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# Lack of Reduction in Buprenorphine Injection After Introduction of Co-Formulated Buprenorphine/Naloxone to the Malaysian Market

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## Abstract

**Background—**Diversion of buprenorphine (BPN) has been described in settings where it is legally prescribed and has resulted in increasing concern. To address this concern, co-formulation of buprenorphine/naloxone (BPN/NLX) replaced buprenorphine alone in Malaysia in December 2006.

**Methods—**To assess the significance of BPN/NLX introduction, 41 BPN/NLX injectors in Kuala Lumpur, Malaysia were recruited using a modified snowball recruitment technique.

**Results—**In January 2007, all subjects had previously injected BPN alone. During the transition from injecting BPN alone to co-formulated BPN/NLX, the mean daily BPN injection dose increased from 1.88 mg (range 1.0–4.0 mg) to 2.49 mg/day ($p < .001$). Overall, 18 (44%) subjects increased their daily amount of injection while 22 (54%) had no change in dose; only one subject reduced the amount of injection. Development of opioid withdrawal symptoms was the primary outcome, however the only symptom that was significantly associated with BPN/NLX dosage was the report of “stomach pains” ($p = .01$). In logistic regression analysis, the development of opioid withdrawal symptoms was associated with increased benzodiazepine injection and increased syringe sharing.

**Conclusion and Scientific Significance—**These data suggests that the introduction of BPN/NLX did not reduce injection related risk behaviors such as syringe sharing and was associated with

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increased benzodiazepine use. Evidence-based approaches to treat BPN injection are urgently needed.

### Keywords

Buprenorphine; buprenorphine-naloxone; injection drug use; Malaysia; substance abuse

## Background

Injection drug use of opioids continues to be a global public health challenge (1,2), but the choice of opioid used is often dependent upon local availability and therefore varies geographically. Buprenorphine, a partial opioid agonist, used widely as an effective, evidence-based treatment of opioid dependence, has been reported as an injectable opioid of abuse in some regions of the world (3,4). In an attempt to reduce the frequency of buprenorphine injection, a co-formulation of buprenorphine with naloxone (BPN/NLX), an opioid antagonist, was developed. Although common concerns regarding the acquisition of an infectious disease (e.g., HIV, viral hepatitis) are established with any injectable substance, less is known about the impact of the co-formulation with naloxone on injection practices in Southeast Asia (5–12).

Buprenorphine was first licensed for prescription in Malaysia in 2003. Until recently, however, buprenorphine's use in Malaysia has not been regulated nor have medical practitioners been required to undergo any specialized training or been subject to supervision or control in order to prescribe buprenorphine. Buprenorphine diversion has been described in multiple settings where it is prescribed legally, including Malaysia (3,13–15). In December 2006, the Ministry of Health in Malaysia introduced BPN/NLX as a tactic that would reduce or eliminate injection of buprenorphine. Medical practitioners were only allowed to prescribe BPN/NLX to patients for the treatment of opioid dependence. After the introduction of the BPN/NLX, we conducted a series of interviews with BPN/NLX injectors in Kuala Lumpur, Malaysia to ascertain if the introduction of BPN/NLX resulted in a decrease in the quantity of BPN injected.

## Methods

In January 2007, outreach workers from the syringe exchange program recruited individuals who self-reported buprenorphine injection and demonstrated facility with buprenorphine injection practices from within Kuala Lumpur, Malaysia. Thereafter, a modified snowball recruitment strategy was used to recruit additional subjects meeting the same criteria. Recruiters were paid 5 Ringgit Malaysia ($1.50 US) for each person recruited and each subject was paid 10 Ringgit Malaysia ($3.00 US) for each 45-minute interview. Subjects provided verbal consent for participation and no personal identifiers were asked for or obtained.

A structured face-to-face interview was utilized with all injectors interviewed in their native language (Bahasa Malaysia). The interviews were conducted after the combination of BPN/NLX had completely replaced BPN alone in Malaysia and comprised several domains including drug use, injection risk behaviors, sexual risk, criminal behavior, social functioning, health status including symptoms of opioid withdrawal, the milligram dosage of BPN/NLX currently injected, and the prior dose of BPN alone.

