Title

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# Editorial

Editorial Text Based on the best available evidence, which analgesic adjuvant is optimal for a particular patient for optimize postoperative pain control? For example, how much opioid sparing will the administration of intraoperative intravenous acetaminophen afford for a typical bariatric patient at Penn State Hershey Medical Center? With patients and surgical procedures across the United States as diverse as species in the rain forest, this can be a difficult question. Often randomized controlled trial yield widely varying estimates of the clinical effectiveness of analgesic adjuvants. RCTs results, seemingly at random, leave clinicians baffled. In this issue, in their article, Baseline morphine consumption may explain between-study heterogeneity in meta-analyses of adjuvant analgesics and improve precision and accuracy of effect estimates, Doleman et al. propose an ingenious new solution to solve this riddle. They synthesize the evidence controlling for baseline risk across all surgical procedures and patient populations. With their new approach, local audit data could be used to predict the reduction in morphine consumption for any analgesic adjuvant in any population. In the same breath, they toss out the established paradigm of procedure specific pain control. If this seems a stretch, it may be worthwhile to entertain and explore.Some randomness in outcome estimates of RCTs investigating the same intervention in the similar population is to be expected. By pure chance alone, each RCT has a chance to over- or to under estimate the effect of an intervention. Larger and smaller studies will lead to more or less precise estimates of effect of interventions. Meta-analysis pools available RCTs to address the expected random variability, to synthesize the evidence, and to reduce the uncertainty in the face of seemingly contradictory results. However, if the heterogeneity of results of RCTs is very large, in other words, if results are too contradictory and disparate, we have to worry that we are mixing apples and oranges. Excessive between-study heterogeneity in meta-analysis raises concerns that the included studies are clinically different, possibly because the study populations or the interventions investigated are too diverse to make pooling all identified RCTs reasonable.

To explain why RCTs yield contradicting results, we can group studies for example by surgical intervention in an attempt to make sense of the between-study variability of effect estimates. Stratification by surgical intervention makes clinically sense, because between-study heterogeneity may be smaller within each stratum. This led to the current paradigm of procedure specific pain control (Kehlet 2007): It is expected that different surgical procedures cause different amounts of pain. Populations undergoing different interventions for different diseases may vary in how they respond to pain, in their comorbidities, pharmacokinetics etc. Clearly, a population of elderly men, status post thoracotomy for smoking induced lung cancer, will differ from a population of young women after cesarean section. It follows that postoperative pain control should be tailored to the specific surgical intervention and the particular population. While this makes sense, it drastically reduces the number of available studies to base clinical decision on for a particular patient population undergoing a particular procedure. For example, on thyroidectomy Doleman et al. found only one single RCT investigating the effect of intravenous acetaminophen. This poses a significant challenge to any evidence based approach to procedure specific postoperative pain management.

Doleman et al. used a Bayesian meta-regression, novel statistical hierarchical modeling approach in evidence synthesis (Sutton 2001) (which we discuss further below), to demonstrate that surgical procedure is not the main predictor of between-study variability in effect estimates for analgesic adjuvants to control postoperative pain, but baseline risk (for pain) is. In a nutshell, the benefit of the analgesic adjuvant is mainly driven by baseline morphine consumption in the control group and not by the surgical procedure. We try to visualize their novel approach in two figures using acetaminophen as an example in point.

Doleman et al. found 25 RCTs investigating intravenous acetaminophen for postoperative pain control. In Figure 1, we plot them in a classical forest plot, ordered by surgical interventions. The 25 RCTs estimate variable effects, the results seem all over the place, varying widely even for the same surgery.

In Figure 2, we reproduce the acetaminophen subplot of Figure 2 of Doleman et al. Each study is represented by a dot. We colored the studies by surgical procedure. If surgery were the best way to explain why studies yield different results, then studies investigating the same surgical procedure should have similar results. Hence the same color dots should be clumped together (along the same value on the y-axis indicating the estimated effect). But studies of the same color (investigating the same procedure) are far apart on the y-axis. By contrast, studies line up neatly around the regression line, when we plot the mean reduction in morphine consumption (y-axis) against the baseline risk (baseline morphine consumption in the control group). The conclusion is that a meta-regression controlling for baseline morphine consumption in the control group is superior to stratification by surgery in explaining between study variance in results.

