Title: Reversing Deficiencies in Thiamine Prescribing Using the Computerized Order Entry System

Running Title: Reversing Deficiencies in Thiamine Prescribing

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GS Day developed the study concept and methods for implementation, and was primarily responsible for analysis and interpretation of data, as well as drafting, revision and finalization of the manuscript. GS Day had full access to all study data, and takes responsibility for the integrity of the data, and the accuracy of the analyses and interpretation.

S Ladak developed the study concept and methods for implementation, and was primarily responsible for data acquisition. She participated in drafting, revision and finalization of the manuscript.

CM del Campo approved study design and methods. He assisted with interpretation of data, and revision and finalization of the manuscript.

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ABSTRACT

Background: Optimal treatment of thiamine deficiency requires rapid reversal of the brain-thiamine deficit. This is best accomplished through administration of parenteral thiamine. Despite this knowledge, oral thiamine is frequently prescribed to at-risk patients admitted to Canadian academic hospitals. We evaluated the effect of changes to the computerized order entry system promoting the use of high doses of parenteral thiamine on prescribing behavior within our academic hospital network.

Methods: Data were obtained from the computerized pharmacy information system, recording thiamine prescribed at University Health Network hospitals (Toronto, Ontario) before (January 1, 2010 to December 31, 2011) and after (November 21, 2013 to April 30, 2017) implementation of changes to the computerized order entry system promoting prescribing of high-dose parenteral thiamine. The effect of the intervention on the proportion of prescriptions for parenteral thiamine (primary outcome) and dosages prescribed (secondary outcome) were determined.

Results: The proportion of prescriptions for parenteral thiamine rose from 55.5% (3386/6105) to 92.5% (11,829/12,787) following our intervention (χ^2=3617.7; p<0.001). Improvements in parenteral prescribing were sustained or increased across the 3.4 year observation period, and were realized across all hospital services (average improvement: 179 ± 59.6%, range: 128.0-298.2%). Prescriptions for higher dosages of thiamine (≥200 mg) increased from 1.1% (65/6105) to 61.4% (7845/12,787; χ^2=6170.5; p<0.0001 following the intervention.

Interpretation: Changes to the computerized order entry system corresponded with abrupt increases in the proportion of prescriptions for high-dose parenteral thiamine at our academic

hospital. Similar approaches may be used to align prescriber behavior with well-accepted practice parameters or guidelines in other areas of clinical practice, and other hospital systems.

INTRODUCTION

Hospitalized patients are at high risk of thiamine deficiency due to a preponderance of risk factors, including poor nutritional intake, increased metabolic demand, resuscitation with glucose-containing fluids and medical conditions that impair thiamine absorption from dietary sources.[1-5] Adequate treatment of thiamine deficiency requires rapid reversal of the brain-thiamine deficit—a feat best accomplished through administration of high doses of parenteral thiamine.[6,7] Despite recommendations endorsing this approach,[7,8,9] observational studies consistently report low rates of parenteral prescribing within academic hospitals.[1,10] When parenteral thiamine is prescribed, the dosages and duration prescribed are often below that recommended,[1,11] exposing vulnerable patients to potential risks of irreversible brain injury and even death. Prior attempts to alter prescribing practices utilizing cost and effort-intensive strategies (i.e., direct pharmacist intervention) have failed to substantially alter prescriber behavior.[12] Similarly, low-cost efforts (e.g., published guidelines or hospital-wide protocols promoting parenteral prescribing) exhibit only modest effects on prescribing.[1,10,13-15] Efficacious means of reversing deficiencies in prescribing are needed.

A review of parenteral thiamine prescribing at university-affiliated Canadian tertiary-care centers established low rates of parenteral prescribing across the majority of hospital services at the majority of hospitals, including our own.[1] In response to these findings, prescribing practices were reviewed at University Health Network hospitals (university-affiliated hospitals in downtown Toronto, Ontario, Canada). This review led to a system-wide change to thiamine order sets within the computerized order entry system (integrated within the electronic medical record), favoring parenteral prescribing. We evaluated the effect of these changes on the overall

rates of parenteral thiamine prescribing (primary outcome) and dosages of thiamine prescribed (secondary outcome) at our exemplar tertiary care center.