An injector's self-perception of opioid withdrawal was defined as affirmatively responding to one of the two following questions: 1) “In the last month (especially since the use of BPN/NLX) have you experienced withdrawal?” and 2) “In the last month (especially since the use of BPN/NLX) have you had a ‘dirty hit’ (made to feel sick)?”

To examine bivariate correlates such as differences in the quantity of BPN vs. BPN/NLX injected, Cochran–Mantel–Haenszel and Student *t*-tests were utilized where appropriate. Pearson correlation coefficients were used for the continuous variables such as BPN/NLX quantity. All bivariate covariates significant at the $p < .10$ level were forced into the logistic regression model. Logistic regression was used to model the data to examine the statistical association between the questions above and the covariates most associated with opioid withdrawal. Potential confounders (e.g., self-reported depression) and other substances of abuse (e.g., methadone, midazolam, and ketamine) were modeled to ascertain if symptoms of withdrawal might be associated with ingestion of other substances. Finally, risk behaviors were modeled to ascertain if subjects' experience of withdrawal was associated with changes in risk behavior.

## Results

This study included 41 BPN/NLX injectors, all of whom were men of Malay descent. The mean age was 33.7 (range 21–53) years. Prior to the introduction of BPN/NLX, the mean dose of BPN injected was 1.88 mg/day. The mean dose of BPN/NLX injected, however, increased to 2.49 mg/day (range 1.0–4.0 mg/day) during the transition. Among the two questions used to assess symptoms of opioid withdrawal, there was no statistically significant difference found between the answers for these two questions ($p = .2297$). Although several individuals reported in the affirmative to questions 1, 2, or both, regression analysis of the quantity of BPN/NLX injected with these self-reported questions showed no significance ($p = .12$ and $p = .86$, respectively). Logistic regression of symptoms of withdrawal (e.g., nausea, vomiting, diarrhea, muscle aches, and stomach pains) revealed that only “stomach pains” was significantly associated with increased BPN/NLX dosage ($p = .01$). Thus, self-perception of withdrawal and most of the symptoms of withdrawal were not related in a statistically significant manner with the quantity of BPN/NLX injected.

Self-reported depression, a potential confounder of symptoms of withdrawal, was not statistically significant when modeled against the covariates of withdrawal ($p = .10$) and “dirty hit”—a proxy for withdrawal symptoms ($p = .10$). Pearson correlation coefficients revealed no statistically significant association between the BPN/NLX quantity and the symptoms of opioid withdrawal. Additionally, the use of other drugs that might be used to manage symptoms of withdrawal was modeled with BPN/NLX dosage. The drugs modeled included ketamine, midazolam, and methadone. Of these, methadone use was significantly associated with BPN/NLX quantity ($p = .03$); however, only four subjects took methadone, and there were no statistical differences in methadone dose between those subjects who experienced withdrawal symptoms and those that did not (two subjects in each group) ($p = .59$). Among BPN/NLX injectors who were also midazolam injectors, however, there was a difference in the quantity of midazolam injected. Specifically, the six subjects without withdrawal symptoms reported injecting a mean of 13.7 mg/day of midazolam, while the seven who did report withdrawal symptoms injected a mean of 24.7 mg/day ($p = .01$).

Compared to subjects not experiencing opioid withdrawal symptoms, BPN/NLX injecting subjects reporting withdrawal symptoms demonstrated 4-fold greater odds (95% CI 1.06–15.14; $p = .04$) of syringe sharing. Importantly, of the 9 HIV-infected injectors experiencing withdrawal, 6 reported sharing in the last 30 days.

A significant difference between the quantity of BPN/NLX currently injected and the BPN mono-formulation previously injected was seen ($p < .0001$). The quantity of BPN/NLX and BPN alone was positively correlated as demonstrated by a Pearson correlation coefficient of .64970 ($p < .0001$). That is, subjects with higher BPN alone quantities have higher BPN/NLX quantities upon changing to BPN/NLX. Upon re-examination of the data, 18 of 41 subjects

reported using a higher quantity of BPN/NLX than BPN alone after the national change, 22 did not change their quantity, and one subject reported a reduction in total BPN dose when transition from the mono-formulation to BPN/NLX.

