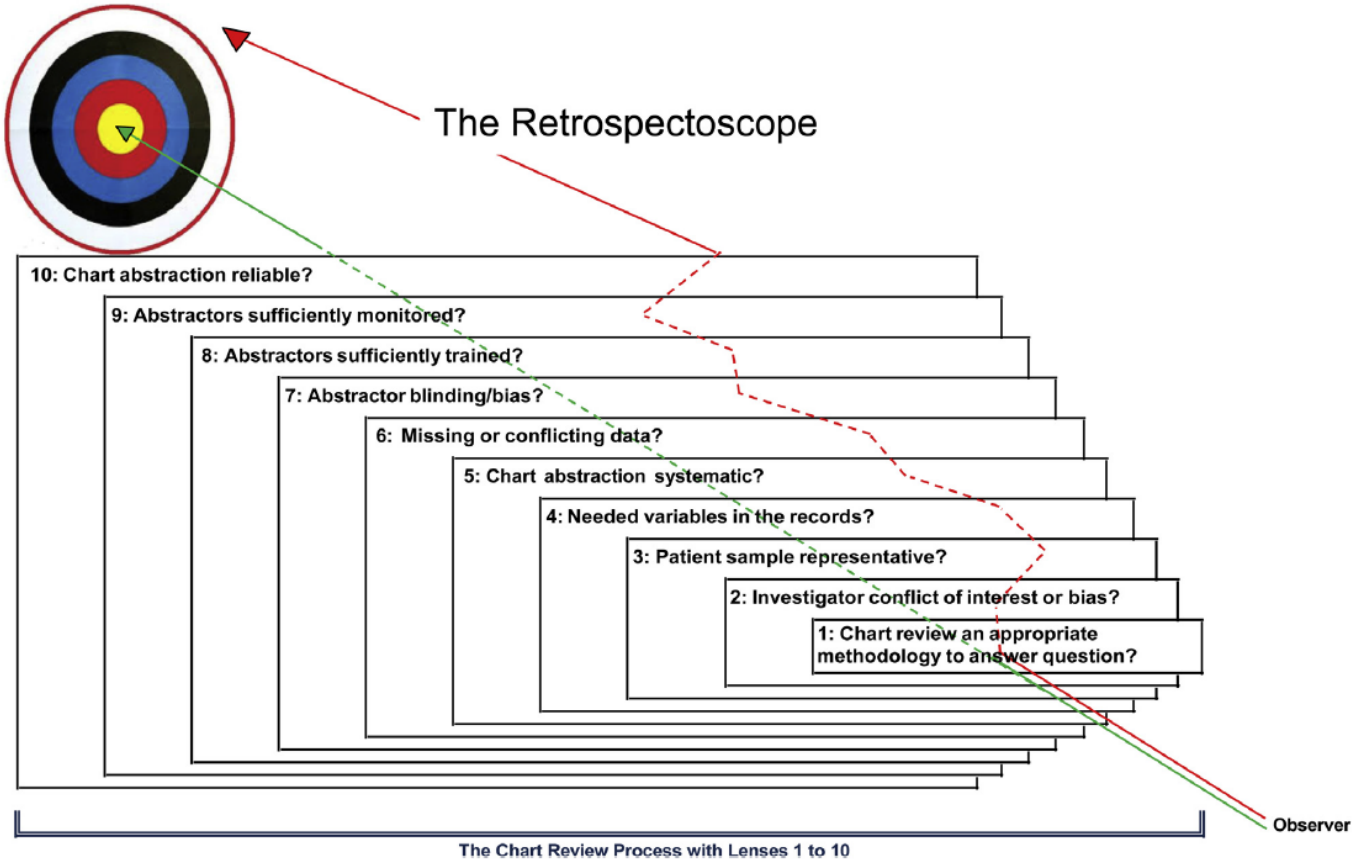
Critical Review Form: Therapy

Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	No, this is a retrospective chart review. No randomization occurred and no comparator group was evaluated.
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	No randomization, no allocation concealment.
Were patients analyzed in the groups to which they were randomized?	No randomization, no role for intention to treat analysis.
Were patients in the treatment and control groups similar with respect to known prognostic factors?	There is no treatment or control group, but the authors could have helped readers understand whether any significant differences between admitted and discharged VOC patients existed by reporting both subsets in Table 1 (p. 478)
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Yes, patients would have been aware of TTO, but not that this "intervention" was being quantitatively evaluated.
Were clinicians aware of group allocation?	Yes, clinicians would have been aware of TTO, but not that this "intervention" was being quantitatively evaluated.
Were outcome assessors aware of group allocation?	Without clear statement of chart abstractor blinding to the study hypothesis, the assumption is yes. Note that in chart review studies, the poor man's effort to reduce abstractor bias is to blind them to the study hypothesis.
Was follow-up complete?	Uncertain. Figure 1 (p. 477) depicts 595/2863 excluded for "miscellaneous reasons". That is 21% of the total cohort (possible attrition bias). Without understanding why they were excluded, it is impossible to know which exclusion criteria (or multiple criterion) applied.
What are the results?	
How large was the treatment effect?	• The analyzed cohort includes 414 visits from 177 patients with median 2 ED visits in preceding year, 67% with Medicaid insurance, and media age 13 years. • Triage occurred in median 2.5 minutes and placement into an ED room within 12 minutes with median first opioid order within 42 minutes and administration within 30 minutes of order entry. • The median total time in ED was 390 minutes (6.5 hours). • **Primary outcome**: 53% were admitted with median TTO 86 minutes for admitted and 87 minutes for those not admitted. Multivariable analysis identified older age, more prior VOC admissions in last year, and pain location in chest as independent predictors of admission (but not TTO). • **Secondary outcome – Improvement in First 2 Pain Scores**: in multivariate analysis decreased TTO was associated with greater improvement in pin scores as were older age and higher first pain score. (pp 477-478) • **Secondary outcome – Pain Score AUC**: In multivariate analysis decreased TTO was associated with decreased pain score AUC, as were lower age and lower first pain score. (p. 478) • **Secondary outcome – Total ED Length of Stay**: In multivariate analysis decreased TTO was associated with decreased ED length of stay as were discharge from the ED, decreased interval between pain scores 1 and 2, and presentation after EMR implementation. (p. 478). • **Secondary Outcome – Total Dose of Parenteral Opioid.** In multivariate analysis decreased TTO was associated with an increased

	total dose of parenteral opioids as were larger number of VOC admissions for the previous year, larger number of pain locations, and admission status. (p. 478)
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	As demonstrated in Tables 2 and 3 (page 479), the majority of 95% Confidence Intervals do not cross unity (either the Odds Ratios in Table 2 or the beta-coefficients of Table 3). The exceptions were unity is crossed include age and first pain score.
How can I apply the results to patient care?	
