Article details: 2020-0029	
Title	Reversing deficiencies in thiamine prescribing using the computerized provider order entry system: a cohort study at an academic hospital network
Authors	Gregory S. Day MD MSc, Safiya Ladak BScPhm, C. Martin del Campo MD
Reviewer 1	Karen Neufeld
Institution	Johns Hopkins University, Baltimore, MD
General comments (author response in bold)	Thank you for allowing me to review this interesting manuscript regarding the effects of a change in the electronic medical record order set on thiamine prescribing in the hospitals in a university network in one Canadian city. This is an important topic and the findings of this study suggest that important changes in prescriber behavior can be influenced by changes to the medical record. The paper would be clearer if some changes were made to the figures and the tables and the manuscript streamlined somewhat. My specific suggestions are as follows: **1) Methods Section: Page 9 line 31. Please outline what kind of approval was received by the Ethics board - Did patients provide consent? or was it considered a non-research quality improvement protocol where patient consent was not required?** **The project was approved as 'research' (minimal risk). A waiver of consent was granted, permitting access and reporting of anonymized patient data. This information has been added to the Methods (paragraph 1).** **"Study objectives, methods and procedures were approved by the University Health Network Research Ethics Board. A waiver of consent was granted, permitting access to and reporting of anonymized patient data."** 2) Interpretation Section: Page 16 line 45: please include a 2019 study Lin et al - Psychosomatics entitled "Prevalence and Improvement of Caine-Positive Wernicke-Korsakoff Syndrome in Psychiatric Inpatient Admissions" which demonstrated Caine positive Wernicke Korsakoff syndrome prevalence in a psychiatric unit with high rates of comorbid substance use of approximately 10%. **Thank you for calling this new reference to our attention. We have added the reference the interpretation, noting that appropriate treatment in psychiatric inpatients at high risk of thiamine deficiency may correct neurocognitive deficits (Interpretation, paragraph 5; Reference #42).** **"It is particularly important to explore alternate or additional approaches to optimize prescribing by psychiatric providers, acknowledging that … and that treatment with high dose parenteral thiamine may correct neurocognitive deficits in high-risk patients.[42]"** 3) Table 1 should be presented as Table 2 and Table 2 should be presented as Table 1. The data in current Table 1 includes linear regression models of the data and should be presented second. Current Table 2 is univariate information and should be presented first. (Please see additional suggestion for changes to this table listed in comments below.) The RESULTS section needs to be revised accordingly as well to reflect these changes in Table order. **We have reordered the tables and presentation of results as suggested.** 4) Figure 1 should remove the screen shot of the order set entry from the figure. It's too small to read in this format. 5) The screen shot of the order set entry should be included in its own figure so

	that it can be easily read. It would be helpful to see the previous version of the order set so the reader can understand the precise changes that were made to influence prescriber behavior. **In response to this suggestion, and comments received from the Editor and Reviewer 2, we created Figure 1 (replicating the order entry screen). We have also included an Appendix providing further details concerning the precise changes that were made to influence prescriber behavior (Appendix 1).** 6) Figure 2: consider deleting as it doesn't seem to include any important new information. This would be particularly true if you included the TOTAL Doses for the overall hospital system in annualized number of prescriptions, first prescriptions and number of doses in the (currently named) Table 2. **We have opted to keep Figure 2 (renamed Figure 3), recognizing that it depicts longitudinal data reflecting pre- and post-intervention periods. This depiction is key to appreciating month-to-month variability in total prescriptions (bar graph, right axis) and % parenteral prescribing (line graph, right axes). This information supports our claim that changes in prescribing were sustained month-to-month following the intervention, and not merely driven by a large change in any given month.** 7) Identify whether Figure 3 refers to oral or parenteral administration or both in the legend. **The previously submitted figure included both oral and parenteral prescriptions. In response to this Reviewer's comment, we decided to reproduce the figure including only data corresponding to parenteral prescriptions (the focus of our intervention). The revised figure is now included (Figure 4—formerly Fig 3), and the focus on parenteral thiamine is highlighted in the figure legend.**
Reviewer 2	Brian Wong
Institution	Medicine, Sunnybrook Health Sciences Centre, Toronto, Ont.