What is illustrated in our Figure 2 with the example of acetaminophen, holds according to Doleman et al. for all analgesic adjuvants across all populations, for all surgical interventions, as shown in Doleman's Figure 2 with the other subplots. Accordingly, when we look at the evidence on analgesic adjuvants, we can pool studies investigating different populations undergoing different surgical procedures, as long as we control for the baseline risk, (measured as mean morphine equivalent in the control group). This contradicts the dominant paradigm of procedure specific postoperative pain control. What is more, Doleman et al explain how clinicians can use local audit data, collected on our own surgical populations, to estimate the reduction of morphine consumption using their results and a very simple calculation. A great feature to have for a new unifying theory on how to synthesize the evidence for postoperative pain control.

Doleman et al. fit a Bayesian model, which differs from classical (AKA frequentist) statistics. The Bayesian approach incorporates prior information and combines it with the newly observed data, much like a physician would in clinical practice: Imagine a medical student excitedly reporting a positive pregnancy test on a patient about to be transfered into the CAT scanner. After this new information (positive pregnancy test) is integrated with existing information (76-year-old man with a long white beard), the clinical inference likely will still be to proceed with CAT scanning… Still, frequentist statisticians sometimes critique the Bayesian approach for adding prior, presumably subjective, information to the newly observed, presumably objective, data. However, classical frequentist statistical models are also based on subjective assumptions and the model choice in itself is often more important for correct inferences. In both the classical frequentist and in Bayesian analysis, we therefore need to explore the sensitivity of results and inferences to the priors, assumptions and model choices. In the online supplement, Doleman et al provided software code, data and model details. They used very weak prior assumptions and in their sensitivity analysis found their results to be robust. We find their Bayesian approach transparent, sound and trustworthy.

Doleman et al speculated that baseline risk might better explain variability in effect and conducted a prospective observations analysis supporting their conjecture, which now suggests a set of testable hypotheses and predictions. This makes their proposed novel and unifying theory attractive. Progress in science and medicine is made by proposing models and hypotheses and then attempting to falsify these. Indeed, investigators can use local audit data to predict the reduction in morphine requirements and then prospectively observe the actual reduction achieved to investigate how well the Doleman model's predictions hold. Meta-analysts can replicate the approach by Doleman et al and for example test if it can be extended to evidence synthesis of regional anesthesia to explain and/or reduce the between study variability of the effects of regional anesthesia versus conventional multimodal pain control for postoperative pain control. If Doleman's theory holds, it would greatly simplify evidence synthesis and provide clinicians with much stronger and much more granular evidence on what analgesic to use for which patient. In fact, in the second part of their paper, Doleman et al go on to use meta-regression to discuss rather refined and specific questions, for example if acetaminophen is more effective if administered intravenously rather than orally, a question of great financial and clinical importance for which there are simply too few studies if we insisted to only combine studies comparing the effects in the same population/surgical intervention. The provide a league table of efficacy of analgesic adjuvants.

Doleman et al acknowledge the many limitations of their work, for example that their meta-regression, like any meta-analysis was an ex post observational study, even if it had an a priori defined analysis plan. The confidence of their predictions and inferences will be weaker for ranges of baseline risk (baseline morphine consumption in the control group) where they have less studies for the particular analgesic adjuvant at hand. We will discuss this and some other limitations pars pro toto using acetaminophen as an example. The range of surgical procedures included in the acetaminophen trials was limited, (as listed in Doleman's manuscript in Table 1). The patient mix in the acetaminophen studies appears to be predominantly female. The standard morphine dose (50 mg) at which dose reduction was estimated is much higher than the mean dose (28 mg) in the included acetaminophen studies. Inferences and predictions in the higher dose ranges therefore rely on fewer studies and/or on problematic extrapolation. For most adjuvants studied, there was little benefit (almost equal benefit) for studies reporting low baseline consumption, which is evidenced in Figure 2 of Doleman's article. The estimates in their regression equation apply to aggregate groups not individual patients.

Readers and the authors of this editorial may remain somewhat skeptical and cautious about the approach and inferences suggested by Doleman et al. Provocative as the novel theory by Doleman et al may be, it would afford great utility and exemplifies the benefit and potential of novel Bayesian meta-regression approaches to answer burning clinical questions of practical utility, like what analgesic adjuvants I should offer my patient this morning.