Were the study patients similar to my patient?	No, these are pediatric sickle cell patients presenting to a children's hospital.
Were all clinically important outcomes considered?	No, retrospective design limits researchers' ability to measure every confounder. Potentially relevant confounders would include health literacy levels, pre-ED analgesic efforts, existence of individualized care plan between patient-SCD provider, individual ED prescribers' biases, and duration of time since last ED visit or hospital admission.
Are the likely treatment benefits worth the potential harm and costs?	Unknown because the investigators did not attempt to measure "harms" in this study. Potential harms would include respiratory depression, hypoxia, intubation, Narcan administration, safety events, or falls.

Limitations:

1. **When conducted and reported perfectly, retrospective chart review studies are purely hypothesis generating (see Gilbert 1996, Worster 2004, or Kaji 2014). When conduct and/or reporting are imperfect, chart reviews lose even that value. Chart review methods are not cited and the investigators report an incomplete description of the chart review process. While the authors appropriately note quality oversight of data abstractors and that "missing data were excluded from the analysis" (p. 477), they neglect to report on blinding of abstractors to study hypothesis, how "extreme or missing values" were quantified, or how inconsistencies in recorded data were adjudicated. They also failed to fully contemplate the 10 lenses of a chart review (see figure from Kaji 2014), including whether the patient sample was representative and whether all essential variables were contained within the medical record.**
2. **Insufficient detail about the multivariate regression provided to replicate. Example: what was the p-value of significance for inclusion? Was that p-value adjusted for multiple comparisons?**
3. **Potential attrition bias: exclusion of 21% for unexplained "miscellaneous reasons"?**
4. **Uncertain external validity for adult sickle cell populations where door to ED room time of ~40 minutes and total ED length of stay of 6.5 hours atypically short.**
5. **No elaboration on whether statistically significant reductions in pain where clinically significant. In fact, scant discussion about the patient-centric outcomes of satisfactory pain control at all including no citations verifying the measures of pain as validated.**
6. **No assessment of potential harms associated with TTO (hypoventilation, hypoxia, intubation, Narcan, etc.).**



7. **Potential confounder with introduction of electronic medical record ordering mid-study, which may have impacted both ability of providers to order opioids as well as data abstractors' access to charting details.**
8. **Inability to fully compare study population to different settings, including no comparison of admitted vs. non-admitted patients in Table 1, no assessment of health literacy, duration of pain prior to ED arrival, existence of personalized SCD VOC pain plan, or interval since last opioid or ED visit or admission.**

Bottom Line: Imperfect single-center chart review which demonstrates no significant reduction in pediatric sickle cell patient admission rates associated with time to parenteral opioid administration in the emergency department. Secondary outcomes suggest a significant trend towards more rapid pain relief, reduced ED length of stay, and higher total dose of ED opioid prescribed. However, multiple limitations noted raise concerns about the reproducibility and accuracy of these results in different time periods or pediatric hospitals. In addition, extrapolation of these results to adult SCD VOC patients with generally longer waiting room times and ED length of stay should be done cautiously.