General comments (author response in bold)	Thank you for the opportunity to review this study of a single institution's evaluation of a change to their computerized order entry system to improve thiamine prescribing in their hospital. Their reported findings are impressive in that they achieved a near 40% absolute improvement in their primary outcome (parenteral thiamine prescribing), which was sustained for over 3 years. The paper is well written, and the analytic approaches are sound. My main comments for consideration relate to the framing of the paper to increase its overall relevance to the field, especially around the issue of potentially overtreating low risk patients in order to ensure that high-risk patients get the treatment as intended, and also some additional detail regarding the actual implementation of the order set to allow other organizations to adopt in their local settings. Major comments: 1) Methods, page 9, lines 17 - 24 -- much more detail is needed here to make clear what actual steps were taken to implement this change to the computerized order entry (CPOE) system. My suggestion to the authors would be to put themselves in the readers' shoes -- what detail would be needed to allow them to determine A) that is this an intervention that we could feasibly implement? and B) what steps would we need to take to implement this change in our local setting? So for example, readers might want to know which CPOE vender is used? Do practitioners enter all orders in the computer or only some? Are order sets routinely used for other types of orders at this hospital? (speaking to the ease of

	introducing a new order set) Did they make the order set the default for thiamine ordering? These elements within the local context are critical when describing a QI intervention. A lot of the detail regarding the specific approaches taken to implement the intervention were actually listed in the Interpretation section, page 15, lines 19-47 -- I would recommend moving all of this to the Methods section. **In response to this suggestion, and comments received from the Editor and Reviewer 1, we opted to include an appendix providing additional details concerning the precise changes that were made to influence prescriber behavior. Requested information concerning CPOE vendor and order-entry practices are now documented in Appendix 1.** 2) Measurement strategy, Methods, page 10, lines 14-20 -- many of the outcome measures are simply a number of different ways to show that more thiamine was prescribed. It's not clear that these various representations of this practice change are all that helpful -- especially since there is little debate based on the results that there was a major increase in parenteral thiamine prescribing. However, there are 2 other measures that authors should strongly consider including if available that would significantly strengthen the paper: a) A process measure of intervention fidelity -- it would be good to report the proportion of thiamine prescriptions that were generated using the order set (vs free text ordering etc.,) in the post-intervention period to provide greater confidence that the CPOE order set is what led to improvement -- this is important because it lends stronger evidence that your technological change was what likely resulted in the improvement -- which is important for other sites to know in order to decide whether to invest time and resources into creating a thiamine order set within their own CPOE systems. b) The second is a balancing measure -- are we over treating patients? In other words, are low-risk patients being overly aggressively treated (not sure if there's an easy way to determine this)...the other balancing measure is 'cost' -- how much more is this costing the UHN? At a minimum, if there is a chance that you are treating some patients unnecessarily in order to ensure those who need high dose parenteral thiamine are getting it, at what cost? You could ask your pharmacy at a minimum to estimate the cost increase of switching from oral to IV thiamine, including the cost of the medication, equipment needed to administer (and if you really wanted to represent this accurately, you could estimate the increase in nursing time required to administer IV thiamine and multiple that by IV thiamine doses administered) **We thank the Reviewer for these excellent suggestions. We reported the total number of prescriptions, number of first prescriptions (paralleling the number of patients treated), and number of doses prescribed to assess the frequency, breadth and means of prescribing. Although these measures are related, they do reflect different aspects of provider behavior, as evidenced by apparent increases in the number of prescriptions issued and numbers of patients treated, *despite* overall decreases in the number of doses prescribed. This manner of reporting also builds upon previously reported data at our center (Day et al 2015—J Hosp Med), facilitating direct comparison of prescribing behaviors.** **Inclusion of a "process measure of intervention fidelity" would indeed be a strength. Unfortunately, however, anonymized data was obtained from our computerized pharmacy information system, which did not specify whether orders were entered via the expected means (through the order entry set) or "free texted". Thus, this cannot be incorporated in the revision. In the**

