Prospective Evaluation

Usefulness of the Brief Pain Inventory in Patients with Opioid Addiction Receiving Methadone Maintenance Treatment

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Background: Chronic pain is implicated as a risk factor for illicit opioid use among patients with opioid addiction treated with methadone. However, there exists conflicting evidence that supports and refutes this claim. These discrepancies may stem from the large variability in pain measurement reported across studies.

Objectives: We aim to determine the clinical and demographic characteristics of patients reporting pain and evaluate the prognostic value of different pain classification measures in a sample of opioid addiction patients.

Study Design: Multi-center prospective cohort study.

Setting: Methadone maintenance treatment facilities for managing patients with opioid addiction.

Methods: This study includes participants from the Genetics of Opioid Addiction (GENOA) prospective cohort study. We assessed the prognostic value of different pain measures for predicting opioid relapse. Pain measures include the Brief Pain Inventory (BPI) and patients' response to a direct pain question all study participants were asked from the GENOA case report form (CRF) "are you currently experiencing or have been diagnosed with chronic pain?" Performance characteristics of the GENOA CRF pain measure was estimated with sensitivity and specificity using the BPI as the gold standard reference. Prognostic value was assessed using pain classification as the primary independent variable in an adjusted analysis using 1) the percentage of positive opioid urine screens and 2) high-risk opioid use (≥ 50% positive opioid urine screens) as the dependent variables in a linear and logistic regression analyses, respectively.

Results: Among participants eligible for inclusion (n = 444) the BPI was found to be highly sensitive, classifying a large number of GENOA participants with pain (n = 281 of the 297 classified with pain, 94.6%) in comparison to the GENOA CRF (n = 154 of 297 classified with pain, 51.8%). Participants concordantly classified as having pain according to the GENOA CRF and BPI were found to have an estimated 7.79% increase in positive opioid urine screens (estimated coefficient: 7.79; 95%CI 0.74, 14.85: $P = 0.031$) and a 4 times greater odds (odds ratio [OR]: 4.10 P = 0.008; 95%CI: 1.44, 11.63) of engaging in a "high risk" level of illicit opioids use. The prognostic relevance of pain classification was not maintained for the additional participants classified by the BPI (n = 143 discordant).

Conclusion: These results suggest that while the BPI may be more sensitive in capturing pain among patients with opioid addiction, this tool is of less value for predicting the impact of pain on illicit opioid use for opioid addiction patients on methadone maintenance treatment. The GENOA CRF showed high predictive ability, whereby patients classified according to the GENOA CRF are at serious risk for opioid relapse. Using the appropriate tool to assess pain in opioid addiction may serve to improve the current detection and management of comorbid pain.

Disclaimer: The authors report no conflict of interest for this study. This work was supported by the Peter Boris Centre for Addiction Research and the CIHR Drug Safety and Effectiveness Network (DSEN) grant (grant number: 126639). The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Manuscript received: 04-29-2015
Revised manuscript received: 06-05-2015
Accepted for publication: 07-02-2015

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Limitations: We caution the interpretation of these result since they are still reflective of participants already maintained on an opioid substitution therapy (OST), which can largely differ from patients who drop out of methadone maintenance treatment (MMT) or never seek treatment altogether.

Key words: Chronic pain, opioid adiction, methadone maintenance treatment, relapse, addiction, measurement, brief pain inventory

Pain Physician 2016; 19:E181-E195

Morbidity and mortality incurring from opioid use outweighs the burden resulting from any other illicit substance and accounts for 9.2 million disability adjusted life-years (DALYs) — a 73% increase since 1990 (1). The global prevalence is rising and recent estimates propose 26 to 36 million people abuse opioids (2). Without treatment, patients with opioid addiction incur a substantial risk for serious comorbidities such as HIV (3), hepatitis (3), infective endocarditis, and mortality (4,5).

Front-line treatments for opioid addiction include opioid substitution therapy (OST), whereby patients are prescribed long-acting synthetic opioids to reduce symptoms of craving and withdrawal under clinical supervision (6). Methadone, buprenorphine, and naltrexone are among the cadre of OSTs used globally, of which methadone is the oldest and most commonly prescribed treatment (7,8). Methadone has been shown to reduce illicit opioid use (9-11) and criminal behavior (11), as well as improve adjunct therapy (e.g., counseling) compliance (10), with higher doses providing the greatest benefit (12-15). Even when compared against other OSTs, methadone proved more effective at reducing illicit opioid use (13,16,17).

Despite the demonstrated benefit of methadone maintenance treatment (MMT), some patients continue to abuse opioids or drop out of methadone treatment altogether (18,19). Lower methadone dose (20), unemployment (20), poly-substance use (21), as well as the presence of physical or psychiatric comorbidity are among a number of risk factors that adversely affect OST compliance and outcomes (22-24). Given the sharp rise in global opioid prescriptions (25) more attention is being directed to chronic pain as an important and prevalent comorbidity. Chronic pain is commonly reported among patients receiving methadone for opioid addiction with estimates ranging from 24 – 55% (26-28). Chronic pain is suggested to impact psychiatric symptoms, social functioning, and methadone pharmacokinetics (28-30). Due to the long-term exposure to opioids, some studies argue chronic pain mediates the effect of methadone by inducing a hyperalgesic state among patients (31,32), which may in part explain the higher rates of opioid abuse reported among patients with comorbid pain (28). However, there remains an uncertainty when assessing the impact of pain on opioid use behavior within the addiction setting. While some studies report chronic pain to be a significant risk factor for substance abuse (26,28,33), other studies report no association (34,35). These discrepancies might stem from the large variability in pain measurement reported across studies (26,28,33-35). The majority of studies both supporting and refuting chronic pain as a significant risk factor for substance abuse rely on the Brief Pain Inventory (BPI) to assess pain in opioid addiction patients, though the definitions and cut-offs used to classify pain with the BPI vary greatly (26,27,36-40). The validity of a measurement tool applies exclusively to the population the tool is created for and tested within (41). While the BPI is commonly cited as a validated tool to assess the presence of pain (26,27,36-40), it has yet to undergo a reliability assessment within opioid addiction patients.