## Discussion

To our knowledge, this is the first examination of injection practices among BPN injectors as they transition from injection of BPN alone to BPN/NLX. This was possible only as a result of a change in governmental and pharmaceutical policies. Prior to the introduction of BPN/NLX into Malaysia, a growing number of opioid dependent individuals were injecting BPN alone. The purpose of rolling out the combination product was the hope that injection of buprenorphine with naloxone might precipitate withdrawal in subjects injecting the naloxone-containing medication and therefore reduce the probability that individuals would inject (16). Although many of these subjects reported symptoms of withdrawal, those symptoms did not result in a decrease in the self-administered BPN/NLX dose. This is consistent with other studies that have demonstrated that at least some individuals may not experience precipitated withdrawal when injecting the BPN/NLX co-formulation (15,17,18). In fact, the data suggest that the change may have resulted in an increase in BPN injection because 18 of 41 (44%) subjects increased the amount of BPN/NLX injected (typically a 1 mg increase in buprenorphine), perhaps to overcome their symptoms of opioid withdrawal. Because subjects consistently inject the same dose of BPN in the same frequency over protracted periods of time, recall bias is less likely.

One unexpected and provocative finding was the association of increased syringe sharing associated with the experience of opioid withdrawal symptoms. While these data do not explore this sufficiently, one explanation may be that the experience of opioid withdrawal symptoms resulted in a subject's perception of withdrawal and their willingness to inject under more desperate circumstances to obviate these symptoms.

Naloxone is a full opioid antagonist and as such should theoretically dislodge the opioid buprenorphine from the receptor site and precipitate withdrawal when administered parenterally. BPN, however, has a high binding affinity to the *mu*-opioid receptor (19–22) and therefore may obviate naloxone's activity at the opioid receptor. In addition, the Malaysian buprenorphine injectors have, for the most part, appeared to inject BPN for the purpose of pharmacological maintenance treatment rather than to experience euphoria (23). As a result, they have a higher degree of motivation to continue using BPN, even if some of the symptoms associated with taking it might otherwise be a disincentive for injection. For the few patients that stated that they had experienced withdrawal symptoms, none of them had ceased injection of the BPN/NLX. In contrast, the concomitant injection of midazolam, especially the significant increase in dose, may have been used to placate some of the symptoms of withdrawal. Our finding supports this notion because the mean dose of midazolam used was higher in the subjects experiencing opioid withdrawal symptoms. Although this subgroup analysis cannot establish causation, it is plausible that subjects may have increased the dose of midazolam injected to placate their symptoms of opioid withdrawal. Though not examined in this study, the increase in midazolam dose may result in increased risk of overdose given the previously proposed pharmacokinetic interaction between BPN and midazolam (23). An alternative explanation for increased midazolam injection in this group experiencing opioid withdrawal symptoms is that they had a higher baseline addiction severity overall.

To date, there is no evidence-based guidance for clinical management of BPN injection. In one trial of 204 chronic buprenorphine (solution and not tablet) injectors in Iran, groups were randomized to receive methadone (50 mg orally), buprenorphine (5 mg sublingually), or naltrexone (50 mg orally) along with standard counseling. Completion rates over a 24-week

treatment period among the three groups favored methadone treatment with 83.8%, 58.8%, and 20.6%, respectively, completing the study. These findings, however, are not entirely applicable to all BPN injectors because of: 1) the variable sublingual absorption of buprenorphine (17,24) and 2) relatively low BPN dose compared to the methadone group in the treatment of opioid dependence (25,26). A higher dose of buprenorphine in this setting would be more appropriate and comparable to the relatively higher methadone dose employed. Until more comparable studies are completed, however, methadone should be prioritized as treatment for buprenorphine injectors or a higher dose of BPN administration sublingually.

Some countries have chosen an alternative approach to address BPN injection by banning it altogether. Such policies are draconian and do not balance the overall benefits from increasing access to effective treatment of opioid dependence with the relatively low risk from BPN injection. It is not likely that BPN injection will ever be entirely eliminated through any single or combined approach. Instead, improved identification of the problem and making alternative and affordable treatments available will likely result in the best outcomes for the individual and society. Further research establishing effective treatments for buprenorphine injection, including pharmacological and behavioral treatments, are urgently needed. Other approaches, such as implementation of structural interventions, such as price controls, mandated training for prescribers, or separation of the prescription and sale of buprenorphine, should also be explored.

