

Neuroticism Is Associated with Chronic Severe Pain among Ex-Opioid Users on Methadone Maintenance Therapy

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ABSTRACT

Introduction: Among ex-opioid users on methadone maintenance therapy (MMT), the prevalence of chronic severe pain (CSP) was reported as 37-48.2%. The CSP causes distress, adversely affects quality of life, addiction treatment outcome and exacerbates patients ambivalence towards MMT. Neuroticism personality trait is associated with CSP, but the similar association has yet to be explored in ex-opioid users on MMT.

Objectives: This study aims to determine the prevalence of CSP among ex-opioid users on MMT, and to examine whether neuroticism is significantly associated with CSP.

Methods: In this cross-sectional study, validated Malay version of big five inventory (BFI), brief pain inventory (BPI), Beck's depression inventory (BDI), and Beck's anxiety inventory (BAI) were utilized for measurement of neuroticism, pain, depression and anxiety symptoms, respectively. Subjects were recruited from two MMT centres in Alor Star, Malaysia.

Results: A total of 151 subjects were recruited, consisting of 104 from Klinik Kesihatan Bandar Alor Setar, and 47 from Hospital Sultanah Bahiyah. The prevalence of CSP, regular use of over-the-counter (OTC) analgesics and kratom product were 22.5%, 28.5%, and 40.4%, respectively. Using multiple logistic regression analyses, neuroticism score ($p < 0.001$), BAI score ($p = 0.012$) and regular OTC analgesic use ($p = 0.016$) were found to be statistically significant in association with CSP, with adjusted odds ratio of 1.60 (95% CI 1.27, 2.12), 1.44 (95% CI 1.08, 1.93), and 3.56 (95% CI 1.27, 10.01), respectively.

Conclusion: Neuroticism, anxiety and regular use of OTC analgesics were independently associated with CSP among ex-opioid users on MMT. Otherwise, no significant association was observed for depression, HIV status, regular use of kratom, and other socio-demographic or clinical characteristics.

KEY WORDS

neuroticism, chronic pain, methadone maintenance therapy, kratom, ex-opioid users

INTRODUCTION

The prevalence of chronic severe pain (CSP) among previous heroin users on methadone maintenance therapy (MMT) is 37-48.2%¹⁻³ compared to 10% in general population⁴. Poorly controlled chronic pain is associated with disability and distress⁵, poor addiction outcome^{1,2}, and poor quality of life⁶ among patients on MMT. Counselors also reported difficulties in helping patients on MMT with chronic pain⁷ whereas attendance at counseling sessions predict good treatment response⁸. Pain symptoms tend to exacerbate patients anxiety and ambivalence towards MMT⁹.

Neuroticism is one of the personality traits in both the three and five factors models of personality, also widely known as the Big Three and Big Five theories, respectively¹⁰. The differences among various definitions of neuroticism have been reconciled in the late 1990s with the consensus definition that, at its core, neuroticism is the propensity to experience negative emotions¹¹. Neuroticism is associated with vigilance to pain and its severity, and these relationships are mediated by pain catastrophizing and pain-related fear¹².

Among patients on MMT, significant associations were found between CSP and depression as well as anxiety disorders^{1,3,6,13}. Long-term use of opioids, like methadone, might actually cause opioid-induced hyperalgesia, where patient become more sensitive to pain perception as compared to unexposed individual¹⁴⁻¹⁶. Nevertheless, kratom

has been used as opioid substitute¹⁷ and analgesic through its activity on opioid receptors^{17,18} by the local people in Thailand and Malaysia. The determinants of chronic severe pain among patients on MMT are likely to be complex and warrant further study.

Previous studies had shown that CSP and neuroticism might adversely affect MMT, which is an important part of harm reduction program in Malaysia¹⁹. Therefore, this study aimed to determine the prevalence of CSP among patients on MMT in Alor Setar, and its association with neuroticism. It is hoped that the findings of this study would help in improving the service of MMT in the future.

METHODS

Study setting and subjects

The ethical approval was sought from the USM Human Research Ethics Committee (HREC) and National Medical Research Register of Malaysia (NMRR). This cross-sectional study was conducted from July to September 2016 at 2 methadone clinics in Alor Setar i.e., Klinik Kesihatan Bandar Alor Star (KKBAS) and Hospital Sultanah Bahiyah (HSB).

