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Title: Randomized controlled trial of a clinical decision support system for painful polyneuropathy

Running Title: RCT of decision support system

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Abstract

Introduction: Despite guidelines, painful neuropathy is often inappropriately treated. We aimed to determine the effectiveness of a clinical decision support system on guideline-recommended medication utilization.

Methods: We randomized neurology providers, stratified by subspecialty, to a Best Practice Alert (BPA) linked to a Smartset or a BPA alone when seeing neuropathy patients. The primary outcome was the proportion of patients with uncontrolled nerve pain prescribed a guideline-recommended medication. Generalized estimating equations were used to assess effectiveness.

Results: 75 neurology providers (intervention:38,control:37) treated 2,697 neuropathy patients (intervention:1026,control:671). Providers did not acknowledge the BPA in 1928 (71.5%) visits. Only 4 of 8 intervention arm neurologists that treated patients with uncontrolled nerve pain opened the Smartset. The intervention was not associated with guideline-recommended medication utilization (OR:0.52,0.18-1.48, intervention:52.0%,control:54.8%).

Discussion: Our intervention did not improve prescribing practices for painful neuropathy. Physicians typically ignored the BPAs/Smartset; therefore, future studies should mandate their use or employ alternate strategies.

Introduction

Neuropathy is a highly prevalent and painful condition[1–3]. Recent guidelines indicate that tricyclic antidepressants (TCAs), serotonin norepinephrine update inhibitors (SNRIs) and gabapentinoids are efficacious for the treatment of neuropathic pain[4–7]. Despite this robust evidence, we previously demonstrated that neuropathy patients rarely receive more than one guideline-recommended medication[8]. Furthermore, almost two thirds of neuropathy patients receive at least one opioid prescription and nearly 9% receive chronic opioid therapy, often prior to any guideline-recommended medications[8]. Since opioid treatment is associated with worse functional outcomes in neuropathy patients, an intervention designed to increase guideline-recommended medication use and decrease opioid use is needed[9].

Clinical decision support systems (CDSS) could improve the utilization of guideline-recommended neuropathic pain medications while decreasing opioid use. Meta-analyses demonstrate that CDSS interventions can improve physician behavior in diverse healthcare processes[10–13]. We developed a CDSS that utilized a best practice alert (BPA) linked to a Smartset to facilitate the ordering of guideline-recommended neuropathic pain medications and recommended against opioid treatment. We tested the effectiveness of the CDSS through a randomized controlled trial (RCT).

Methods

Simulation study and power calculation

Prior to implementation, we performed simulations to determine the appropriate sample size. We utilized 3 months of preliminary data from neurologists at the University of Michigan to estimate the frequency of patients with uncontrolled neuropathic pain, proportion of patients treated with guideline-recommended medications, and the typical number of patients treated per provider. We estimated 80.1% power to detect a 5% increase in guideline-recommended prescriptions for 1000 patients over 1 year using a generalized estimating equations (GEE) model with exchangeable correlation structure.

Intervention

Neurologists at the University of Michigan were provided study information through a presentation at a mandatory faculty meeting and several subsequent emails. Each provider was given an opportunity to opt out, but none did. The 103 neurologists were assigned to receive the BPA with or without the Smartset using block randomization, stratified by provider subspecialty (general neurologists(n=7), neuromuscular specialists(n=4), neurologists with specialties other than neuromuscular(n=46), neurology fellows(n=19), neurology residents(n=17) and neurology nurse practitioners(n=10)). Neuropathy patients were identified using ICD-10 codes (G60-G65,E08-11.40/42,E13.40/42,M79.2,A36.83,B27.01/11/81/91,B26.84,B02.23,M34.83) or when "peripheral neuropathy" was included as the chief complaint or in the problem summary list. When a neuropathy patient met inclusion criteria, the BPA was automatically triggered with (intervention group) or without (control group) the Smartset. Supplementary Figures 1A and 1B display images

of the BPA and Smartset respectively. Providers received the BPA and then determined nerve pain status and entered medication status as follows (Supplementary Figure 1A):

1. No nerve pain
2. Well controlled nerve pain, off medication
3. Well controlled nerve pain, on medication
4. Uncontrolled nerve pain

If the patient had uncontrolled nerve pain, the intervention group would receive a link to the Smartset, which gave information involving guideline-recommended medications including dosage information, typical medication pricing, advice to avoid opioid medication use, and a link to the American Academy of Neurology guidelines (Supplementary Figure 1B)[5]. Both the BPA and Smartset were delivered through the electronic medical record used at the University of Michigan (Epic, Verona, WI).

