

The use of metformin is associated with decreased lumbar radiculopathy pain

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Abstract: Lumbar radiculopathy pain represents a major public health problem, with few effective long-term treatments. Preclinical neuropathic and postsurgical pain studies implicate the kinase adenosine monophosphate activated kinase (AMPK) as a potential pharmacological target for the treatment of chronic pain conditions. Metformin, which acts via AMPK, is a safe and clinically available drug used in the treatment of diabetes. Despite the strong preclinical rationale, the utility of metformin as a potential pain therapeutic has not yet been studied in humans. Our objective was to assess whether metformin is associated with decreased lumbar radiculopathy pain, in a retrospective chart review. We completed a retrospective chart review of patients who sought care from a university pain specialist for lumbar radiculopathy between 2008 and 2011. Patients on metformin at the time of visit to a university pain specialist were compared with patients who were not on metformin. We compared the pain outcomes in 46 patients on metformin and 94 patients not taking metformin therapy. The major finding was that metformin use was associated with a decrease in the mean of “pain now,” by -1.85 (confidence interval: -3.6 to -0.08) on a 0–10 visual analog scale, using a matched propensity scoring analysis and confirmed using a Bayesian analysis, with a significant mean decrease of -1.36 (credible interval: -2.6 to -0.03). Additionally, patients on metformin showed a non-statistically significant trend toward decreased pain on a variety of other pain descriptors. Our proof-of-concept findings suggest that metformin use is associated with a decrease in lumbar radiculopathy pain, providing a rationale for larger retrospective trials in different pain populations and for prospective trials, to test the effectiveness of metformin in reducing neuropathic pain.

Keywords: neuropathy, mTOR, adenosine monophosphate activated kinase, diabetes

Introduction

Lumbar radiculopathy pain is one of the most common forms of chronic pain in developed nations and is challenging to treat with existing therapeutics.^{1,2} Many drugs are prescribed as treatment, but few have been shown to be effective in retrospective or prospective trials.³ Commonly prescribed drugs for this condition include nonsteroidal anti-inflammatory drugs (NSAIDs), opiates, anticonvulsants, antidepressants, benzodiazepines, corticosteroids, muscle relaxants, and transdermal anesthetics. The majority of patients with this condition are seen by primary care doctors, with only a small percentage referred to see a pain specialist.⁴ Lumbar radiculopathy pain can be disabling, negatively affecting a patient’s ability to function and altering his or her quality of life. Only one in four patients with neuropathic pain as a result of lumbar radiculopathy receives a 50% relief from pain, indicating there is a great need for more effective therapies for this and similar conditions.⁵

The oral biguanide metformin has been widely used for the treatment of prediabetes and type 2 diabetes for several decades. It is an orally available drug with a long history of safe use in a diverse patient population, now estimated to reach at least the tens of millions. It is known to suppress hepatic gluconeogenesis and increase insulin sensitivity. More recently, metformin's mechanism of action was found to involve the activation of adenosine monophosphate activated protein kinase (AMPK).⁶ Metformin regulates AMPK via inhibition of mitochondrial complex I, and its effects on AMPK are thought to be crucial for its beneficial effects on metabolism,⁷ although recently, a novel mechanism of action for metformin has been proposed, involving the inhibition of cyclic adenosine monophosphate (cAMP) accumulation in adipocytes.⁸ An end result of AMPK activation by metformin is the inhibition of cellular anabolic processes, including the inhibition of the mammalian target of rapamycin (mTOR) pathway.⁶ AMPK can also be regulated by more potent and specific experimental tools, such as 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and A769662.^{9,10} These drugs have been shown to mimic the effects of metformin in laboratory animals, further suggesting that the clinical effects of metformin are mediated by AMPK activation.