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## References

1. Bruce, RD.; Altice, FL.; Friedland, GH. HIV Disease among Substance Users: Treatment Issues. In: Volberding, P., editor. Global HIV/AIDS Medicine. New York: Elsevier; 2007.
2. Bruce RD, Altice FL. Clinical care of the HIV-infected drug user. Infect Dis Clin North Am 2007;21:149–179. ix. [PubMed: 17502234]
3. Auriacombe M, Fatseas M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. American Journal on Addictions 2004;13(Suppl 1):S17–28. [PubMed: 15204673]
4. Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? Addiction 2005;100:197–205. [PubMed: 15679749]
5. Loo HW, Yam AK, Tan TC, Peng YP, Teoh LC. Severe upper limb complications from parenteral abuse of Subutex. Ann Acad Med Singapore 2005;34:575–578. [PubMed: 16284682]
6. Lai SH, Teo CE. Buprenorphine-associated deaths in Singapore. Ann Acad Med Singapore 2006;35:508–511. [PubMed: 16902730]
7. Lee CE. Tackling Subutex abuse in Singapore. Singapore Med J 2006;47:919–921. [PubMed: 17075655]
8. Lo HY, Leong CS. Surgical complications in parenteral Subutex abusers. Singapore Med J 2006;47:924–927. [PubMed: 17075657]
9. Chua SM, Lee TS. Abuse of prescription buprenorphine, regulatory controls and the role of the primary physician. Ann Acad Med Singapore 2006;35:492–495. [PubMed: 16902726]
10. Winslow M, Subramaniam M, Ng WL, Lee A, Song G, Chan YH. Seroprevalence of hepatitis C in intravenous opioid users presenting in the early phase of injecting drug use in Singapore. Singapore Med J 2007;48:504–508. [PubMed: 17538746]
11. Winslow M, Ng WL, Mythily S, Song G, Yiong HC. Socio-demographic profile and help-seeking behaviour of buprenorphine abusers in Singapore. Ann Acad Med Singapore 2006;35:451–456. [PubMed: 16902719]

12. Ng WL, Mythily S, Song G, Chan YH, Winslow M. Concomitant use of midazolam and buprenorphine and its implications among drug users in Singapore. Ann Acad Med Singapore 2007;36:774–777. [PubMed: 17925988]

13. Loo HW, Yam AK, Tan TC, Peng YP, Teoh LC. Severe upper limb complications from parenteral abuse of Subutex. Annals of the Academy of Medicine, Singapore 2005;34:575–578.

14. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. Addiction 2001;96:267–272. [PubMed: 11182872]

15. Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. Drug and Alcohol Dependence 1993;33:81–86. [PubMed: 8370341]

16. Nigam AK, Srivastava RP, Saxena S, Chavan BS, Sundaram KR. Naloxone-induced withdrawal in patients with buprenorphine dependence. Addiction 1994;89:317–320. [PubMed: 8173501]

17. Harris DS, Jones RT, Welm S, Upton RA, Lin E, Mendelson J. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. Drug and Alcohol Dependence 2000;61:85–94. [PubMed: 11064186]

18. Singh RA, Mattoo SK, Malhotra A, Varma VK. Cases of buprenorphine abuse in India. Acta Psychiatrica Scandinavica 1992;86:46–48. [PubMed: 1414399]

19. Villiger JW, Taylor KM. Buprenorphine: high-affinity binding to dorsal spinal cord. Journal of Neurochemistry 1982;38:1771–1773. [PubMed: 6281389]

20. Huang P, Kehner GB, Cowan A, Liu-Chen LY. Comparison of Pharmacological Activities of Buprenorphine and Norbuprenorphine: Norbuprenorphine Is a Potent Opioid Agonist. J Pharmacol Exp Ther 2001;297:688–695. [PubMed: 11303059]