Whether it be uncertainty concerning the prognostic value of the BPI for assessing pain in opioid addiction patients, the stigma of drug-seeking behavior, or the under treatment of pain in the addiction setting, there is a lack of consensus as to the real impact of pain on illicit substance use behavior in MMT patients. Addressing the discrepancies reported across the literature may

improve the current management of comorbid pain. How well does the BPI work to classify pain among opioid addiction patients? Is there a pain measure that better predicts opioid relapse in this population? Are there specific characteristics associated with comorbid pain in opioid addiction patients or that explain the differences in pain classification? Answering these questions will 1) clarify the prognostic values of the BPI in opioid addiction patients, 2) resolve whether pain is a risk factor for important treatment response outcomes, and 3) provide a profile of the clinical, demographic, and social characteristics of patients with comorbid pain. We aim to evaluate these questions using evidence gathered from a prospective cohort study of 444 MMT patients.

Objectives

1. Evaluate the prognostic value of different pain classification measures in a sample of opioid addiction patients
    a. Provide performance characteristics of the simple self-reported pain measure (sensitivity, specificity, positive predicted value [PPV] and negative predicted value [NPV]) using the BPI as the gold-standard reference measure
    b. Estimate the prognostic significance of each pain classification measure using opioid relapse confirmed by urine toxicology screening as an indicator of response to MMT
    c. Confirm the association between continued opioid abuse and the presence of chronic pain using different measures of pain
2. Determine the clinical and demographic characteristics of patients reporting pain reported by different pain classification measures
    a. Explore employment history, medical comorbidities, psychiatric comorbidity, pain severity and interference, sexual functioning, criminal activity, HIV risk behavior, and domestic conflict

Methods

GENetics of Opioid Addiction (GENOA) Prospective Cohort Study

This study included participants from an investigation known formally as Genetics of Opioid Addiction (GENOA). GENOA is a research collaborative between the Population Genomics Program at McMaster University and the Canadian Addiction Treatment Centres (CATC). Methods of the GENOA pilot study are published elsewhere (42). GENOA expanded out of the cross-sectional pilot design and is now conducting an ongoing 12-month prospective cohort study. Modifications were made to the address the challenges noted during the cross-sectional stage (42). These modifications include the addition of 13 new recruitment sites across southern Ontario as well as validated addiction severity, psychiatric comorbidity, and pain assessment. Baseline measures include the collection of demographic characteristics such as educational background, employment, marital status, addiction treatment history (e.g., number of previous treatments), source of opioid use, methadone dose (mg/day), and full medical history. Information has been collected on physical comorbidities include HIV, hepatitis C, diabetes, liver disease, epilepsy, chronic pain, and any other chronic disorders. Participants are followed up by the onsite nursing staff every 3-months. Follow-up assessments include urinalysis and demographic questionnaires.

Eligibility criteria include patients 18 years on methadone for opioid addiction treatment meeting DSM-IV criteria for opioid dependence (assessed by clinical interviews during admission to MMT) able to provide informed consent. The Hamilton Integrated Research Ethics Board (HiREB) approved this study (HiREB Study ID 11-056). This study adheres to the STROBE guidelines (43).

Measures

We employed the M.I.N.I. International Neuropsychiatric Interview version 6.0 (44) to assess for psychiatric comorbidities and the Maudsley Addiction Profile (MAP) instrument to assess addiction severity across personal, physical, and social functioning domains (45). We used the BPI to capture pain severity and interference. This tool has been validated in the assessment of pain in patients with and without neuropathic etiology (46,47). The BPI uses the primary question, "throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches), have you had pain beyond these everyday kinds of pain?" to determine whether patients are currently experiencing any pain. Participants answering yes to this question are prompted to completed follow-up questions to assess pain severity and interference. Participants completing the full BPI assessment were defined as a positive pain case. Participants were also asked directly whether they have a history of pain, whereby those responding yes to the question, "are you currently experiencing or have been diagnosed with chronic pain?" were classified as positive pain case according

to the GENOA case report form (CRF). This assessment has not been traditionally validated using test re-test reliability. In comparison to the BPI the GENOA pain assessment is simplified and provides a direct inquiry about patients' current and past history of pain with limited additional probing for pain symptoms.

Participant substance use behavior was assessed using weekly urine specimens, which are collected as part of CATC routine clinical care. Qualitative and semiquantitative urine analysis using iMDx Prep Assay (NOVX Systems novxsystems.com) were performed on all samples to assess for illicit opioid, cocaine, benzodiazepine, and marijuana use. The iMDx Prep Assays assess urine pH and creatinine levels to identify when urine samples have been tampered with. Trained CATC clinical staff performs all adjudication of urinalysis results. The prep assays used in CATC clinics can discern specific types of opioids such as prescribed synthetic medications (e.g., oxycontin), naturally occurring opioids (heroin), and methadone (48).

Statistical Analysis

Baseline demographic characteristics including employment history, physical comorbidity, sexual activity, criminal activity, psychiatric comorbidity, injecting behavior, domestic conflict, and MAP domain scores are reported by pain classification. Pain classification categories include participants concordantly classified as having pain by GENOA CRF and BPI, participants concordantly classified as not having pain by GENOA CRF and BPI, and those discordantly classified as having pain by the BPI but not GENOA CRF. The participants classified as having pain according to the GENOA CRF but not the BPI are considered false-positive classifications. These additional participants captured by the GENOA pain measure are likely a product of measurement error (random error) or differential misclassification. While this subgroup of participants is small (n = 16), we chose to exclude them from later analyses examining the predictive validity of pain classification for illicit opioid consumption.

Continuous measures are summarized using means and standard deviations (SD), while dichotomous measures are reported by percentage. To evaluate the differences in the clinical and demographic characteristics between groups based on pain classification we performed a univariate logistic regression with pain classification as the dependent variable. Baseline demographic characteristics were then evaluated independently as covariates in the logistic regression models. For example, characteristics such as age, gender, and employment status would be individually evaluated in a cross-sectional association with pain classification. We did not use this as a univariate analysis to inform the selection of covariates for the construction of a multivariable regression model to evaluate prognostic significance. We performed these cross-sectional analyses to determine the clinical and demographic profile of patients classified by different pain measures. The odds ratio and corresponding *P*-values are reported in the baseline demographic characteristics table.