The inclusion criteria were MMT minimum duration of 12 months,

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Table 1. Socio-demographic and clinical characteristics subjects

Characteristics (n = 151)	n (%)
Sex	
Male	147 (97.4)
Female	4 (2.6)
Race	
Malay	138 (91.4)
Chinese	8 (5.3)
Indian	5 (3.3)
Marital Status	
Married	75 (49.7)
Single	63 (41.7)
Divorced	3 (2.0)
Widowed	10 (6.6)
Employment Status	
Unemployed	28 (18.5)
Employed	123 (81.5)
Educational Status	
Primary	10 (6.6)
Secondary	134 (88.7)
Tertiary	7 (4.6)
History of bone fracture > 6 months	
Yes	38 (25.2)
No	113 (74.8)
Diagnosis of mental illness	
Yes	28 (18.5)
No	123 (81.5)
Chronic medical illness ^a	
Yes	47 (31.1)
No	104 (68.9)
Regular use of over-the-counter analgesics ^b	
Yes	43 (28.5)
No	108 (71.5)
Regular use of kratom ^c	
Yes	61 (40.4)
No	90 (59.6)
Chronic smoker	
Yes	135 (89.4)
No	16 (10.6)
Urine toxicology screen for the past month ^d	
Positive	8 (5.3)
Negative	143 (94.7)
Hepatitis C status	
Reactive	112 (74.2)
Non-reactive	39 (25.8)
Hepatitis B status	
Reactive	15 (9.9)
Non-reactive	136 (90.1)
HIV status	
Positive	15 (9.9)
Negative	136 (90.1)
	Mean(SD)
Age (years)	42.08 (8.66)
Duration of MMT (months)	74.00 (37.02)
Current dose of methadone (mg/day)	64.93 (29.61)
Neuroticism score	23.90 (5.77)
BDI score	8.51 (6.82)
BAI score	9.93 (10.50)

^a Except hepatitis B, hepatitis C, and HIV

^b Use of over-the-counter analgesics for at least 3 times a week for the past 3 months

^c Use of any kratom products daily

^d Urine positive for any of the following: morphine, amphetamine, methamphetamine, benzodiazepines or tetrahydrocannabinol

Table 2. Factors significantly associated with CSP using simple logistic regression

Variable	Regression Co-efficient (b)	Crude Odds Ratio (95%CI)	Wald statistic	p-value
Neuroticism score	0.313	1.367 (1.212, 1.541)	26.07	< 0.001
BAI score	0.056	1.057 (1.022, 1.094)	10.27	0.001
BDI score	0.125	1.133 (1.068, 1.202)	17.2	< 0.001
Positive HIV	1.262	3.532 (1.178, 10.595)	5.07	0.024
Regular use of kratom	0.974	2.648 (1.212, 5.785)	5.97	0.015
Regular use of OTC analgesics	1.253	3.500 (1.571, 7.799)	9.4	0.002

* SLR for all other independent variables yield p value > 0.25

Table 3. Factors significantly associated with CSP using multiple logistic regression

Variable	Regression Co-efficient (b)	Adjusted ^a Odds Ratio (95%CI)	Wald statistic	p-value
Neuroticism score	0.300	1.349 (1.187, 1.534)	20.89	< 0.001
BAI score	0.050	1.051 (1.009, 1.095)	5.60	0.018
Regular use of OTC analgesics	1.100	3.004 (1.117, 8.078)	4.75	0.029

^a Forward LR and Backward LR Multiple Logistic Regression model were applied and similar

variables were retained in the model. Multicollinearity was checked and not found.

Interaction term was checked and it showed interaction between neuroticism score and BAI score (p = 0.028, b = -0.012).

Table 4. Factors significantly associated with CSP using multiple logistic regression with interaction term included (final model)

Variable	Regression Co-efficient (b)	Adjusted ^a Odds Ratio (95%CI)	Wald statistic	p-value
Neuroticism score	0.472	1.603 (1.274, 2.016)	16.24	< 0.001
BAI score	0.368	1.444 (1.082, 1.927)	6.24	0.012
Regular use of OTC analgesics	1.269	3.558 (1.265, 10.011)	5.78	0.016
BAI score* Neuroticism score b	-0.012	0.988 (0.978, 0.999)	4.81	0.028

^a Interaction term was checked and it showed interaction between neuroticism score and BAI score (p = 0.028, b = -0.012).

^b Interaction term created for interaction between neuroticism score and BAI score is included into the final model.

stable dose of methadone, chronic pain symptoms of at least 6 months, and adequate command of Malay language and literacy to complete the self-rated questionnaires. A complete patient information sheet was given to eligible subjects for their reading, and the study was explained to them verbally, before consent being acquired. Consented subjects

were requested to complete a series of questionnaires, including a data sheet on socio-demographic and clinical characteristics. Patients who declined the invitation to participate were being assured that the standard of their MMT in the future will not be affected. This was explicitly stated in patient information sheet to address the issue of subjects' vulnerability.