	revised version, we have been careful to report the relationship between our association and prescribing behaviors as an association. Causal language has been avoided, recognizing the limitations of this project (which are discussed in the Interpretation, paragraph 6). **We agree that there is a high potential to "over-treat" patients via this strategy. However, we argue that this strategy is justified by the modest cost of IV thiamine (approximately $2 / 100 mg at UHN), the low efficacy / questionable absorption of oral thiamine in hospitalized patients, the negligible side effects of oral thiamine, and the high cost / potential morbidity and mortality associated with missed or under-treatment in patients with severe thiamine deficiency. Attention is now called to this in the Interpretation (paragraph 3). A cost-analyses at our center is an excellent idea, but is beyond the scope of the present study, which was designed to assess the association between changes in the CPOE and prescriber behaviors. In response to this comment, we have included a reference to a recent publication (Reference #35) and have updated our Interpretation (paragraph 3) to call attention to the perceived cost benefits associated with the use of parenteral thiamine within the acute care setting.** **In this case, our strategy was justified by the high potential for misdiagnoses or under-recognition of hospitalized patients at risk of thiamine deficiency (particularly those without a history of alcohol use disorder),15,24,30,31 the importance of rapid replacement of thiamine in acutely deficient patients,10,13 the low risk of side effects associated with parenteral administration,32-34 and the comparatively high morbidity,9-11 mortality7,8 and costs35 associated with missed- or under-treatment of at-risk patients.** 3) Methods, page 9, lines 38-42 -- the authors elected to exclude thiamine prescribed for the purposes of total parenteral nutrition (TPN) because ordering was already automated and unlikely to be affected by the intervention. However, there is an opportunity here to again strengthen our degree of belief that the technological change actually led to the improvement by treating TPN patients as a tracer condition. This study is an uncontrolled before-after study and so there is no way to account for secular trends. However, showing that there is no impact on thiamine prescribing for TPN patients, a practice that should not change as a result of their new order set, strengthens the findings of this paper. An example for how this has been used previously is in a hand hygiene study, which showed that hospital ward rates of nosocomial infection MRSA went down, while in the operating room (OR) (a tracer condition since people already wash their hands consistently in the OR and so a hospital-based hand hygiene intervention should not impact MRSA rates in the OR), MRSA rates actually went up a bit. See the full article here: Kirkland KB, Homa KA, Lasky RA, et alImpact of a hospital-wide hand hygiene initiative on healthcare-associated infections: results of an interrupted time series BMJ Quality & Safety 2012;21:1019-1026. **This is another excellent suggestion (with appreciated exemplars /references). However, data were not collected concerning thiamine prescribed as part of TPN as thiamine prescribing is automated, does not require clinician engagement, is by definition provided parenterally to patients receiving TPN 100% of the time. We acknowledge that omission of such an internal control may raise questions concerning additional contributors to the measured effect. This point is now articulated in the Interpretation (paragraph 5). However, given the magnitude of the effect and**

	the absence of prominent "secular trends" in thiamine prescribing over the study period, we are confident in concluding that "Changes to the CPOE system associated with sustained increases in the proportion of prescriptions for high-dose parenteral thiamine at our academic hospital." "…unmeasured factors may have contributed to the reported effect, including publication and distribution of articles promoting the use of parenteral thiamine during the intervention period.