Performance characteristics of the GENOA CRF pain measures were estimated using sensitivity, specificity, PPV, and NPV. The performance characteristics were calculated using the BPI as the "gold standard" measure. We recognize pain is a subjective experience, and while there is no standard "gold standard" measure of identifying this phenomenon, we aimed to demonstrate the performance characteristics of a new pain classification measure in relation to the BPI since it is the most commonly used tool among studies determining the impact of pain in patients receiving OST (26,27,36-40). We determined the prognostic significance of pain classification using multi-variable regression analysis to estimate an association between pain measure and illicit opioid consumption. We quantified the effect of pain on illicit opioid consumption with a multivariable linear regression using the percentage of positive opioid urine tests at 3-month follow-up as the dependent variable. All analyses were adjusted for age (in years), gender, duration on MMT (in months), number of opioid urine screens, and infectious disease status (presence of HIV or hepatitis C). All participants on prescribed opioid medications for pain were removed from any analysis evaluation of illicit opioid use behavior (n = 18).

The association between pain and different risk categorizations of opioid use behavior were assessed using multivariable logistic regression. Independent models were constructed using high and moderate risk categorizations of the percentage of positive opioid urine tests provided over the 3-month period following the pain assessment as the dependent variable. Participants with ≥ 50% positive opioid urine screens were categorized as high-risk and deemed non-responsive to MMT. This cut off was selected in accordance with previous research suggesting regular use of heroin and other opioids is significantly predictive of mortality among methadone maintenance patients thus indicating a treatment failure (49). To demonstrate "high risk" opioid use behavior participants would need to exhibit

a minimum of 6 weeks of continued opioid abuse to have obtained ≥ 50% positive opioid urine tests and be considered regular users of illicit opioids, indicating a clinically significant risk for treatment failure. Participants with 30% positive opioid urine screens will be considered at moderate risk. This categorization of high and moderate risk participants was used as the binary dependent variable in 3 logistic regression models. These models were adjusted for age (years), gender, duration on MMT (months), number of opioid urine screens, and infectious disease status (presence of HIV or hepatitis C). The adjusted and unadjusted predicted probability for high-risk opioid use was evaluated for each pain classification. Adjusted predicted probability was estimated using the results from the multi-variable logistic regression models.

All covariates included in the regression models were assessed for multi-colinearity. Box-plots were constructed to identify outlier observations. Sensitivity analyses were performed for both regression analyses, removing outlier observations. All continuous variables were assessed for normal distribution, whereby proper transformations were applied when necessary.

Determining the Percentage of Positive Opioid Urine Screens at 3-month Follow-up Assessment

Due to the unequal number of urine tests administered among participants, we evaluated the relationship between number of urine test administrations and the percentage of positive opioid urine tests at 3-months. Visual plots of the data (Fig. 1) suggest no relationship between number of opioid screens and the percentage of positive tests. Thus, we chose against adjusting for the number of opioid urine tests administered.

An imputation of zero percent positive opioid urine screens was used for participants successfully completing the methadone program before the 3-month urine assessment period (n = 2). For participants discharged from the MMT due to non-compliance with the treatment regime (e.g., providing urine samples, receiving daily methadone doses) an imputation of 100% positive opioid urine screens was used for the 3-month opioid urine assessment (n = 1). We carried the baseline urine assessment forward (% of positive opioid urine screens at baseline) for participants lost to follow-up

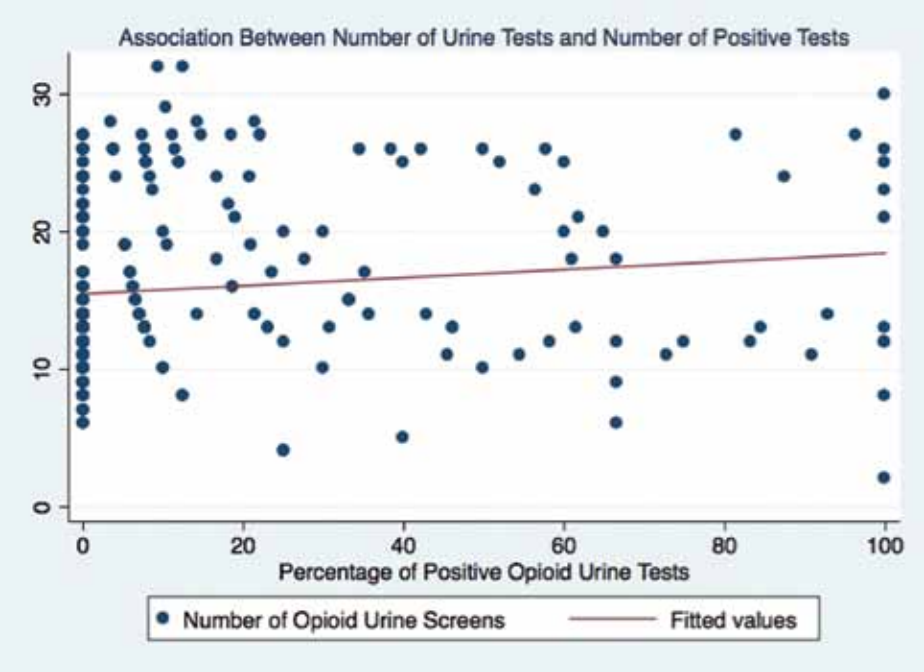

Fig. 1. *Association between number of urine tests and number of positive tests.*

at 3 months due to moving to a non-CATC treatment program (n = 10).