Recent evidence from preclinical pain models implicates the mTOR pathway as a major contributor to nociceptive hypersensitivity in preclinical pain models.¹¹⁻¹³ A major peripheral factor involved in the sensitization of nociceptors, nerve growth factor (NGF), signals via mTOR,¹⁴ and there is strong evidence that other algogenic factors, including inflammation, stimulate this pathway in sensory afferents.¹¹⁻¹³ Collectively these findings create a compelling rationale for developing compounds that inhibit mTOR signaling as pain therapeutics.^{11,12} One mechanism through which this can be achieved is the activation of AMPK.¹² Indeed, in preclinical pain models, AMPK activators, such as metformin and A769662, have been shown to be remarkably effective in reducing mechanical allodynia and nociceptor excitability, and in inhibiting basal and evoked mTOR signaling in nociceptors.^{10,15-17} Hence, the activation of AMPK with metformin and other AMPK activators has led to decreased pain in neuropathic and postsurgical pain models, suggesting that these drugs and this mechanism of action might be effective in humans.¹⁸ Recent case reports support this notion.¹⁸ Because metformin is commonly prescribed for prediabetes and diabetes, we reasoned that patient populations may exist wherein we could test the hypothesis that metformin would have a positive impact on pain outcomes. We tested this

hypothesis through a chart review of patients with lumbar radiculopathy who visited a pain clinic in Tucson, AZ between 2008 and 2011. Our findings suggested that metformin is associated with reduced lumbar radiculopathy pain and provides the rationale for a prospective investigation of metformin as a novel drug for the treatment of neuropathic pain.

Materials and methods

This study was a retrospective chart review designed to examine a possible positive impact of metformin use on lumbar radiculopathy pain. Using the electronic health record (EHR), we performed a chart review of patients who sought care for lumbar radiculopathy from one university pain specialist between Jan 2008 and Nov 2011. The study was approved by our local internal review board (IRB), and an informed consent was waived.

Patient selection

The EHR was queried for patients possessing International Classification of Disease (ICD) 9 codes for lumbar radiculopathy who had seen the pain specialist. We searched this group for patients on metformin, excluding those with peripheral neuropathy, retinopathy, neuropathy, or other diabetic complications. All of the patients on metformin had diabetes. To select a control group, we attempted to match them as closely to the experimental group as possible, with the major exception being metformin. We recorded the number of pain medications (including anticonvulsants, antidepressants, benzodiazepines, corticosteroids, muscle relaxants, NSAIDs, opiates, and transdermal anesthetics) between the experimental and control group to obtain similar distributions. The numbers of diabetics who did not have diabetes complications and who were not on metformin were few in our community. The rest of the controls were selected at random from the group of patients who had a diagnosis of lumbar radiculopathy and had seen the pain specialist and who did not meet the exclusion criteria, noted below. We recorded the onset of lumbar radiculopathy in years, given that most of the subjects had a long duration of radiculopathy pain. The baseline characteristics are presented in Table 1.

Exclusion criteria

Patients with preexisting peripheral neuropathy were excluded since this may affect their report of lumbar radiculopathy pain. Patients with preexisting diabetes complications, such as retinopathy or nephropathy were also excluded because this implies an advanced disease state that may also affect their pain from lumbar radiculopathy.

Table 1 Baseline demographics

	Baseline demographics		
	Control	Metformin	P-value
Number of subjects	98	46	
Age (years)	54 ± 16	56 ± 15	0.46
Sex (male:female)	34:64	24:22	
BMI (kg/m ²)	29 ± 6	34 ± 7	0.002
Diabetes (n)	18	43	0.001
Duration of pain (years)	10 ± 11	10 ± 13	0.96
Number of pain medications	3 ± 2	4 ± 2	0.16

Note: Data are presented in mean ± standard deviation.

Abbreviation: BMI, body mass index.

Demographic information, including age, sex, body mass index (BMI), and socioeconomic status (such as retired/disability vs employed), was noted. No exclusions were made based on comorbidities; however, the presence of stroke, depression, diabetes, or heart disease was also recorded.