METHODS

Study design and recruitment

Thiamine prescribing practices at University Health Network hospitals (Toronto General Hospital, Toronto Western Hospital; Toronto, Ontario, Canada) were evaluated through a retrospective observational study collecting data from computerized pharmacy information systems from January 2010 to December 2011 (results previously reported: Hospital 6A).[1] On the basis of these findings, changes to thiamine order sets, promoting parenteral prescribing, were proposed and approved by the University Health Network Pharmacy and Therapeutics Committee (June 3, 2013), and implemented within the computerized order entry system on November 21, 2013. A medical bulletin describing the proposed changes and rationale was communicated to all hospital staff (November 28, 2013). Thiamine prescribing patterns were prospectively tracked to determine the intervention effect (Figure 1). Study objectives, methods and procedures were approved by the University Health Network Research Ethics Board.

Data were obtained from the computerized pharmacy information system, recording all thiamine prescriptions processed by the centralized hospital pharmacy before (January 1, 2010 to December 31, 2011) and after the intervention (November 21, 2013 to April 30, 2017). Thiamine prescribed as part of total parenteral nutrition was excluded from analysis, as prescribing was automated and was, therefore, unlikely to be affected by the intervention. Participant data were fully anonymized. Briefly, partients were assigned a random study number linked to prescription information, and specifying the prescribed dose of thiamine, route of administration (oral: per os, nasogastric tube, orogastric tube, gastric tube; versus parenteral: intravenous, intramuscular), frequency of dosing (daily, twice daily, three times daily, etc), start/end date of the prescription, prescribing physician and inpatient location. Subspecialty designations were assigned according

to the prescriber, and were simplified to emergency department (ED), intensive care unit (ICU: including medical, surgical and trauma ICUs), medical subspecialty (i.e., cardiology, endocrinology, gastroenterology, medical oncology, rheumatology, etc.), general internal medicine, neurology, psychiatry and surgical services (i.e., general surgery, cardiac surgery, neurosurgery, orthopedics, gynecology, etc.).

The total number of prescriptions, number of *first* prescriptions (a proxy measure defining the number of unique patients treated), and number of doses of thiamine prescribed were measured before and after changes to the computerized order entry system were implemented. Prescriptions were stratified by the route of administration (parenteral versus oral), and annualized prescribing rates derived by dividing by the number of years of observation to facilitate comparison across pre- and post-intervention periods.

Statistical Analysis

Changes in parenteral prescribing pre- and post-intervention were compared using chi-square tests (pairwise comparison, df=1). Univariate regression was used to evaluate the relationship between the rate of parenteral prescribing (dependent variable) and time following the intervntion. Pairwise comparisons (chi-square tests) were also used to assess differences in parenteral prescribing across services, and pre- and post differences in prescribing behaviors within services. Statistical analyses were performed using IBM SPSS Statistics 24 (IBM Corporation, NY). Significance was defined as $p<0.05$, with adjustment for multiple comparisons where appropriate (Bonferroni correction).

Data Sharing

Anonymized data will be made available to qualified researchers upon reasonable request addressed to the corresponding author.

RESULTS

In total, 18,892 prescriptions for 36,807 doses of thiamine were provided to 10,939 patients across the study period. Changes to the computerized order entry system promoting prescribing of parenteral thiamine for patients at risk of thiamine deficiency were associated with a dramatic shift in prescribing practices. Prescriptions for parenteral thiamine rose from 55.5% (3386/6105) to 92.5% (11,829/12,787; χ^2=3617.7; p<0.001) following the intervention, while the proportion of parenteral doses prescribed increased from 44.2% (7052/15,947) to 92.8% (19,357/20,860; χ^2=10,520.1; p<0.001). Improvements in parenteral prescribing were matched by increases in the average number of prescriptions issued per year (rising from 3053 to 3719 per year post-intervention—a 21.8% increase), and numbers of patients treated (rising from 1454 to 2336 per year post-intervention—a 60.7% increase). The average number of doses prescribed decreased by 23.9% following the intervention, declining from 7974 to 6066 per year post-intervention.