Results

Among the 460 MMT patients recruited in the GENOA investigation, 444 patients completed both the GENOA CRF and BPI. Fig. 2 summarizes the participant inclusion process. Demographic and diagnostic performance characteristics are presented using data from participants completing both pain measures during the baseline assessments (n = 444). Demographic and clinical characteristics are presented by pain classification and summarized in Table 1. The mean age of all participants included in this study was 38.4 years (SD 11.0). Findings from the classification of pain using the BPI and GENOA CRF suggest the BPI captures pain in a

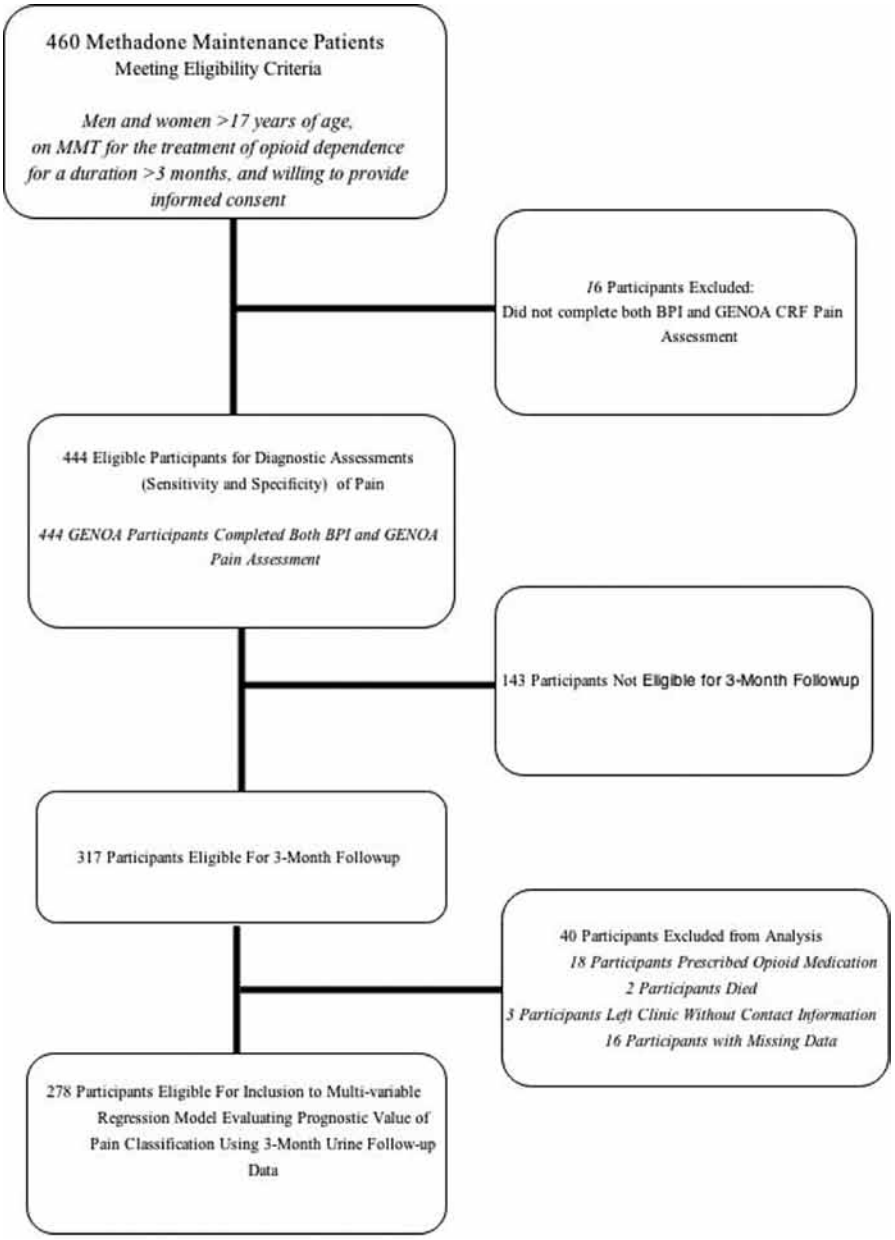

Fig. 2. *Participant flow diagram of the participant inclusion process.*

Table 1. *Baseline demographic characteristics of methadone maintenance patients.*