Questionnaire

In all cases, a pain questionnaire was completed by patients. The questionnaire was a modification of the McGill short-form pain questionnaire¹⁹ and included four sections assessing the full spectrum of pain, its perception, and its effect on daily life (Table 2). Section 1 included 15 indices of pain characteristics, assessed on a three-point Likert scale (patients were to circle 0 [no pain] to 3 [severe pain]). Section 2 assessed the patient's "pain now," which is usually interpreted as pain at the time of the visit, assessed on a 0–10 scale. In section 3, the "total pain experience," encompassing overall feelings, was assessed on a 0–5 scale. Section 4 assessed the effect of the pain on the patient's daily function; this was scored on a scale of 0–5, indicating the range of "does not interfere" to "completely interferes." In this study, we defined the primary outcomes as "pain now" and the "total pain experience." Other outcomes are listed in Table 2.

Data analysis

For the primary outcomes, all of the patients completed the "pain now" section, and all except one subject completed the "total pain experience" section. For the other indices studied, there were several cases with missing values. We removed the missing cases from the analysis of these particular indices. As some patients marked their scores with half values, such as 2 ½ rather than 2 or 3, the indices were treated as continuous variables for statistical purposes. Since the data are observational, we considered two approaches based on the Rubin Causal Model (RCM)²⁰

Table 2 Pain questionnaire given to patients at initial visit

	Pain scale
1. Pain characteristics	
Throbbing	0 = none
Shooting	1 = mild
Stabbing	2 = moderate
Sharp	3 = severe
Cramping	
Gnawing	
Hot/burning	
Aching	
Heavy	
Tender	
Splitting	
Tiring/exhausting	
Sickening	
Fearful	
Punishing	
2. Pain now	0–10
3. Total pain experience	0 = none
	1 = mild
	2 = discomforting
	3 = distressing
	4 = horrible
	5 = excruciating
4. Interference with daily function	
General activity	0–3 = does not interfere
Mood	4–5 = completely interferes
Working ability	
Normal working routine	
Relations with other people	
Sleep	
Enjoyment of life	
Ability to concentrate	
Appetite	

Notes: Sections 1 and 2 are adapted from the short-form McGill pain questionnaire. Patients were asked to identify their pain with the provided scale.

in order to accurately assess the effect of metformin on indices in the McGill short-form pain questionnaire. The RCM estimated the probability that individuals received the treatment based on pretreatment information (covariates), called the propensity score, via a binary regression. The propensity score was then used to statistically reestablish balance and overlap between the metformin and untreated groups, based on the measured covariates. We used propensity scoring because it selects matched subjects between the two groups for comparison, thus adjusting for the unequal distribution of diabetes (and BMI) between our two groups. The first approach taken matched each treated individual with an untreated individual based on his or her propensity scores (1:1 matching with replacement), creating a matched data set. This approach was designated as the matched analysis. To account for the uncertainty in the propensity score using the matched analysis, we considered

a second modeling approach using the Bayesian inferential procedure, as outlined by McCandless et al.²¹ By using the Bayesian analysis, we were able to account for the variability of the estimated propensity score, which was not accounted for by the matched analysis approach, even if more one-to-many matches were considered. For both methodological approaches considered in the manuscript, see the Supplementary material. The propensity score (probability of being in the treated group) was modeled based on the following covariates: age at visit, gender, height, weight, BMI, coronary artery disease (Y/N), retired (Y/N), disabled (Y/N), employed (Y/N), coronary artery disease (Y/N), stroke (Y/N), depression (Y/N). We used the R software environment version 3.0 (<http://www.r-project.org/>) for statistical analysis. Results were considered significant if 2.5%–97.5% confidence or credible intervals did not cross zero indicating either a decrease with treatment (for negative values) or an increase with treatment (for positive values).

Results

After reviewing the charts of patients with radiculopathy from 2008–2011, we found 46 patients who were taking metformin who did not meet our exclusion. Almost all of the subjects on metformin treatment had diabetes. A total of 94 patients not on metformin were identified to serve as controls, based on the predesignated matching criteria. Eighteen of the controls had diabetes but were not on metformin therapy, reflecting the widespread metformin use in our local diabetes population. There are several etiologies for lumbar radiculopathy, and the most common etiologies in our study included disc or facet disease, stenosis, and postsurgical lumbar pain.