# Figures

```
## Classes 'tbl_df', 'tbl' and 'data.frame':    147 obs. of  10 variables:
##  $ Study          : chr  "Arici 2009" "Arslan 2011" "Arslan 2013" "Atef 2008" ...
##  $ X              : num  62.93 11.25 9.1 8.2 0.35 ...
##  $ Y              : num  -32.19 -7 -5.02 -6.4 -0.08 ...
##  $ Type of surgery: chr  "Hysterectomy" "ENT" "Cholecystectomy" "ENT" ...
##  $ Regression line: num  -23.696 -3.552 -2.714 -2.363 0.696 ...
##  $ 95% CI         : num  -28.35 -5.62 -4.9 -4.61 -2.1 ...
##  $ 95% CI__1      : num  -19.042 -1.48 -0.524 -0.12 3.497 ...
##  $ Adjuvant       : chr  "Acetaminophen" "Acetaminophen" "Acetaminophen" "Acetaminophen" ...
##  $ Surgery        : Factor w/ 19 levels "Abdo","Arthroplasty",..: 10 7 6 7 15 16 10 10 16 10 ...
##  $ Agent          : Factor w/ 3 levels "Acetaminophen",..: 1 1 1 1 1 1 1 1 1 1 ...
```

## Figure 2

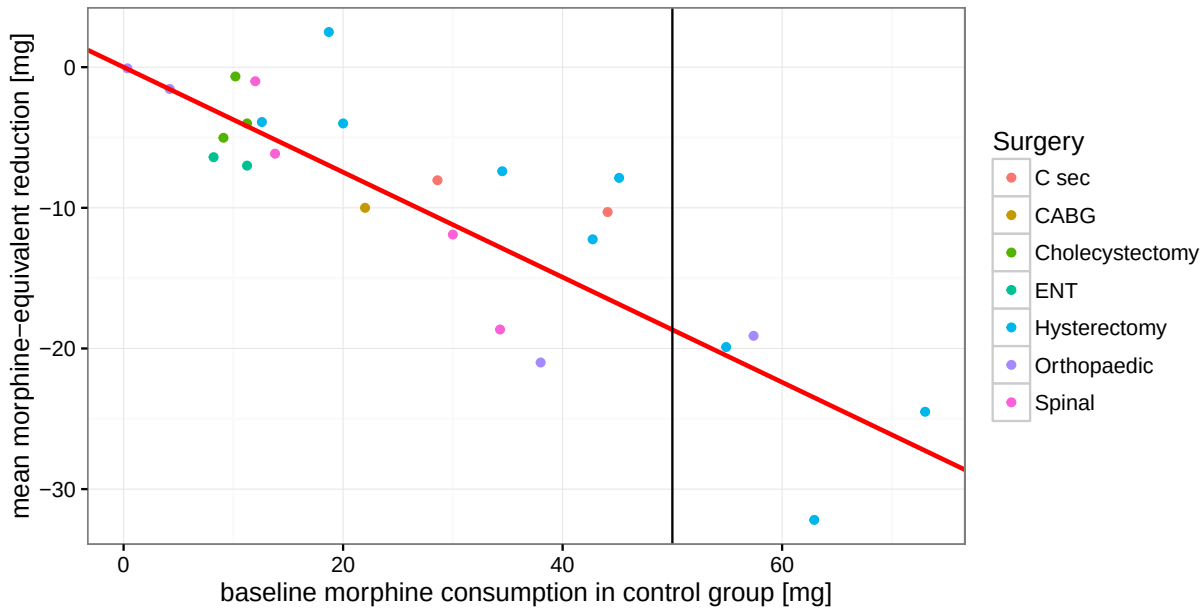


**Figure 2 Caption**

In Figure 2, we reproduce the acetaminophen subplot of Figure 2 of Doleman et al. Each study is represented by a dot. We colored the studies by surgical procedure, according to the adjacent colour legend. If surgery were the best way to explain why studies yield different results, then studies investigating the same surgical procedure should have similar effects Hence the same color dots should be clumped together,(and the green cholecystectomy studies somewhat are). But most studies of the same color are far apart, for example orthopedic (blue) or hysterectomy (violett) study dots are spread out over the entire range of the plot. By contrast, all studies line up neatly around the red regression line, when we regress the mean reduction in morphine consumption (y-axis) against the baseline risk (baseline morphine consumption in the control group) in the x-axis. The conclusion is that a meta-regression controlling for baseline morphine consumption in the control group is superior to stratification by surgery in explaining between study variance in results.

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