	Participants Classified as Having Pain by BPI and GENOA CRF (n = 138)	Participants Classified as Having Pain by BPI but Not GENOA CRF (n = 143)	Participants Classified as Having No Pain (n = 147)	Logistic Regression Model Using Pain Classification as the Dependent Variable Unadjusted Odds Ratio, *P*-value		
				Concordant Classification (n = 285)[a]	Discordant Classification (n = 290)[b]	Comparison of Concordant and Discordant (n = 281)[c]
Mean Age (SD)	42.7 (10.6)	37.4 (10.3)	34.8 (10.4)	1.1, P < 0.0001	1.0, 0.037	1.0, *P* < 0.0001
Gender (% Female)	46.7	47.6	46.3	1.0, 0.939	1.1, 0.825	1.0, 0.888
Marital Status (% Participants Married or Common Law)	33.3	31.2	32	1.1, 0.807	1.0, 0.889	1.1, 0.704
Employed	28.3	37.3	42.9	0.5, 0.011	0.8, 0.338	0.6, 0.107
Smoking Status (% Participants Smoking)	97.1	93.6	92.5	2.7, 0.095	1.2, 0.726	2.3, 0.174
Family History of Addiction						
Father	37	44.1	40.1	0.9, 0.582	1.2, 0.499	0.7, 0.226
Mother	32	31.5	32	0.9, 0.987	1.0, 0.927	1.0, 0.940
Brother	26.1	25.2	22.4	1.2, 0.474	1.2, 0.586	1.0, 0.861
Sister	18.8	18.8	17.7	1.1, 0.801	1.1, 0.793	1.0, 0.993
Comorbid Medical Disorders						
HIV	0.7	0.6	0.7	1.1, 0.964	1.0, 0.984	1.0, 0.980
Epilepsy	3.6	2.1	2	1.8, 0.425	1.0, 0.973	1.8, 0.448
Hepatitis C	26.8	21	20.4	1.4, 0.204	1.0, 0.905	1.4, 0.252
Liver Disease	9.4	1.4	4.8	2.1, 0.131	0.3, 0.120	7.3, 0.010
Diabetes	6.5	5.6	4.1	1.6, 0.361	1.4, 0.550	1.2, 0.745
Illicit Drug Use (Mean Percent of Positive Urine Screens During Baseline Assessment)						
Opioids	18.5 (30.8)	14.5 (24.3)	14.7 (26.7)	1.0, 0.283	0.9, 0.939	1.0, 0.240
Cannabis	28.6 (41.9)	35.7 (45.0)	30.6 (41.6)	1.0, 0.776	1.0, 0.489	1.0, 0.298
Cocaine	13.9 (27.8)	15.5 (28.6)	13.5 (25.6)	1.0, 0.972	1.0, 0.536	0.9, 0.641
Amphetamine	7.9 (24.3)	3.2 (16.9)	2.0 (9.5)	1.0, 0.105	1.0, 0.622	1.0, 0.174
Ecstasy	7.8 (24.5)	3.4 (17.2)	1.7 (9.2)	1.0, 0.108	1.0, 0.516	1.0, 0.208
Mean Scoring for BPI Intensity and Interference Scales						
Composite Pain Intensity Scoring (SD)	20.1 (7.6)	15.2 (8.0)	/	/	/	
Composite Pain Interference Scoring (SD)	39.8 (17.9)	25.8 (18.5)	/	/	/	
Maudsley Addiction Profile Scoring						
Mean Physical Symptoms Score (SD)	19.3 (7.1)	15.8 (7.5)	12.1 (6.5)	1.2, *P* < 0.0001	1.1, *P* < 0.0001	1.1, *P* < 0.0001
Mean Psychological Symptoms (SD)	14.1 (8.4)	13.4 (8.9)	11.4 (8.4)	1.02, 0.008	1.02, 0.046	1.0, 0.513
MAP Health Risk Behavior						
Number of Days of Injecting Drug Use	2.8 (7.6)	1.9 (5.9)	2.8 (7.4)	0.9, 0.926	1.0, 0.398	1.0, 0.448
Number of Time of Sharing Equipment for Injecting Drug Use	0	0.01 (0.1)	0.2 (1.2)	n/a	0.6, 0.527	/
Number of Sexual Partners Without a Condom	0.5 (0.6)	0.6 (0.5)	0.8 (0.7)	0.6, 0.056	0.6, 0.066	0.9, 0.768
Personal and Social Functioning						
Conflict Scoring Partner	20.1 (33.1)	15.8 (28.9)	16.1 (25.1)	1.0, 0.358	1.0, 0.932	1.0, 0.356
Conflict Scoring Family	11.7 (25.6)	15.5 (30.0)	10.4 (21.9)	1.0, 0.666	1.0, 0.126	1.0, 0.312

Table 1 (cont). *Baseline demographic characteristics of methadone maintenance patients.*

	Participants Classified as Having Pain by BPI and GENOA CRF (n = 138)	Participants Classified as Having Pain by BPI but Not GENOA CRF (n = 143)	Participants Classified as Having No Pain (n = 147)	Logistic Regression Model Using Pain Classification as the Dependent Variable Unadjusted Odds Ratio, *P*-value		
				Concordant Classification (n = 285)[a]	Discordant Classification (n = 290)[b]	Comparison of Concordant and Discordant (n = 281)[c]
Conflict Scoring Friends	6.7 (19.5)	4.6 (16.0)	2.7 (10.3)	1.0, 0.073	1.0, 0.294	1.0, 0.387
Criminal Activity						
Percentage of Participants Reporting Any Criminal Behavior	3.6	11.9	12.2	0.3, 0.012	0.9, 0.926	0.3, 0.015
Mean Number of Days Selling Drugs (SD)	0.3 (2.6)	0.9 (4.9)	0.6 (3.7)	0.9, 0.451	1.0, 0.490	1.0, 0.200
Mean Number of Days Committing Fraud (SD)	0	0	0	/	/	/
Mean Number of Days Shoplifting (SD)	0	0.2 (1.9)	0.2 (1.4)	/	1.0, 0.981	/
Mean Number of Days of Theft of Property (SD)	0.1 (0.9)	0	0	/	/	/
Mean Number of Days of Theft from Vehicle (SD)	0	0	0.03 (0.3)	/	/	/
Mean Number of Days of Theft of a Vehicle (SD)	0	0	0	/	/	/
Percentage of Participants with Psychiatric Disorders Diagnosed by MINI[d]						
Major Depressive Disorder (including current, past, or recurrent)	37.7	44.6	42	0.8, 0.478	1.1, 0.669	0.8, 0.266
Current Bipolar Disorder	1.6	3.1	1.4	1.1, 0.901	2.2, 0.379	0.5, 0.462
Generalized Anxiety Disorder	18.1	25.9	13	1.5, 0.303	2.3, 0.013	0.6, 0.196
Anorexia	0	0	0	/	/	/
Bulimia	0.8	2.3	2.2	0.4, 0.394	1.1, 0.941	0.3, 0.366
Alcohol Dependence	4.1	6.9	5.8	0.7, 0.532	1.2, 0.706	0.6, 0.333
Alcohol Abuse	6.6	11.5	8.7	0.7, 0.520	1.4, 0.441	0.5, 0.175
Post Traumatic Stress Disorder	4.9	11.2	3.6	1.4, 0.606	3.5, 0.019	0.4, 0.065
Suicidal Ideation	29.5	33.1	31.9	0.9, 0.679	1.1, 0.835	0.8, 0.542
Antisocial Personality Disorder	14.8	23.8	18.1	0.8, 0.467	1.4, 0.250	0.6, 0.071

Results not reported for 16 participants not captured by BPI (assuming measurement error)
a results from the univariate logistic regression evaluating the differences between those classified as having pain according to both the BPI and GENOA CRF and those classified as having no pain, pain classification is the dependent variable
b results from the univariate logistic regression evaluating the differences between those classified as having pain according the BPI but NOT the GENOA CRF and those classified as having no pain, pain classification is the dependent variable
c results from the univariate logistic regression evaluating the differences between those classified as having pain according the BPI but NOT the GENOA CRF and those classified as having pain according to both the BPI and GENOA CRF, pain classification is the dependent variable
d the number of participants from each group evaluated with the MINI are not reflective of the number of participants listed at the top of the table, for participants completing the MINI there were 121 concordantly classified as having pain according to both GENOA CRF and BPI, 130 discordant participants (classified as having pain according to BPI but not GENOA CRF), and 138 without pain.