The first analysis examined the effect of diabetes on the pain scores. Using a simple linear regression, we found that having diabetes in our cohort did not significantly alter pain scores or descriptors, as queried by the questionnaire, in this patient population with lumbar radiculopathy. However, we did not have data on the duration of diabetes or onset of metformin use, which can potentially impact pain scores. We also cannot positively exclude the early and still undetectable presence of neuropathy, which might also have an impact on pain scores.²² Subjects in the metformin group were diabetics and had an increased BMI compared with the control group (Table 1). There were also more males. To adjust for these covariates, mainly diabetes and increased BMI, data were analyzed using the RCM.²³ Due to computational issues, based on quasi separation with standard logistic regression, a penalized likelihood method was used²⁴ to estimate the propensity score. From this model, the only significant

variables to predict receiving metformin were diabetes (as expected by the nature of the drug) and male gender. The onset of radiculopathy pain did not differ between the subjects who were on metformin and the non-metformin treated subgroups (Table 1).

Table 3 presents the analysis based on the matched analysis using the RCM. The results indicate that patients receiving metformin reported a significantly reduced “pain now” score (95% confidence interval did not contain zero). Additionally, nearly all of the average treatment effect estimates were negative, although were not significantly different from the non-metformin treated group, indicating metformin may have additional effects on decreasing pain.

We conducted a secondary analysis, which accounts for the uncertainty in the propensity score, using a Bayesian analysis. The posterior means and 95% credible intervals for the regression coefficient related to estimate in the metformin group are shown in Table 3. Consistent with observations using the matching analysis, the mean of “pain now” was significantly decreased in the metformin treatment group. Again, consistent with the matched analysis data (Table 3), most of the other pain descriptors had negative numbers, suggesting a potential reducing effect of metformin on multiple pain modalities.

Discussion

This is the first retrospective study of the effect of metformin on lumbar radiculopathy pain. Our proof-of-concept findings suggest that metformin may have a beneficial effect on pain in lumbar radiculopathy. The major finding of this study is that “pain now” was significantly decreased in lumbar radiculopathy pain patients who were taking metformin, using two separate propensity-scoring methods. While many of the other indices were not statistically significantly different from those of patients not on metformin, many patients reported less pain (ie, point estimates were negative). Importantly, this finding is supported by mechanistic and therapeutic studies in preclinical pain models.^{10,12,15–17} We propose that the preponderance of current clinical and preclinical evidence warrants larger retrospective trials using EHR databases to continue to test the hypothesis that metformin might be effective for neuropathic or other types of pain. However, ultimately a prospective trial investigating the efficacy of metformin in chronic neuropathic pain conditions will be needed to exclude the potential confound of diabetic neuropathy²² in the patient population that takes metformin.

Metformin is one of the most widely prescribed drugs in the world and is used almost exclusively for the treatment