Changes in prescribing behavior were sustained or increased across the 3.4 year post-intervention observation period (Figure 2). The number of total prescriptions for thiamine and doses prescribed remained stable month-to-month following the intervention, while the number of patients prescribed thiamine gradually increased. Sustained increases in parenteral prescribing were observed following changes to the computerized order entry system, with the total prescriptions, number of patients treated, and total prescribed doses of parenteral thiamine continuing to increase with time from intervention (Table 1).

The proportion of annualized prescriptions for parenteral thiamine across services increased, on average (± SD), by 179.0% (59.6%; range: 128.0-298.2%). Prescribers from all but one service, achieved parenteral prescribing rates >80% following the intervention (average=91.4±6.8%; range: 77.9-98.9%). Psychiatry providers demonstrated greater-than-

average increases in rates of parenteral prescribing, with the proportion of parenteral prescriptions increasing from 26.1% to 77.9% post-intervention (z=2.0; p=0.045), although annualized rates of parenteral prescribing were lower than observed with other services (z=-1.98; p=0.048). Similar relationships were observed when the annualized number of doses prescribed were considered. When only first prescriptions were considered, all services achieved parenteral prescribing rates >80% (Table 2). Increases in the proportion of parenteral prescribing were matched by increases in the total numbers of prescriptions issued by ED and ICU providers. The opposite relationship was observed with providers affiliated with other services, where proportional increases in parenteral prescribing were driven by disproportionate decreases in prescriptions for oral thiamine.

Changes to the computerized order entry system promoting use of higher doses of parenteral thiamine were also associated with changes in the dosages prescribed and schedule. Pre-intervention, prescribers exhibited a near-universal approach to thiamine dosage, with 91.6% (5592/6105) of prescriptions issued for 100 mg of thiamine. Following the intervention, prescriptions for 100 mg of thiamine decreased to 34.9% (4457/12,785; χ^2=5342.07; p<0.0001). Conversely, prescriptions for higher dosages of thiamine (≥200 mg) increased from 1.1% (65/6105) to 61.4% (7845/12,787; χ^2=6170.5; p<0.0001; Figure 3A). Although the vast majority of thiamine continued to be prescribed one-time or once daily (before: 99.3%, 6060/6100; after: 93.8%, 11,994/12,785; χ^2=300.3; p<0.0001), prescriptions for thiamine three times daily (or more frequently) increased from 0.5% (33/6100) to 6.1% (774/12,785; χ^2=306.8; p<0.0001; Figure 3B).

INTERPRETATION

Acute thiamine deficiency is commonly encountered in inpatient settings where it contributes to substantial morbidity—including Wernicke encephalopathy and Koraskoff syndrome—and mortality if untreated or undertreated.[16-19] Despite wide dissemination of recommendations emphasizing the need to prescribe higher doses (≥200 mg) of parenteral thiamine to rapidly reverse brain-thiamine deficiency,[6-9] a recent review of prescribing practices within Canadian academic hospitals established that the majority of thiamine was prescribed via the oral route at dosages of 100 mg.[1] The introduction of changes to the computerized order entry system promoting prescribing of higher dosages of parenteral thiamine to at-risk patients at our tertiary care hospital resulted in an abrupt improvement in rates of parenteral prescribing (the primary outcome), and the number of patients prescribed thiamine per year. Interestingly, these gains were accompanied by a decrease in the annualized number of doses of thiamine prescribed, suggesting that clinicians opted for shorter courses of parenteral thiamine, consistent with recommendations for the treatment of thiamine deficiency.[6-9] Most encouraging, these changes were sustained or amplified across the 3.4 year observation period and were realized across all prescribing services. Improvements were also noted in the proportion of prescriptions for higher dosages (≥200 mg) of thiamine (secondary outcome), and to a lesser degree, frequency of administration. Analyses of effects on hospital services demonstrated greatest effect on front-line services, including ED and ICU, with these services experiencing substantial improvements in the rates of parenteral prescribing and the numbers of overall prescriptions and patients treated. These changes may have pre-empted subsequent prescribing by receiving services, accounting for post-intervention decreases in total numbers of thiamine prescriptions issued by providers affiliated with general and subspecialty medical, neurology, psychiatry and surgical services.