[1,13,15]" 4) Implications -- I think that the major implication of this study is that the authors opted to make a system change to essentially default to parenteral thiamine -- they were very successful in designing a change that resulted in near 100% uptake of this practice by making it much easier to order parenteral thiamine. However, because there is no way to know what the indication was that prompted the providers to order thiamine in this study, we do not know whether parenteral thiamine was actually appropriate for all the patients that received it (chances are they ended up over-treating some patients). And so what I think would be important to explore in the Implications section is how organizations negotiate the tension of potentially over-treating some low-risk patients with IV thiamine in order to ensure that those at high risk are treated appropriately -- and what types of circumstances would we advocate for this approach. For example, in the early days of VTE prophylaxis, there were definitely situations where low risk patients were being prophylaxed unnecessarily as a result of institutions adopting VTE order sets -- what lessons can we learn about adopting these types of changes? On one hand, one might argue that over-treatment of low risk patients is potentially acceptable if the overall risks of the intervention are minimal (like giving thiamine parenterally instead of orally). On the other hand, there may be excess costs (e.g., IV medications, nursing time, equipment etc.,) that are not trivial and so organizations need to know how much 'extra' they are paying to make the more expensive treatment option the 'default' option. I do think that eventually we will need a framework to work through these types of considerations to help organizations decide on whether to invest, and a paper like this one would be very informative if framed in this new way. **As outlined in response to the earlier comment (point #2), over-treatment was likely in our cohort… and indeed, by design. Although justified in patients at-risk for thiamine deficiency, the Reviewer is correct that such an approach may not be appropriate when the intervention in question may associate with adverse events (e.g., VTE prophylaxis and bleeding). The need to balance perceived benefits associated with treatment with risks and costs is now discussed in Interpretations (paragraph 3).** **"We acknowledge that such a simplified approach may not be appropriate in other clinical scenarios. It is critical to carefully weigh the potential risks and benefits associated with any proposed intervention before implementation, including potential medication costs and effort/burden associated with administration. This is especially important when considering interventions that may be associated with specific risks or high costs (e.g., pharmacological prophylaxis of venous thromboembolism). In this case, our strategy was justified by the high potential for misdiagnoses or under-recognition of hospitalized patients at risk of thiamine deficiency (particularly those without a history of alcohol use disorder),15,24,30,31 the importance of rapid replacement of thiamine in acutely deficient patients,10,13 the low risk of side effects associated with parenteral administration,32-34 and the comparatively high morbidity,9-11 mortality7,8**

	and costs35 associated with missed- or under-treatment of at-risk patients." Minor comments: 1) Page 7, line 40 -- It's fine to say that there were low prescribing rates, but a brief statement around the guidelines would be helpful here -- cannot assume that all readers will know what the indications are for parenteral high dose thiamine. **The crux of guideline recommendations advocating for high dose parenteral treatment are now presented in the Introduction (paragraph 1). We have also elaborated on the consequences of missed or under-treatment in the same paragraph.** **"…acute thiamine deficiency is commonly encountered in inpatient settings where it may lead to death in 20% of untreated or undertreated patients,[7,8] or substantial morbidity—including Wernicke encephalopathy and Koraskoff syndrome—in upwards of 85% of survivors included in historical case series.[9-11] Although the minimally-sufficient dose of thiamine required to correct deficiencies in inpatients is unknown, doses of parenteral thiamine in excess of 200 mg are commonly recommended to rapidly reverse brain-thiamine deficiency.[12-15,16]"** 2) Page 8, line 6 -- what do you mean by 'exemplar'? Do you mean your organization as an example or case study? Or do you mean your outstanding organization? Please clarify. **"Exemplar" in this context was intended to imply an "example" or "case study". Noting that this was not clear, we have removed this term in the Introduction (paragraph 2).** 3) Page 9, line 16 -- what does Hospital 6A mean? Also, can you please clarify wording to make it absolutely clear where you implemented this change? Was it both Toronto General and Toronto Western? **This sentence references findings reported in Day et al 2015 (J Hosp Med). Data from University Health Network was published under the label of "Hospital 6A" in this report. This has been clarified in Methods (paragraph 1).