Table 3 Analysis of pain questionnaire data using two statistical methodologies

	Matched analysis			Bayesian analysis				
	ATT estimate	2.5% to 97.5% confidence intervals		Paired sample size	Bayes estimate	2.5% to 97.5% credible intervals		Sample size
Pain characteristics								
Throbbing	0.52	-0.72	1.75	31	-0.14	-1.13	0.85	93
Shooting	-0.50	-1.41	0.41	31	0.04	-0.67	0.76	95
Stabbing	-0.54	-1.48	0.39	35	-0.24	-0.98	0.52	99
Sharp	-0.33	-1.07	0.41	36	-0.44	-1.06	0.17	101
Cramping	-0.82	-2.17	0.54	30	-0.56	-1.59	0.43	88
Gnawing	-1.00	-2.29	0.29	26	-0.32	-1.54	0.92	80
Hot/burning	-0.15	-1.82	1.53	31	-0.49	-1.63	0.60	97
Aching	-0.29	-1.29	0.72	35	-0.33	-0.93	0.27	100
Heavy	0.18	-1.09	1.44	28	0.27	-0.89	1.44	82
Tender	0.39	-0.93	1.71	28	-0.28	-1.33	0.75	84
Splitting	-0.46	-2.00	1.09	24	-0.43	-1.67	0.83	71
Tiring/exhausting	0.03	-0.76	0.83	31	-0.68	-1.22	-0.18	95
Sickening	-1.00	-2.48	0.48	25	-0.43	-1.66	0.79	73
Fearful	1.50	-0.23	3.23	24	0.41	-1.12	1.90	71
Punishing	-0.76	-2.70	1.18	25	0.47	-0.85	1.84	79
Pain now								
	-1.85	-3.61	-0.08	46	-1.36	-2.68	-0.03	139
Total pain experience								
	-0.07	-0.82	0.69	45	-0.17	-0.73	0.41	138
Interference with daily function								
General activity	-0.33	-1.17	0.52	43	0.11	-0.53	0.75	134
Mood	-0.52	-1.60	0.56	42	-0.11	-0.82	0.62	132
Working ability	0.00	-0.83	0.83	42	-0.12	-0.74	0.50	133
Normal working routine	-0.40	-1.39	0.41	39	-0.16	-0.84	0.51	127
Relation with people	-0.79	-2.16	0.59	42	-0.33	-1.35	0.69	130
Sleep	-0.07	-1.31	1.16	41	-0.40	-1.33	0.49	134
Enjoyment of life	-0.82	-1.75	0.11	42	-0.35	-0.98	0.29	133
Ability to concentrate	-0.21	-1.50	1.07	42	0.68	-0.30	1.65	130
Appetite	-0.60	-2.10	0.91	42	-0.01	-1.11	1.08	130

Note: The “pain now” index did not cross zero in both the matched and Bayesian Model analyses, indicating that pain now was significantly reduced.

Abbreviation: ATT, average treatment effect on the treated.

of type 2 diabetes. Some recent clinical trials have been instigated for the treatment or prevention of breast cancer, based on larger retrospective trials showing a decreased incidence of breast cancer in patients taking metformin.²⁵ The mechanistic rationale for metformin use as a cancer therapeutic is similar to that for its possible effect on pain – AMPK activation and concomitant decreases in mTOR activity.^{26,27} Based on a variety of preclinical pain models, it is now clear that mTOR signaling plays a major role in the sensitization of the nervous system in chronic pain conditions.^{11–13} As indicated above, direct mTOR inhibitors (eg, rapamycin) are effective in preclinical models; however, these drugs also induce immune suppression clinically and may promote pain through feedback activation of other signaling pathways,¹⁵ and are unlikely to be used as pain therapeutics for this reason. On the other hand, metformin and other

AMPK activators do not induce immune suppression but still achieve strong attenuation of behavioral pain hypersensitivity and neuronal excitability.^{10,12} Based on existing preclinical evidence, including the report of a possible role of AMPK in diabetic neuropathy,²⁸ case reports of metformin efficacy in chronic neuropathic pain,¹⁸ and the present findings in a lumbar radiculopathy pain cohort, we propose that metformin might have clinical utility for chronic pain conditions involving injury to the peripheral nervous system.¹² It has recently been proposed that metformin also decreases cAMP levels in cells.⁸ However, it is not clear whether this mechanism is engaged in neurons because protein kinase A activity is also linked to nociceptor excitability,²⁹ and this mechanism would likewise be expected to reduce pain signaling.