larger number of participants. Those classified as having pain according to the GENOA CRF are almost completely captured within the larger sample of patients classified according to the BPI (Fig. 3). Among all participants classified as having pain according to one or both of these measures (n = 297), there is 46.4% concordance between measures (n = 138). There is 53.6% discordance between the BPI and GENOA CRF, whereby

5.5% (n = 16) of patients are classified as having pain according to the GENOA CRF but not the BPI and 48.1% (n = 143) of patients are classified as having pain according to the BPI but not the GENOA CRF. Fig. 3 displays the concordance and discordance of pain classification using these 2 measures. Assessment of the clinical and demographic characteristics of participants based on pain classification revealed differences between the concordant and discordant groups (Table 1). Participants classified as having pain according to the GENOA CRF and the BPI were found on average to be older (OR: 1.05, 95% CI 1.02, 1.07; $P < 0.0001$), with a higher severity of physical symptoms based on MAP scoring (OR: 1.07, 95% CI 1.03, 1.11; $P < 0.0001$), lower involvement in criminal activity (OR: 0.28, 95% CI 0.10, 0.78; $P = 0.015$), and with a lower rate of post-traumatic stress disorder (OR: 0.40, 95% CI 0.15, 1.06; $P = 0.065$).

Evaluation of the diagnostic performance characteristics suggest the GENOA CRF pain classification to be highly specific (90.2%, 95% CI: 84.5, 94.4), indicating patients classified as having no pain according to the GENOA pain classification are unlikely to have pain. Accordingly, these results also suggest the BPI to be highly sensitive, classifying a much larger number of GENOA participants with pain (n = 281, 63.3%; n = 444 for participants with BPI measures) in comparison to the GENOA CRF classification (n = 150, 33.4%; n = 460 for GENOA CRF measure). Results from the diagnostic performance statistics also suggest the GENOA CRF classification to have a high PPV (PPV = 89.6, 95%CI: 83.7, 93.9), indicating the GENOA CRF has a very low false-positive rate. Diagnostic performance tests are summarized in Table 2.

To demonstrate the prognostic significance of the GENOA pain measure we evaluated the predictive performance of pain classification using concordant (classified as having pain according to GENOA CRF and BPI) and discordant (classified as having pain according to BPI but not GENOA CRF) categorizations. GENOA is an active study with ongoing recruitment, rendering a portion of the recently recruited participants (n = 143) ineligible for follow-up at this time. Results from these analyses are performed in a reduced sample of 278 participants (Fig. 2). The models were adjusted for age (years), gender, duration on MMT (months), and infectious disease status (presence of HIV or hepatitis C). Evaluation of the percentage of positive opioid urine specimens collected over the 3 month period following the pain assessments suggests participants concordantly clas-

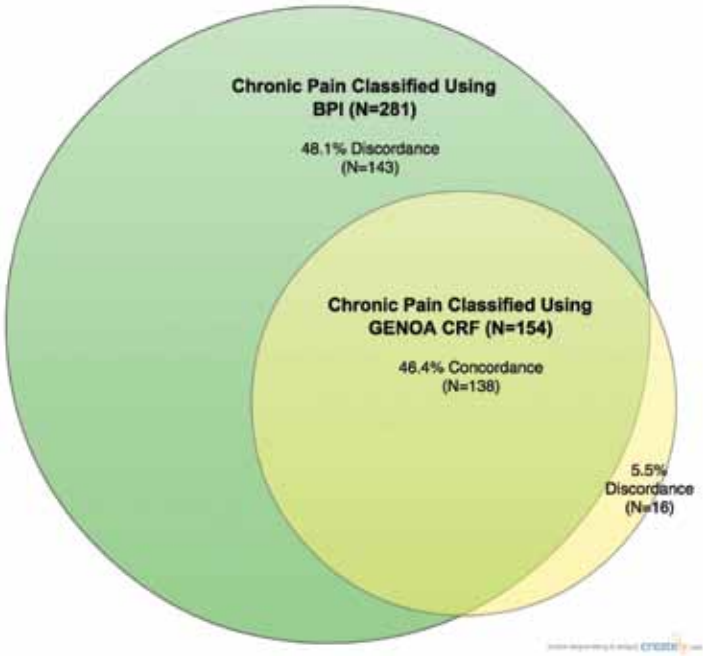

Fig. 3. *Classification of pain in the GENOA sample.*

Table 2. *Summary of performance characteristics of chronic pain classifications (n = 444).*

Diagnostic Performance Tests (BPI as Gold Standard)		95% Confidence Interval
Prevalence of Chronic Pain According to BPI (Gold Standard Reference)	63.0%	59.0, 67.8
Sensitivity	49.1%	43.0, 55.0
Specificity	90.2%	84.5, 94.3
ROC area (Sensitivity + Specificity)/2	0.70	0.66, 0.73
Positive predictive value	89.6%	83.7, 93.9
Negative predictive value	50.7%	44.8, 56.6

sified as having pain according to the GENOA CRF and BPI were found to have an estimated 7.79% increase in positive opioid urine screens (estimated coefficient: 7.79; 95% CI 0.74, 14.85: *P* = 0.031). Patients classified as having pain according to both measures were also found to have a 4 times greater odds (OR: 4.10 *P* = 0.008; 95% CI: 1.44, 11.63) of consuming a "high risk" level of illicit opioids (≥ 50% positive opioid urine screens over 3-month period following pain assessment).

The prognostic relevance of pain classification was not maintained for the additional participants classified by the BPI (n = 143 discordant), whereby pain classification is no longer predictive of positive opioid urine screens (estimated coefficient: 1.78; 95% CI -4.66, 8.21: *P* = 0.588) or a "high-risk" level of opioid consumption BPI (OR: 1.08, 95% CI: 0.35, 3.29; *P* = 0.898). Results from these analyses are summarized in Tables 3 and 4. Similar findings were observed when evaluating the prognostic relevance of the GENOA classification in comparison to the BPI across moderate risk opioid use outcomes; however, the observed predictive significance of the GENOA CRF classification was slightly diminished (OR: 2.13; 95% CI: 0.93, 4.90 *P* = 0.075).