Robust changes in prescriber behavior observed following changes to the computerized order entry system far exceeded the modest benefits attributed to hospital-wide protocols promoting the use of parenteral thiamine in at-risk patients.[10,13-15] The observed response also exceeded benefits associated with the use of a clinical decision support tool promoting high-dose parenteral thiamine prescribing to patients with suspected alcohol use disorder admitted to an urban New York hospital. The tool, which autopopulated thiamine order sets in appropriate patients, led to an increase in the number of patients receiving appropriate treatment from 2.7% (3/113) to 20.2% (19/94).[20] Better-than-expected responses in our study may reflect key differences in design and implementation of the intervention. By codifying recommendations as the default selection within computerized order entry systems, our intervention made it easy for prescribers to "do the right thing", and more difficult to deviate from recommended thiamine prescribing strategies. By not tying recommendations to specific clinical diagnoses (i.e., those meeting criteria for alcohol use disorder), we also simplified the prescribing process, removing the need for clinicians to identify eligible patients. This 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),[8,13,21,22] the importance of rapid replacement of thiamine in acutely deficient patients,[6,23] and the low risk of side effects associated with parenteral administration.[24,25] We acknowledge that such a simplified approach may not be appropriate in other clinical scenarios—particularly those where the recommended treatment may be associated with specific risks or high costs.

We leveraged an existing computerized order entry system to efficiently and cost-effectively implement our intervention. This strategy offered compelling advantages over more traditional approaches that rely on labor-intensive pharmacy-based interventions and manual

chart review,[12] or educational initiatives, which need to be revised and repeated to keep up with staff turn-over and changes in clinical rotations that are especially common in academic hospitals.[26] As electronic medical records become increasingly ubiquitous in healthcare, it may be possible to extend this approach to address diagnostic and therapeutic shortcomings in other areas of medicine that are supported by well-accepted practice parameters or guidelines (e.g., infection risk reduction in intensive care units,[27] management of acute exacerbations in patients with chronic obstructive pulmonary disease exacerbations[28]). With this in mind, it will be increasingly important to decipher the factors that influence response to interventions designed to modify prescriber behavior, including the degree of consensus concerning the recommended treatment approach, potential for benefit versus adverse effects associated with the intervention, and perceived costs and barriers associated with prescribing and administration. It is likely that some of these factors contributed to the lower-than-expected rates of parenteral prescribing amongst psychiatric prescribers at our hospital, recognizing that difficulties with parenteral administration may be unique to this patient population (attributed to difficulties maintaining parenteral access in agitated patients). It is particularly important to explore alternate or additional approaches to optimize prescribing by psychiatric providers, acknowledging that acute thiamine deficiency may cause or exacerbate presenting symptoms,[19] and that patients with psychiatric illnesses may be at particularly high risk of thiamine deficiency due to malnutrition associated with eating disorders, substance abuse or somatoform disorders,[29-31] and higher rates of comorbid physical illnesses.[32] Similar efforts are needed to understand the factors that underlie the strong preference for one-time or once daily dosing of thiamine noted within our hospital network and others.[1,11] While most studies to date have considered the impact of one intervention on prescribing practices, future studies are needed to assess the effect of

multifaceted approaches integrating changes to computerized order entry systems together with educational approaches targeting specific services and prescribing patterns.