** **"Thiamine prescribing practices at University Health Network hospitals (Toronto General Hospital, Toronto Western Hospital; Toronto, Ontario, Canada) were evaluated through a retrospective observational study using data collected from computerized pharmacy information systems from January 2010 to December 2011 (results previously reported1: University Health Network hospitals = "Hospital 6A")."** 4) Page 10, line 40 -- typo **The typographical error has been corrected.** 5) Consider using statistical process control chart to analyze percentage of thiamine prescriptions ordered parenterally (would be a p-chart) **Thank you for this suggestion. We have revised the manuscript in-line with recommendations from the CMAJ statistician.** 6) Results section -- page 12 -- in reading this section, in order to make room for my suggested changes above to report on the tracer condition, fidelity process measure and balancing measure, the authors could definitely edit this section as the findings currently reported are mostly a number of different ways of saying that

	thiamine prescribing was affected by this intervention -- basically simplify to say parenteral thiamine prescribing went up, total dose prescribed increased, mostly consistent across programs (except psychiatry), and was sustained -- and then move to the other suggested findings if possible. 7) Page 12, lines 19-29 -- these results are difficult to understand -- could they be presented more clearly? **The Results section has been revised in line with the Reviewers recommendations. The results in lines 19-29 (Results, paragraph 1) have been removed, as they did not specifically address changes in parenteral prescribing and are not essential to the evaluation of the effect of our intervention.** 8) Page 14, lines 5-20 -- this is repetitive -- I would remove. **The recommended lines have been removed from the Interpretation (paragraph 1).** 9) Page 14, line 31 -- you say that your measure of annualized total doses might indicate that practitioners opted for shorter courses of thiamine, but couldn't you just figure that out from your pharmacy data? **Yes, this is what the data suggests. We have revised this statement to more directly state this (Interpretation, paragraph 1).** 10) Page 16, lines 8-18 -- it is well accepted that a transition to CPOE will enable these types of technological fixes -- I would remove this and instead focus on the tension I recommended above about the balance of over-treating low risk patients to ensure high risk patients receive treatment of interest **We have opted to retain these exemplars and associated references to ensure that the reader has appropriate context to apply these results.** **"…gains were associated with a decrease in the annualized number of doses of thiamine prescribed, confirming that clinicians opted for shorter courses of parenteral thiamine."** 11) Page 16, line 38 -- the findings amongst psychiatric patients is not surprising and I think speaks to an issue of context -- most other inpatients already have an IV in place, and so prescribing parenteral thiamine comes up against less resistance. But for psychiatric patients, IV/IM treatments are associated with stigma, and many patients don't normally have IVs put in 'just in case', and so the intervention in psychiatry is going to involve much more than just changing the order set -- I would make this more explicit. **The reasons contributing to lower rates of parenteral prescribing in this population are now stated more clearly in Interpretations (paragraph 5).** **"It is likely that some of these factors contributed to the lower-than-expected rates of parenteral prescribing amongst psychiatric prescribers at our hospital. For instance, patients admitted to psychiatry may have declined or resisted intravenous access due to perceived stigma (less common on other services where intravenous access is universally established), while psychiatric care providers may have encountered additional barriers when attempting to establish or maintain intravenous access outside of medical wards."** 12) Page 17, limitations -- please also mention that your data do not actually speak

	to the group of patients who might have a strong indication for thiamine, who did not get any thiamine at all **This limitation has been added to Interpretations (paragraph 6).** 13) Page 17, line 24 -- not only non-academic centres, but want to know about other centres with different CPOE systems, different degree of order set use etc., -- essentially list a few other contextual features that might influence the success of implementation, and list these as relevant limitations in terms of your findings. **This information has been added to Interpretation (paragraph 5).** **"As anonymized data were obtained from computerized pharmacy information systems, it was only possible to determine how much thiamine was prescribed, not what was actually delivered to patients, or whether our intervention improved recognition and treatment of patients at the highest risk of thiamine deficiency."**