The adjusted and unadjusted predicted probability for high-risk opioid use was evaluated for each pain classification. Again, we find those participants classified by the GENOA CRF and BPI were found to have a high-predicted probability (17%) for high-risk opioid consumption. There were no differences in the predicted probability for high-risk abuse between the additional participants classified by the BPI and those without pain. These results are summarized in Fig. 4.

Discussion

Findings from this study emphasize the prognostic impact of different pain classification measures for patients with opioid addiction. While the BPI may be the most commonly used measure to assess pain among MMT patients (26,27,36-40), results from this study suggest the BPI holds poor prognostic value for distinguish-

Table 3. *The prognostic significance of pain classification for predicting percentage of positive opioid urine screens - results from multi-variable linear regression (n = 278).*

	Estimated Coefficient	*P*-value	95% Confidence Interval
Pain Classification (Reference: Participants Concordantly Classified Without Pain)			
Participants Concordantly Classified With Pain By Both Measures	7.79	0.031	0.72, 14.85
Discordantly Classified Participants (Classified as Having Pain According to BPI not GENOA CRF)	1.78	0.588	-4.66, 8.21
Age	-0.15	0.296	-0.44, 0.13
Methadone Dose (mg/day)	-0.11	0.002	-0.18, -0.04
Gender	0.95	0.73	-4.45, 6.35
Duration on MMT (months)	0.00	0.903	-0.06, .06
Infectious Disease Status (Positive for HIV or Hepatitis C)	2.29	0.49	-4.23, 8.82

Table 4. *Impact of pain classification on high-risk opioid use behavior (n = 278).*

	Odds Ratio	*P*-value	95% Confidence Interval
Pain Classification (Reference Participants Concordantly Classified Without Pain)			
Participants Concordantly Classified With Pain By Both Measures	4.10	0.008	1.44, 11.63
Discordantly Classified Participants (Classified as Having Pain According to BPI not GENOA CRF)	1.08	0.898	0.35, 3.29
Age	0.98	0.37	0.94, 1.02
Methadone Dose (mg/day)	0.99	0.026	0.98, 0.99
Gender	1.01	0.983	0.44, 2.30
Duration on MMT (months)	1.00	0.822	0.98, 1.01
Infectious Disease Status (Positive for HIV or Hepatitis C)	0.96	0.944	0.36, 2.62

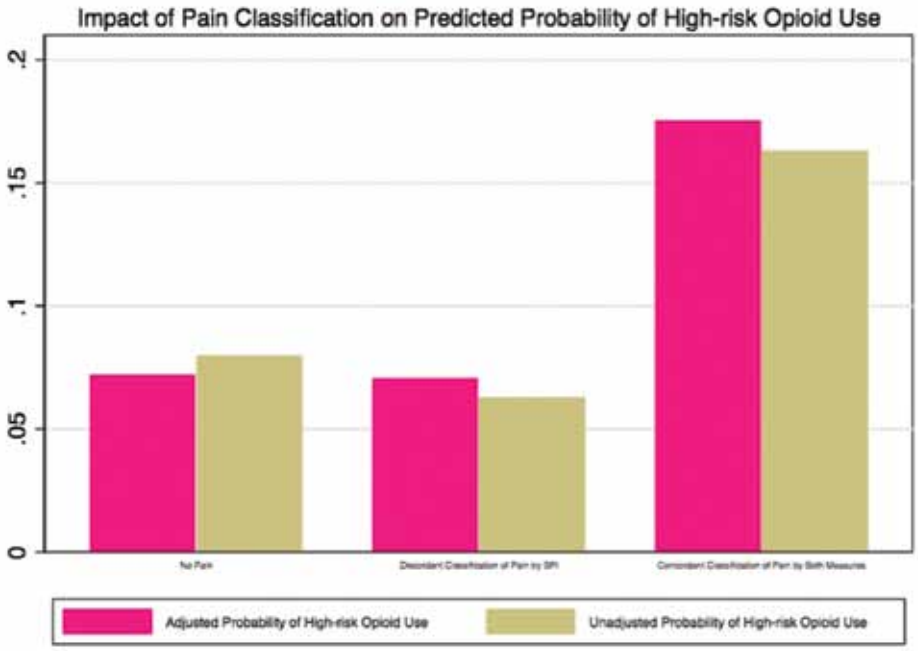

Fig. 4. *Impact of classification on predicted probability of high-risk opioid use.*

ing patients at high risk for opioid abuse. The BPI classifies a large number of patients with comorbid pain; however, simpler evaluations such as the question "are you currently experiencing or have been diagnosed with chronic pain?" demonstrate a stronger prognostic significance for distinguishing patients at high risk for continued opioid abuse. The BPI showed high sensitivity when compared against the simpler pain classification question used in the GENOA CRF, however the additional participants identified by the BPI classification weakened the predictive ability of the measure. Classification of pain based on the BPI alone biased the results to suggest participants with pain are not at risk for engaging in problematic opioid consumption behavior. However, the subgroup of patients within the BPI classified concordantly by both measures were shown to be a serious risk for engaging in concerning levels of illicit opioid consumption. In light of the findings, we are likely to question the validity of the results of previous studies using BPI to classify pain among MMT patients.