Interpretation of our results are subject to limitations. 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. Similarly, we were unable to consider the specific indications for prescribing—precluding subanalyses of prescribing behavior in patients with suspected Wernicke encephalopathy—or whether our intervention led to measurable improvement in patient outcomes. Additionally, as this study was completed within a single hospital network, our findings need to be replicated within other hospital environments, including non-academic centers, to establish generalizability and to better understand how center-specific factors influence compliance with existing recommendations and response to changes to the computerized order entry system. These limitations notwithstanding, our results demonstrate that changes to computerized order entry systems led to dramatic changes in thiamine prescribing behaviors within our hospital network. These changes were sustained across the observation period and realized across all prescribing services. If validated in other populations, practice areas and hospitals, changes to computerized order entry systems may be leveraged to efficiently and cost-effectively modify prescriber behavior, improving compliance with clinical recommendations and patient care.

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Figure Legends

Figure 1: Timeline of review and implementation of changes to the computerized order entry system.

Figure 2: Longitudinal changes in prescribing behavior. Changes in total thiamine prescriptions (A), first prescriptions for thiamine (B) and doses of thiamine prescribed (C) are shown before (January 1, 2010 to December 13, 2011) and after (November 21, 2013 to April 30, 2017) the intervention (dashed line). The red trend line corresponds to the percentage of prescriptions for parenteral thiamine at each timepoint.

Figure 3: Changes in dose and frequency of thiamine prescribed. Dosage (in milligrams; A) and frequency of administration (B) of thiamine prescribed before and after the intervention.
**=$p<0.001$ QD = once daily; BID = twice daily; TID = three times daily

Table 1: Longitudinal changes in thiamine prescribing following changes to the computerized order entry system.

Prescribing behavior	**Beta**	**95% CI**	**p value**
All prescriptions (parenteral and oral), per month			
Total prescriptions provided	0.51	-0.22, 1.24	0.16
Number of patients prescribed	0.83	0.34, 1.31	0.001
Total doses prescribed	1.21	-0.28, 2.71	0.11
Proportion of parenteral prescriptions, per month			
Prescriptions provided	0.11	0.06, 0.17	<0.001
Number of patients prescribed	0.13	0.06, 0.21	0.001
Doses prescribed	0.08	0.005, 0.15	0.038

β±95% CI describing magnitude of association between prescribing behavior and months-from-intervention, determined using univariate linear regression (41 observations).

Table 2: Annualized thiamine prescribing before and after changes to the computerized physician order entry system, stratified by service.

Prescribing service	Before		After		Percentage change		
	Total, n	Parenteral, %	Total, n	Parenteral, %	Total, n	Parenteral, %	p value*
Annualized number of prescriptions for thiamine							
ED	675	62.7	1592	87.9	235.8	140.2	<0.0001
ICU	181	77.3	747	98.9	413.7	128.0	<0.0001
Medical Subspecialty	309	49.9	82	91.8	-73.5	183.9	<0.0001
Medicine	968	46.2	752	94.5	-22.3	204.7	<0.0001
Neurology	90	70.4	56	93.7	-37.9	133.1	0.0063
Psychiatry	44	26.1	20	77.9	-55.1	298.2	0.0009
Surgery	787	57.8	471	95.1	-40.2	164.7	<0.0001
Annualized number of first prescriptions for thiamine							
ED	320	64.5	1394	88.0	435.6	136.3	<0.0001
ICU	97	72.5	369	99.1	382.1	136.7	<0.0001
Medical Subspecialty	145	47.2	40	90.4	-72.7	191.4	<0.0001
Medicine	505	45.6	251	95.0	-50.3	208.4	<0.0001
Neurology	44	77.3	21	97.2	-53.1	125.8	0.0203
Psychiatry	20	25.0	11	84.6	-43.3	338.5	0.0004
Surgery	324	57.5	251	96.4	-22.5	167.7	<0.0001
Annualized number of doses of thiamine prescribed							
ED	1386	31.1	1683	88.5	121.5	284.5	<0.0001
ICU	482	70.1	1340	97.9	278.0	139.5	<0.0001
Medical Subspecialty	969	40.6	189	93.2	-80.5	229.6	<0.0001
Medicine	2457	43.3	1810	93.0	-26.3	214.6	<0.0001
Neurology	248	67.1	129	94.1	-48.1	140.2	<0.0001
Psychiatry	167	15.9	44	71.9	-73.3	451.7	<0.0001
Surgery	2266	48.8	870	93.8	-61.6	192.0	<0.0001