21. Cowan A. Buprenorphine: New pharmacological aspects. International Journal of Clinical Practice 2003;(Supplement):3–8. [PubMed: 12665117]discussion 23–24

22. Mcance-Katz E, Moody DE, Morse GD, Pade P, Baker J, Alvanzo A, Smith P, Ogundele A, Jatlow P, Rainey PM. Interactions between Buprenorphine and Antiretrovirals. I. The Nonnucleoside Reverse-Transcriptase Inhibitors Efavirenz and Delavirdine. Clinical Infectious Diseases 2006;43:S224–S234. [PubMed: 17109309]

23. Bruce RD, Govindasamy S, Sylla L, Haddad MS, Kamarulzaman A, Altice FL. Case series of buprenorphine injectors in Kuala Lumpur, Malaysia. Am J Drug Alcohol Abuse 2008;34:511–517. [PubMed: 18584580]

24. Mendelson J, Upton RA, Everhart ET, Jacob P 3rd, Jones RT. Bioavailability of sublingual buprenorphine. Journal of Clinical Pharmacology 1997;37:31–37. [PubMed: 9048270]

25. Ahmadi J, Ahmadi K. Controlled trial of maintenance treatment of intravenous buprenorphine dependence. Irish Journal of Medical Science 2003;172:171–173. [PubMed: 15029983]

26. Ahmadi J, Ahmadi K, Ohaeri J. Controlled, randomized trial in maintenance treatment of intravenous buprenorphine dependence with naltrexone, methadone or buprenorphine: A novel study. European Journal of Clinical Investigation 2003;33:824–829. [PubMed: 12925043]

## TABLE 1

Correlates of symptoms of opioid withdrawal among BPN/NLX injectors

| Characteristic | Opioid Withdrawal (*N* = 20) | No Opioid Withdrawal (*N* = 21) | Bivariate Comparison*t*-Test (*p*-value) | Logistic Regression Analysis (OR, 95% CI) |
|---|---|---|---|---|
| Mean age, years | 33.9 | 33.6 | .5952 | |
| Heroin or morphine | *N* = 6<br>1.8 tubes | *N* = 1<br>2 tubes | N/A | |
| Methadone | *N* = 2<br>47.5 mL | *N* = 2<br>25 mL | .5903 | |
| Ketamine | *N* = 7<br>1.71 tablets | *N* = 3<br>1.17 tablets | .2941 | |
| Crystal methamphetamine | *N* = 5<br>39 | *N* = 1<br>30 | N/A | |
| Benzodiazepines | *N* = 6<br>13.7 mg | *N* = 7<br>21.4 mg | .0095 | |
| Frequency of injection (injections per day) | 4.25 | 3.9048 | .4245 | OR = 3 (.1153–78) *p* = .3291 |
| Syringe sharing | .75 | .43 | .5679 | OR = 4 (1.0569–15.1280) *p* = .0392 |
| • Yes | *N* = 9 | *N* = 15 | < .0001 | |
| • No | *N* = 12 | *N* = 5 | .0201 | |
| Sexual partners | .35 | .57 | .8798 | OR = .4 (.11–1.43) *p* = .1604 |
| • None | *N* = 9 | *N* = 13 | < .0001 | |
| • One or more | *N* = 12 | *N* = 7 | .0045 | |
| Housing status over past six months | 1.25 | .7619 | .4439 | OR = 2 (.57–7.06) *p* = .2849 |
| • Same place | *N* = 10 | *N* = 14 | | |
| • More than one place | *N* = 10 | *N* = 7 | | |
| Friends who provide social support | 1.85 | 2.0476 | .7704 | OR = 1.8 (.48–7.06) *p* = .3737 |
| • None | *N* = 5 | *N* = 8 | | |
| • One or more | *N* = 15 | *N* = 13 | | |
| Satisfaction with social support | 1.55 | 1.8095 | .3121 | OR = 2.8 (.6158–13.04) *p* = .1771 |
| • Satisfied | *N* = 14 | *N* = 17 | | |
| • Not satisfied | *N* = 7 | *N* = 3 | | |
| BPN dose (mg per day) | 2.6 | 2.24 | .8078 | |
| HIV positive status | 1.45 | 1.71 | .6674 | |