Measurements

The brief pain inventory (BPI) is a widely used instrument in clinical pain assessment. It has been used in hundreds of studies and has been shown to be an appropriated measure for pain due to a wide range of clinical conditions. BPI was initially used to measure the pain in malignancy, but it has been validated for use in chronic non-malignant pain as well²⁰. Malay version of BPI was validated and used in this study²¹. A subject is said to have CSP if he or she scores 5 or higher on the BPI 'worst pain' scale in the past one week, or obtain the mean 'pain interference' score of 5 or above, given that at least four out of the seven interference scales are scored. Furthermore, the pattern of pain should present for at least 6 months^{1,3}.

The big five inventory (BFI) is a valid and reliable instrument to measure personality traits according to big five theory or five-factor model of personality^{22,23}. It is an efficient measuring instrument whereby it only takes about 5 minutes to be completed, as compared to NEO-FFI that usually take 15 minutes to complete. It was shown to be at least as efficient and easily understood as the 60 item NEO-FFI. It has good internal consistency, as well as convergent validity with NEO-FFI²³. The translated Malay version of BFI had been validated for use in Malaysian population²⁴. The inventory consists of 44 items that measure big five attributes, i.e., neuroticism (8 items), extraversion (8 items), agreeableness (9 items), conscientiousness (9 items), and openness (10 items). Only the neuroticism items were used in this study.

The Beck's depression inventory (BDI) is a well-established self-reported instrument²⁵, and has been used worldwide for the past 5 decades to measure depressive symptoms. It had since been translated into various languages²⁶, including Malay language²⁷, and its psychometric properties have been extensively evaluated. The Beck's anxiety inventory (BAI) is widely used for measurement of anxiety symptoms. It has good internal consistency and high test-retest reliability. The Malay version of BAI was validated by local researchers²⁸ and used in this study.

Statistical analyses

The data were analysed by using SPSS Statistic version 22. The association between potential associative factors and the presence of CSP were first analysed using simple logistic regression (SLR). The associative factors with p-value < 0.25 by SLR were then further analysed using multiple logistic regression (MLR). During the variable selection processes, forward selection was coupled with backward elimination in order to acquire preliminary main effect model. Alpha was set at 0.05. Multicollinearity and interaction were checked, and the fitness of the preliminary final model was assessed using Hosmer-Lemeshow test, classification table, and area under the receiver operating characteristic (ROC) curve tests.

RESULTS

A total of 34 subjects (22.5%) reported chronic severe pain. The socio-demographic and clinical characteristics of study subjects (n = 151) were summarized in table 1. The mean age of subjects was 42 (SD 8.66). Over 90% of the subjects were Malay and only 4 (2.6%) female subjects were recruited in the study. The employment rate was 81.5%. The mean daily dose of methadone was 64.9mg (SD 29.6), ranging 5.0 to 190.0mg daily. Thirty-eight (25.2%) subjects had a history of bone fracture within 6 months of study, and all of them reported full recovery from the injuries. Twenty-eight (18.5%) subjects had a diagnosis of any mental illness, whereas 31% reported having at least one chronic medical illness, such as diabetes mellitus, hypertension, bronchial asthma, and cardiovascular disorders. The rate of hepatitis C infection was 74.2%, while hepatitis B and HIV infection were reported to be similar (15%). Regular over-the-counter (OTC) analgesics usage was common (28.5%), and it was interesting to note that the prevalence of regular use of kratom product was 40.4%. Though no subject reports active use of any illicit substance, 5.3% were positive in urine toxicology screening done within 1 month from sampling date. The rate of active smoking was 89.4%.

Table 2 summarizes all factors that found to be associated with the presence of CSP using SLR analyses. Neuroticism (p < 0.001), BAI (p = 0.001) and BDI (p < 0.001) scores were noted to be positively associated with CSP. Besides, HIV infection (p = 0.024), regular use of kratom (p = 0.015) and OTC analgesics (p = 0.002) were also significantly associated with CSP, all with crude OR of over 2.50.

Table 3 listed the three factors from above that remained statistically significant after MLR analyses were performed, i.e. neuroticism score (p < 0.001), BAI score (p = 0.018) and regular use of OTC analgesics (p = 0.029), with adjusted OR of 1.35 (95% CI 1.19, 1.53), 1.05 (95% CI 1.01, 1.10) and 3.00 (95% CI 1.12, 8.08), respectively. Although no multicollinearity detected, a significant interaction was found between neuroticism score and BAI score (p = 0.028). Thus, an interaction term (neuroticism score*BAI score) was created and was included into the analysis for the final model.