*p-value reflects changes in rates of parenteral prescribing following the intervention (chi-square, df=1)

ED=Emergency Department, ICU=Intensive Care Unit

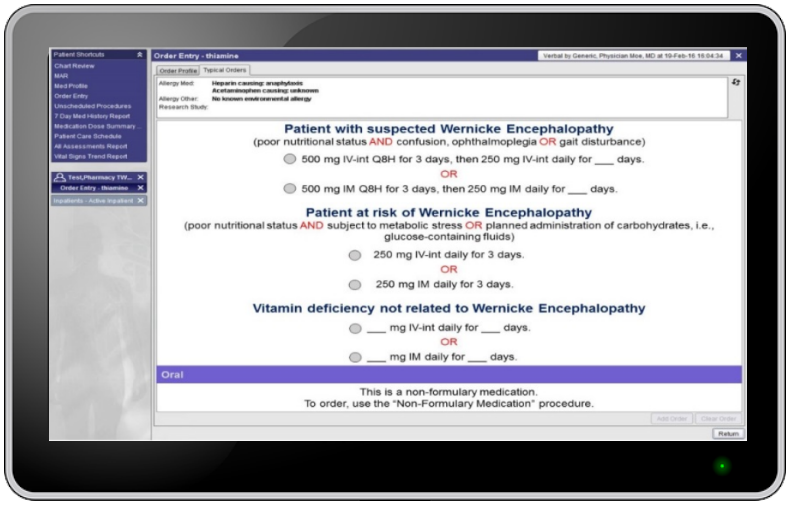
JAN 2010 – JAN 2011
- Thiamine prescribing practices reviewed and deficiencies identified.

MAR 2013
- Thiamine order set revised for University Health Network hospitals, emphasizing higher parenteral doses.