Outcomes

The primary outcome was the proportion of patients with uncontrolled nerve pain that were prescribed a guideline-recommended medication. The secondary outcome was the proportion of patients with uncontrolled nerve pain that were prescribed an opioid. To understand the utilization of our CDSS, we collected two process outcomes: the proportion of BPAs acknowledged, and the proportion of Smartsets opened.

Statistical Analysis

Descriptive statistics were used to characterize patients with uncontrolled nerve pain. We report the frequencies that guideline-recommended medications, opioids, or other potential neuropathic pain medications were prescribed. The primary analysis utilized GEE with a logit link to assess the effects of the intervention on guideline-recommended prescriptions. In addition to adjusting for patient factors (age, sex, race, insurance plan type) and provider subspecialty, the GEE approach accounts for clustering at the neurologist level, because the same provider may treat multiple patients. Data analysis was completed using Rv.3.4.2. This study was approved by the University of Michigan IRB(HUM00109137).

Results

Between 7/14/2016-7/13/2017, 75 neurology providers (intervention:38(50.7%), control:37(49.3%)) treated 2,697 neuropathy patients (intervention:1026(38.0%), control: 1,671(62.0%)). Providers did not acknowledge the BPA in 1928(71.5%) visits (intervention:789(77.3%), control:1139(68.0%)). When the BPA was acknowledged, 6.9% of patients had controlled nerve pain without medication (intervention: 14(5.4%), control: 39(6.7%)), 27.2% of patients had controlled nerve pain with medication (intervention: 7(30.2%), control: 131(22.4%)), 37.6% of patients had no nerve pain (intervention:99(38.5%), control:190(32.5%)) and 28.4% of patients had uncontrolled nerve pain (intervention:41(15.9%), control:177(30.3%)). There were 8 neurologists in the intervention arm and 20 in the control arm that treated patients

with uncontrolled nerve pain. Only 4/8 neurologists in the intervention arm (25/41 patients), opened the Smartset during follow-up.

Demographic, health plan and provider subspecialty for patients with uncontrolled nerve pain is summarized in Table 1. Despite stratifying by provider subspecialty, we observed different patterns of providers that treated patients with uncontrolled nerve pain. Patients in the intervention arm were treated by residents and attending neurologists. Patients in the control arm were treated by general neurologists, neuromuscular specialists, residents, fellows and attending neurologists.

Frequencies of relevant medications that were prescribed to patients are displayed in Table 2. The proportion of patients receiving guideline-recommended medications was similar in the intervention and control arms. No patients were prescribed with an opioid in the intervention arm, compared to 11 patients in the control arm.

The GEE revealed that the intervention was not associated with guideline-recommended medication utilization (crude OR: 0.89,0.36-2.24, adjusted OR: 0.52,0.18-1.48). Male patients (adjusted OR: 2.10,1.14-3.89) and patients treated by residents (adjusted OR: 2.18,1.12-5.66, ref=general neurologists) had an increased odds of guideline-recommended medication use. Insurance type, patient race, and age were not significantly associated with guideline-recommended medication use. We were unable to fit a GEE model for the secondary outcome because there were no opioids prescribed in the intervention arm.

Discussion

Our intervention failed to improve either the primary or secondary outcome measures. Future interventions should be informed by the lessons learned from our negative trial. Our CDSS failed in two major capacities. First, our process outcomes indicated that physicians usually did not acknowledge the BPA or use the Smartset intervention. The low utilization rate resulted in an insufficient sample size to assess the effectiveness of the intervention. Our observed low utilization is not unusual: a previous meta-analysis found that most RCTs (8/12) observed poor physician utilization of CDSS interventions (however this information was rarely reported)[11]. One solution involves implementing a mandatory BPA with an automatically fired Smartset. A mandatory response BPA would improve CDSS utilization, however, previous studies found no difference in the rate by which physicians accepted the CDSS recommendation when responses were required.[11] Therefore, it is unclear whether higher utilization would improve prescribing patterns. Rather than a mandatory response CDSS, other strategies could be employed to incentivize providers to use the intervention through financial bonuses or other means[14]. Furthermore, the intervention may have led to alert fatigue.[15] One potential solution is to focus future interventions on patients that self-report pain and/or are not on current guideline recommended medications. Finally, embedding a predictive tool into the BPA to help determine which patients would most benefit from a specific medication, could increase the perceived utility of the CDSS[16,17]. Future CDSS interventions should (A) implement a more intensive implementation strategy to increase provider participation or (B) plan for low utilization rates when determining sample size and follow-up length. The

second shortcoming was that the distribution of patients in the two arms of our trial was asymmetric despite stratification by provider type. To mitigate this issue, future studies could increase the number of physicians randomized through a multi-center study, or stratify physicians based on previous frequencies of outpatient neuropathy visits.