An important question concerning the therapeutic potential of metformin is whether the drug acts as an analgesic

or as an antihyperalgesic agent in chronic pain conditions. Based on preclinical findings where metformin failed to increase pain thresholds beyond control levels but had a clear antihyperalgesic effect,^{10,15,17} we feel that it is likely that the drug has only antihyperalgesic effects. This idea is strongly supported by the clinical history of metformin use, where analgesic effects have not been reported despite decades of use in millions of patients. This explains, at least in part, why metformin has not previously been tested as a potential pain therapeutic. However, it is unusual that such a widely described drug has not been reported to have effects on pain, at least anecdotally, previously. In respect to this, we note that a common complication of diabetes is diabetic neuropathy.²² This complication is commonly painful. Unfortunately, because metformin is glucose lowering in type 2 diabetics, the potential direct effects of metformin on sensory neurons and/or sensitization of the pain pathway cannot be separated from its metabolic effects. However, at least one study has suggested that diabetics treated with insulin rather than metformin have a higher incidence of diabetic neuropathy than those taking metformin.³⁰ Moreover, a recent preclinical investigation demonstrated that diabetic neuropathy is accompanied by decreased AMPK activity and that augmenting AMPK activity pharmacologically or genetically alleviates signs of diabetic neuropathy.²⁸

The main limitation of this study is that it was a retrospective chart review, and we could not establish the dose, duration, or timing of metformin use in regards to the onset of radiculopathy pain. We were also not able to obtain the duration or dose of pain medications, and these factors could have impacted the pain scores. Patients with longer duration of diabetes might have had higher pain scores. However, we excluded subjects with diabetic neuropathy²² to attenuate the confounding effect of peripheral neuropathy on lumbar radiculopathy pain. There were multiple pain indices recorded, and it could be conceived that the decreased “pain now” in the metformin group was observed by chance. However, we used two analysis approaches using propensity scoring, both of which revealed estimates of decreased pain with confidence or credible intervals that do not cross zero, making this type of error unlikely. The estimate of pain in the second primary outcome, “total pain experience,” suggested less pain. This is supportive of the hypothesis that being on metformin is associated with less radiculopathy pain. Another potential issue is that the control group had fewer diabetics (and a lower BMI), but our analysis suggests that having diabetes did not significantly affect pain indices between the two groups. The propensity scoring selected matched subjects

between the two groups for comparison, thus adjusting for the unequal distribution of diabetes and high BMI between our two groups.^{21,31} Finally, there were more males in the metformin group than in the control group. Again, this unequal distribution was handled by the propensity scoring approach; however, it is well known that many chronic pain disorders primarily affect females.³² Interestingly, lumbar radiculopathy is evenly distributed between males and females.³³

We conclude that metformin therapy is associated with the decreased severity of lumbar radiculopathy pain. Our finding is in line with mechanistic studies from preclinical models demonstrating a powerful antihyperalgesic/antiallodynic effect of metformin and other AMPK activators on chronic pain^{10,12,15–17,28} and a recent case report suggesting efficacy of metformin in humans.¹⁸ Thus, we propose that larger retrospective and, potentially, prospective studies of metformin use on chronic neuropathic pain are warranted.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

In this paper we examined the effect of receiving metformin (treatment group) on 17 pain and nine daily activity indices based on 140 patients. For each index, if an individual did not provide a value for that index (missing value) it was removed only for that particular analysis. In order to compare patients in the treatment group versus the control group (not on metformin) we considered two approaches for matching patients based on the probability that they would receive the treatment (propensity score π) using only pre-treatment information (the design vector c in Equation 1 is based on: age at visit, sex, height, weight, body mass index, coronary artery disease (yes/no), retired (yes/no), disabled (yes/no), employed (yes/no), stroke (yes/no), depression (yes/no). In order to estimate the propensity scores a logistic regression was considered (treatment = 1 if patient i is in the metformin group and 0 otherwise):

$$\text{logit}[\pi_i] = \log \left(\frac{\pi_i}{1 - \pi_i} \right) = \gamma' c_i, \quad \text{treatment}_i \overset{\text{indep.}}{\sim} \text{Bernoulli}(\pi_i), \quad (1)$$

Because of computational issues with standard logistic regression due to quasi-separation for these data, a type of penalized likelihood method was used to estimate the propensity scores.¹ In the next two sections, the propensity score will be utilized in two ways: 1) an approach which formally matches treated patients with control patients; and 2) an approach which informally “matches” patients based on a binned ordered factor of the propensity scores.