Table 4 summarizes the results of MLR with the interaction term included. The three associative factors remained statistically significant after controlling for the interaction, with adjusted OR of 1.60 (95% CI 1.27, 2.12), 1.44 (95% CI 1.08, 1.93), and 3.56 (95% CI 1.27, 10.01), respectively. The fitness of this final model was confirmed using Hosmer-Lemeshow test (p = 0.282), classification table (overall correctly classified percentage = 83.4%), and area under the receiver operating characteristic (ROC 87.9%) curve test. In essence, the results show that after controlling for each other, neuroticism score, BAI score, and regular use of OTC analgesics were positively associated with the presence of CSP among patient on MMT.

The following predictor equation summarizes the above findings: $\text{Log (P/1-P)} = -14.79^c + 0.47(\text{neuroticism score}) + 0.37(\text{BAI score}) + 1.27(\text{regular OTC analgesic use}) - 0.01(\text{neuroticism score*BAI score})^D$. C is the regression coefficient of constant in the table of Variable in Equation from SPSS analysis for the final model, and D is the interaction term included in the final model.

DISCUSSION

Current study established that CSP is a highly prevailing problem among patients on MMT in Alor Star, though the prevalence is lower compared to other studies^{1,3,29}. Neuroticism score, BAI score, and regular use of OTC analgesics emerged as significant predictors of CSP among patient on MMT in the final model.

Neuroticism as an important associative factor with CSP among patients on MMT is consistent with previous studies^{30,32}. Earlier studies postulated neuroticism as a vulnerability factor in chronic pain development and was demonstrated by a later study that it predict the development of chronic pain. Neuroticism has also been associated with internet addiction³³ and depression³⁴. Anxiety was found to be independently associated with CSP, which is consistent with other studies^{3,35}. The presence of anxiety adversely affect the efficacy of cognitive behavioural therapy provided to the clients with chronic pain³⁶.

Use of OTC analgesics as predictors suggested that when CSP was not adequately addressed, patients resorted to OTC analgesics to relieve their pain. OTC use as a way of self-medication was reported to be common, but the practice actually exposes the patient to adverse drug reactions, which is avoidable³⁷. Stone and colleagues reported that 95% of their surveyed subjects use OTC medication without doctor's prescription, and analgesics are among the commonly reported. They further reported that among the subjects, as a result of their OTC use, exposure to the risk of drug-to-drug interaction is high. This implication is important for patients on MMT, especially those with chronic medical illnesses that required other medication, because drug-to-drug interaction with methadone can be fatal³⁸. Thus, steps must be taken to address the problem of OTC analgesic use among patients on MMT, one of which is proper assessment and treatment of CSP.

It is interesting to note that over 40% of the study subjects reported daily use of kratom product. Though its association with CSP was not statistically significant, its implication to our MMT patients cannot be ignored. Kratom has been increasingly reported locally, as well as globally, as an emerging illicit substance with high abuse potential^{17,39,40-42}. Kratom is reported being used by local people to manage opioid withdrawal symptoms, and current study result suggests that the same phenomenon might be happening among local MMT patients. Due to its opioid-like chemical properties¹⁷, concomitant use of kratom while undergoing MMT is expected to affect methadone dose adjustment, symptom control, and may defeat the purpose of MMT in the first place. Thus, routine assessment of kratom use among patients on MMT is recommended. However, more robust studies are needed to clarify the

impact and the severity of kratom use among this group of patients.

The authors recognized a few limitations in the study. Firstly, as the study was conducted in only one area of the state of Kedah (urban area, also the capital of the state), thus the result cannot be generalized to the whole state of Kedah, or Malaysia at large. The sample population was heterogeneous in the sense that the time of participation and the duration of MMT varied considerably among subjects.

Based on the findings, several steps may improve the MMT program. Firstly, routine assessment for CSP might be warranted for all MMT patients, as detection is the first step in addressing the problem. Then, if CSP is detected, other associated factors, including the ones observed to be significant in this study, should be sought for and managed accordingly. For instance, if CSP is found to coexist with anxiety or depression in a particular patient, treatment of the anxiety or depression is paramount in the management of the CSP. Besides, even if the patient does not complain of CSP to the treating physician, the presence of associated factors like regular OTC analgesic use and persistent anxiety or depression should alert the clinician to the possibility of distressing pain symptoms. Pain with physical causes might require multidisciplinary comprehensive pain management, such as referral to a pain clinic, while pain symptom with obvious psychological component is likely to require psychological intervention.

CONCLUSION

This study established a significant positive association between neuroticism and CSP among ex-opioid users on MMT. Similarly, independent association with CSP were also observed for anxiety and regular use of OTC analgesics. Kratom use is common, and its negative impact on MMT programme cannot be underestimated. Future studies with more rigorous methodology, such as a prospective cohort study, should be conducted in the future in order to further clarify the nature of the association between neuroticism and CSP among ex-opioid users on MMT.

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