Changing physician behavior is difficult, even when implementing a CDSS that follows the typical workflow for ordering medications. One possible solution would be to target physicians with less experience, such as residents. Unfortunately, previous meta-analyses have found no association between physician experience and CDSS intervention effectiveness[12,18,19]. Our finding that residents have higher rates of CDSS utilization warrants further study.

Limitations include the small sample size and the asymmetric distribution of physicians in each group. Given the small sample size, we were unable to account for the nested, networked nature of trainees being supervised by different attendings. Whether our results are generalizable to other provider specialties is unclear. We did not have baseline data from the time period immediately prior to the intervention; therefore, we do not know whether the two groups were balanced at baseline in terms of medication use. This study was unable to address whether the intervention would be successful with mandatory BPAs.

Our proposed CDSS was unsuccessful, both in its utilization, and in altering prescribing patterns of guideline-recommended medications. Performing RCTs to assess the effectiveness of CDSS interventions is essential. Lack of rigorous testing may lead to ineffective CDSS that add

unnecessary work to physicians. Our negative trial allowed us to delete this BPA and lessen the burden on neurologists at the University of Michigan.

Author contributions: Evan Reynolds and Brian Callaghan were involved in the study design, interpretation of the statistical analysis, and wrote the manuscript. James Burke was involved in the interpretation and presentation of the results, and critical revisions of the manuscript. Mousumi Banerjee was involved in the statistical analyses, interpretation and presentation of the results, and critical revisions of the manuscript.

Abbreviations:

Best Practice Alert (BPA)

Clinical decision support systems (CDSS)

generalized estimating equations (GEE)

randomized controlled trial (RCT)

serotonin norepinephrine update inhibitors (SNRIs)

tricyclic antidepressants (TCAs)

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Table 1: Patients Demographic, Health Plan and Provider Information

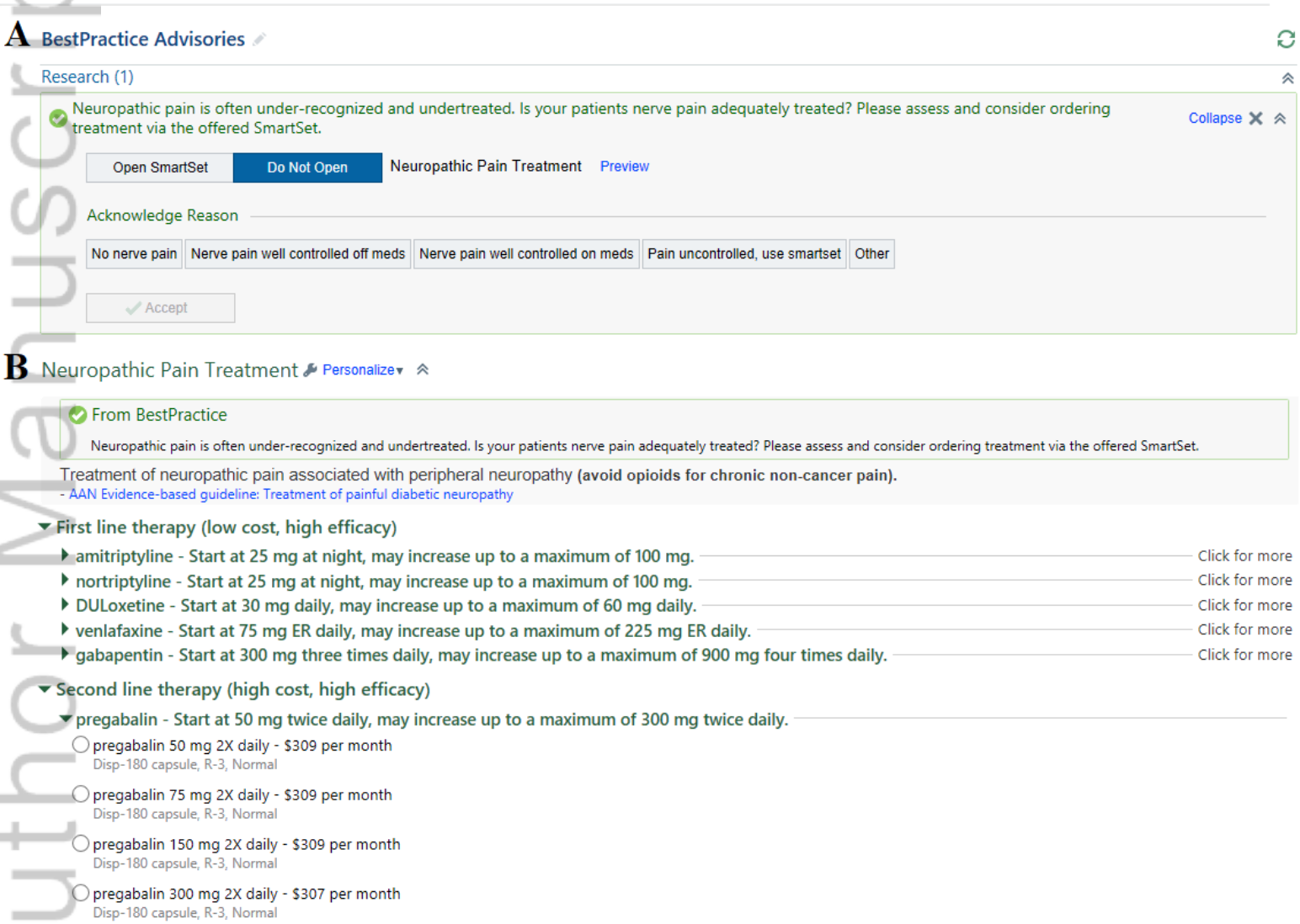
	Intervention Patients (n=25)	Control Patients (n=177)
Age	58.3 (15.2)	56.6 (13.9)
Sex (Male)	17 (68.0%)	73 (41.2%)
Race		
White	23 (92.0%)	158 (89.3%)
Black	2 (8.0%)	15 (8.5%)
Asian	0 (0.0%)	2 (1.1%)
Other	0 (0.0%)	2 (1.1%)
Ethnicity (Hispanic)	0 (0.0%)	6 (3.4%)
Health Plan		
Medicare	9 (36.0%)	55 (31.1%)