Numerous studies evaluating the effect of pain on response to MMT use the BPI to classify pain, citing its previous validation as justification (26,27,36,39,40). However, this suggestion is problematic since the validity of a measurement scale is applied exclusively to the population the tool is developed for and tested within (41). To our knowledge no previous reliability estimates are reported for the BPI within the opioid addiction population. For instance, neither the psychometric properties such as internal consistency nor the test-retest reliability have been reported for a population of addiction patients. The BPI was originally generated and validated within a population of cancer and rheumatoid arthritis patients (50), resting our confidence in the BPI's ability to distinguish pain on the assumption that there are strong similarities between the addiction population and the population the tool was created within, of which we have serious concerns. Contention in the literature may stem directly from the use of pain classification measures with limited prognostic value. Among studies evaluating the association between comorbid pain and illicit opioid use (26-28,33,36,39,40,51), those measuring pain using the BPI report no effect of pain on illicit opioid consumption (26,27,36,39,40). To the contrary, studies reporting a significant effect of pain on opioid abuse behavior did not classify pain using the BPI (28,33). We acknowledge the BPI was not intended to predict high-risk opioid use among the MMT population, and in fact the BPI may indeed appropriately identify participants with comorbid

pain. However, it appears pain classification according to the BPI casts a net so wide it loses prognostic value. Findings from this study demonstrate pain is related to how people progress through treatment at an etiologic level. Thus, the BPI may be capturing domains that are not associated with prognostically relevant pain. The alternative explanation may be that the simpler measure captures a specific subgroup of patients who self-identify as having pain. The GENOA pain assessment includes a direct pain assessment whereby patients are classified as having pain if they identify with any chronic pain symptoms. Overall, participants endorsing the GENOA pain assessment may experience significant pain such that it has become a core part of their identify and possibly a core part of the reason they abuse drugs. We acknowledge this pain assessment has not been validated in the traditional sense; however, its singularity as an assessment (using only one question) renders the majority of reliability analyses inappropriate. For instance, factor analysis which validates the existence of domains or interclass correlation coefficients which evaluate the clustering of participant responses would be inappropriate to perform on a single item assessment.

As the most common complaint among drug seeking patients with substance use disorder, chronic pain can be a challenging symptom to ascertain and treat (52). High-intensity comorbid pain among patients with a history of addiction is a significant risk factor for opioid misuse (53). Patients catastrophizing pain are also found to have higher rates of opioid abuse (54). Distinguishing between drug seeking patients and those with real pain is challenging. Pain is a subjective phenomenon, as such, the measurement and classification of pain is sensitive to the population being assessed. Thus, it could be claimed the GENOA CRF pain classification is capturing a specific group of "drug seeking" patients. However, findings from a previous study of an independent sample of 235 patients with opioid addiction treated with MMT using the same pain measure as the GENOA CRF found patients reporting pain to have significantly elevated Interferon-Gamma (IFN-α), indicating a biological distinction between patients classified according to the GENOA CRF (28).

Major studies evaluating pain among addiction patients emphasize the need for future research to replicate their findings as well as develop validated questions for assessing treatment response (26,36). The current study provides evidence to suggest the selection of pain measure may be driving previous findings. To our knowledge this is the first study to demonstrate the effect of pain on opioid consumption over a 3-month follow-up using a prospective cohort design. Precautions were taken to ensure we employed objective measurements; this includes electing to use urine toxicology screening over self-report to assess opioid consumption. Using the CATC network of clinics guarantees all participants receive care according to a standardized treatment protocol, which includes weekly physician visits and urine samples, as well as dosing and tapering procedures. For participants without 3-month data due to switching clinics, treatment failure, or successful treatment completion, we imputed missing data based on the participant's treatment response history. For instance, participants terminated from the MMT program due to non-compliance (e.g., not willing to provide urine, serious comorbid substance use), we imputed 100% positive opioid urine to reflect a high-risk patient. The total number of individuals with imputed data is small (n = 13) and thus may have no effect on the results. However, we caution the interpretation of these results since they are still reflective of participants already maintained on an OST, which can largely differ from patients who drop out of MMT or never seek treatment altogether. Employing an observational study design in addition to using multiple centers to capture differing socioeconomic populations increases our confidence that these results reflect the treatment prognosis for the larger population of opioid addiction patients receiving methadone treatment. Additionally, demographic characteristics of GENOA participants are consistent with those reported in previous population based studies (55).

Conclusion

Acknowledging chronic pain is predictive of high-risk opioid use will improve relapse prevention management, prevent opioid overdose, and encourage clinicians to target appropriate adjunct therapies to patients with comorbid addiction and pain conditions. Findings from this study suggest the most common pain measure — the BPI — is not only time consuming to administer, it fails to classify distinguish prognostically relevant pain. Directly inquiring into patients' history of pain using question such as, "are you currently experiencing or have been diagnosed with chronic pain?" will distinguish patients at high-risk for dangerous opioid consumption behavior. Health care providers often report dissatisfaction with managing pain due to the lack of training in addiction treatment. Providing clinicians with information on the

distinguishing risk factors for high-risk opioid consumption is imperative for enhancing the management of addictive disorders. It is also important we identify measures that are no longer useful for evaluation of pain impact on substance use behavior.

Acknowledgments

The authors report no conflict of interest for this study. This work was supported by the Peter Boris Centre for Addiction Research and the CIHR Drug Safety and Effectiveness Network (DSEN) grant (grant number: 126639). The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Zainab Samaan, Brittany B. Dennis, and Pavel S. Roshanov were responsible for conceiving the research question. Zainab Samaan and Brittany B. Dennis drafted the study protocol. Brittany B. Dennis and Pavel S. Roshanov were responsible for designing the statistical analyses for this study. Brittany B. Dennis performed all statistical analyses. All authors contributed to the development, writing, and revisions of the manuscript (BBD, PSR, MB, JP, AW, MV, JD, CP, DD, GP, DCM, LT, ZS).

Brittany B. Dennis and Monica Bawor are supported by the Intersections in Mental Health Perspectives and Addiction Research Training fellowship from the Canadian Institutes of Health Research (CIHR) and the British Columbia Centre of Excellence for Women's Health. Brittany B. Dennis is also a David L. Sackett Scholar. Pavel S. Roshanov is supported by an American Society of Nephrology Medical Student Scholar Grant and a CIHR-Institute for Health Services and Policy Research Rising Star Award.

We would like to thank the Canadian Addiction Treatment Centres for their partnership in this study. We thank Jackie Hudson for her outstanding work as our senior research coordinator. We extend our gratitude to Sheelagh Rutherford for her excellence as our senior project nurse recruiting and managing GENOA participants. We recognize the hard work of all the McMaster University undergraduate students who have contributed to this project, namely Anjua Bhalerao, Kritika Badhan, and Bianca Bantoto. We also thank the GENOA participants for generously donating their time to be involved in this study, without whom none of this would be possible.

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