Formal matching

Utilizing the estimated propensity scores, each treatment case was matched with a control case (1:1 matching), where the matching was with replacement for the controls. For all the indices, this approach led to matched data sets where all the patients had diabetes (ie. perfect matching on diabetes). After creating a matched data set, the mean paired difference between treated and control patients for a particular index (y ; eg Pain Now) was estimated and the estimator can be seen in Equation 2 (average treatment effect on the treated [ATT]). Since the same control can be matched to several treatments, the usual standard error based on a paired mean difference estimate is incorrect. Abadie and Imbens² suggest an alternative founded on an asymptotic argument. Using this asymptotic result, 95% confidence intervals, based on the standard normal

distribution, for each estimate were computed. While the variability in the matching is accounted for by the Abadie and Imbens' standard error,² variability in the estimated propensity is not.³ The R statistical software and Matching library were used for the analyses in this section.⁴

$$\widehat{ATT} = \frac{\sum_{i=1}^{n_{\text{paired}}} y_{\text{Treat},i} - y_{\text{Con},i}}{n_{\text{paired}}}. \quad (2)$$

Informal matching

As mentioned, the estimation procedure in the previous section does not account for uncertainty in the estimated propensity score. To address this problem, McCandless, Gustafson and Austin consider a model that does not formally use a matching algorithm but accounts for the probability of being treated (the propensity score), and uses all available cases in the data (not just a matched subset).⁵ Since McCandless, Gustafson and Austin⁵ based their approach on binary outcomes (y), consider the following revised model which assumes y is a continuous variable (eg Pain Now):

$$y_i = \beta \text{treatment}_i + \zeta' g(\pi(c, \gamma))_i + \epsilon_i, \quad \epsilon_i \overset{\text{iid}}{\sim} \text{normal}(0, \sigma^2), \quad (3a)$$

$$\text{treatment}_i \overset{\text{indep.}}{\sim} \text{Bernoulli}(\pi_i), \quad \text{logit}[\pi_i] = \gamma' c_i, \quad (3b)$$

where:

$$g(\pi_i) \gamma = \begin{cases} (1, 0, 0, 0) & \text{if } 0 \leq \pi_i < q_1 \\ (1, 1, 0, 0) & \text{if } q_1 \leq \pi_i < q_2 \\ (1, 0, 1, 0) & \text{if } q_2 \leq \pi_i < q_3 \\ (1, 0, 0, 1) & \text{if } q_3 \leq \pi_i < 1. \end{cases} \quad (3c)$$

The outcome variable (y) is modeled as a function of the treatment and an ordinal factor based on the propensity score (π ; see Equation 3a). Whether an individual receives the treatment is then modeled based on the same set of pre-treatment covariates discussed above (c ; see Equation 3b) which is the same as Equation (1). The knots (q_1, q_2, q_3, q_4) are the quartiles of the maximum likelihood estimates of the propensity scores based solely on Equation 3b and are set a priori (see Equation 3c). As previously discussed due to computational issues, a type of penalized likelihood function was maximized to obtain the estimated propensity scores that were used to determine the knots. In order to estimate the parameters in the model a Bayesian inferential procedure was considered. The analyses used the following set of diffuse priors:

$$\begin{aligned}
 \beta &\sim \text{normal}(0,100), \\
 \xi_j &\stackrel{\text{iid}}{\sim} \text{normal}(0,100); \quad j = 1, \dots, 3, \\
 \gamma_k &\stackrel{\text{iid}}{\sim} \text{normal}(0,100); \quad k = 1, \dots, 13, \\
 \sigma^2 &\sim \text{inverse gamma}(1,1).
 \end{aligned}
 \tag{3d}$$

Estimation of the model was conducted through Markov chain Monte Carlo sampling, including adaptive sampling techniques,⁶ through computer code written in the R statistical software.⁴ For each analysis, 500,000 scans were conducted. After a burn-in of 200,000 scans, the remaining 300,000 scans were thinned by every 100th, leaving 3,000 scans to examine the joint posterior distribution.

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