Blue Cross Blue Shield	8 (32.0%)	54 (30.5%)
Blue Care Network	2 (8.0%)	20 (11.3%)
Priority Health	1 (4.0%)	13 (7.3%)
Meridian Health Plan	3 (12.0%)	8 (4.5%)
Mclaren	0 (0.0%)	6 (3.4%)
United Healthcare	0 (0.0%)	5 (2.8%)
Other	2 (8.0%)	16 (9.0%)
Provider Subspecialty		
General Neurology	0 (0.0%)	61 (34.5%)
Residents	22 (88.0%)	37 (20.9%)
Neuromuscular	0 (0.0%)	39 (22.0%)
Fellows	0 (0.0%)	31 (17.5%)
Attendings	3 (12.0%)	9 (5.1%)
Nurse Practioners	0 (0.0%)	0 (0.0%)

Table 2: Frequency of Neuropathic Pain Medication Prescriptions

	Intervention	Control
Guideline Recommended Medications	13 (52.0%)	97 (54.8%)
Gabapentin	4 (16.0%)	40 (22.6%)
Nortriptyline	5 (20.0%)	27 (15.3%)
Pregabalin	2 (8.0%)	15 (8.5%)

Duloxetine	1 (4.0%)	15 (8.5%)
Amitriptyline	0 (0.0%)	10 (5.7%)
Venlafaxine	1 (4.0%)	3 (1.7%)
Doxepin	0 (0.0%)	2 (1.1%)
Opioid	0 (0.0%)	11 (6.2%)
Oxycodone	0 (0.0%)	6 (3.4%)
Methadone	0 (0.0%)	3 (1.7%)
Morphine	0 (0.0%)	3 (1.7%)
Buprenorphine, Naloxone	0 (0.0%)	2 (1.1%)
Fentanyl	0 (0.0%)	1 (0.6%)
Hydrocodone	0 (0.0%)	1 (0.6%)
Other Potential Pain Meds		
Tramadol	0 (0.0%)	14 (7.9%)
Topiramate	1 (4.0%)	7 (4.0%)
Zonisamide	0 (0.0%)	8 (4.5%)
Carbamazepine	0 (0.0%)	7 (4.0%)
Lamotrigine	0 (0.0%)	7 (4.0%)
Baclofen	2 (8.0%)	4 (2.3%)
Levetiracetam	0 (0.0%)	5 (2.8%)
Lidocaine	1 (0.0%)	4 (2.3%)
Other	4 (16.0%)	13 (7.3%)



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