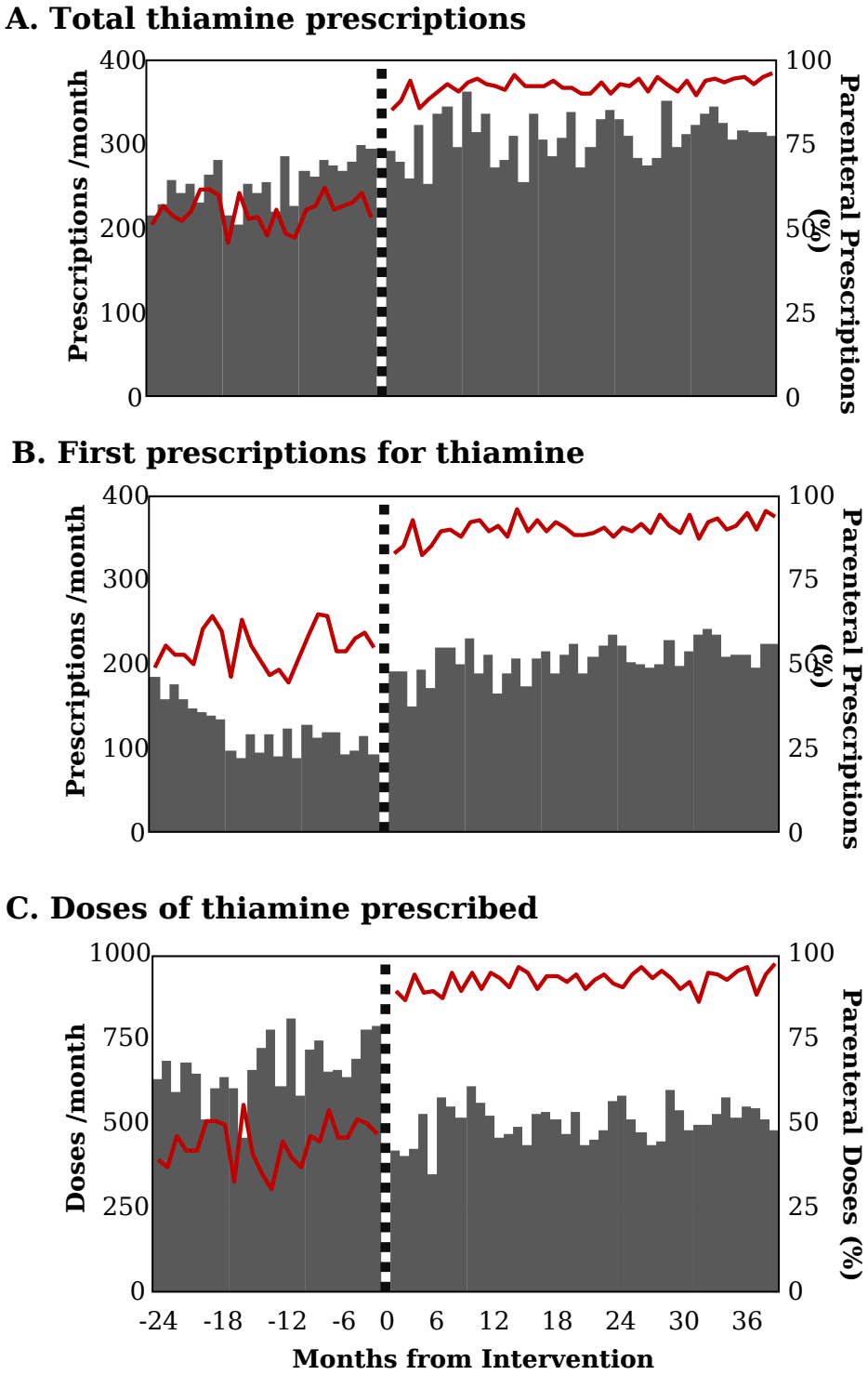
JUN 2013
- Revised thiamine order set approved by hospital Pharmacy and Therapeutics Committee.

NOV 2013
- Bulletin outlining changes to order set communicated to hospital staff.

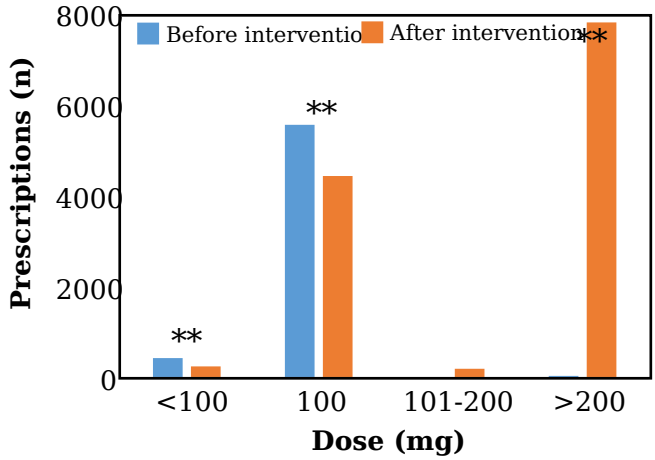
NOV 2013
- Thiamine order set implemented within the computerized order entry system.



JAN 2017
- Prescribing patterns reviewed to assess the effect of the intervention.


A. Total thiamine prescriptions
Prescriptions /month
400
300
200
100
0
100
75
50
25
0
Parenteral Prescriptions (%)
B. First prescriptions for thiamine
Prescriptions /month
400
300
200
100
0
100
75
50
25
0
Parenteral Prescriptions (%)
C. Doses of thiamine prescribed
Doses /month
1000
750
500
250
0
100
75
50
25
0
Parenteral Doses (%)
-24 -18 -12 -6 0 6 12 18 24 30 36
Months from Intervention

A. Dose of thiamine prescribed



B. Frequency of thiamine administration prescribed