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Injecting buprenorphine-naloxone film: Findings from an explorative qualitative study

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Abstract

Introduction and Aims Experiences of buprenorphine-naloxone (BNX) sublingual film injection are not well documented or understood. We examined how people who inject BNX film seek and share information about this practice, document the methods used to prepare BNX film for injection, and report participants' experiences of this practice. Design and Methods Interviews were (n = 16) conducted with people who indicated that they had injected BNX film since its introduction onto the Australian market. Semistructured interviews were recorded and transcribed. NVivo10 program (QSR International) was used to analyse the data using qualitative description methodology. Results Participants largely reported similar BNX film preparation techniques, although the texture of BNX film during preparation to inject was reported to be unusual (gluggy), and there were many varied accounts associated with the amount of water used. Physical harms reported as associated with injecting BNX film were described (including local and systemic issues); participants reported injecting the film to enhance its immediate effects, yet generally reported that sublingual administration provided longer-lasting effects. Discussion and Conclusions Understanding knowledge acquisition about injecting new formulations of opioid substitution therapy is crucial in developing more effective harm-reduction strategies. Dissemination by peer networks to those who are currently or planning to inject BNX film regarding the 'gelatine like' texture when mixing, using only cold water and double filtering is important to ensure safer injecting practices. Findings from this study highlight the importance of peer networks for the dissemination of harm-reduction information. Introduction of new formulations internationally requires more qualitative studies to inform safer practices.

Keywords

film:, findings, explorative, qualitative, study, injecting, buprenorphine-naloxone

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Injecting buprenorphine-naloxone film: Findings from an explorative qualitative study

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Introduction and Aims: Experiences of buprenorphine-naloxone (BNX) sublingual film injection are not well documented or understood. We examined how people who inject BNX film seek and share information about this practice, document the methods used to prepare BNX film for injection, and report participants' experiences of this practice.

Design and Method: Interviews (n=16) conducted with people who indicated that they had injected BNX film since its introduction onto the Australian market. Semi-structured interviews were recorded and transcribed. NVivo10 program (QSR International) was used to analyse the data using Qualitative Description methodology.

Results: Participants largely reported similar BNX film preparation techniques, although the texture of BNX film during preparation to inject was reported to be unusual (gluggy), and there were many varied accounts associated with the amount of water used. Physical harms reported as associated with injecting BNX film were described (including local and systemic issues); participants reported injecting the film to enhance its immediate effects, yet generally reported that sublingual administration provided longer-lasting effects.

Discussion: Understanding knowledge acquisition about injecting new formulations of OST is crucial in developing more effective harm reduction strategies. Dissemination by peer networks to those who are currently or plan to inject BNX film regarding the 'gelatine like' texture when mixing, using only cold water, and double filtering is important to ensure safer injecting practices.

Conclusions: Findings from this study highlight the importance of peer networks for the dissemination of harm reduction information. Introduction of new formulations internationally requires more qualitative studies to inform safer practices.

Key words: Patient non-adherence, buprenorphine-naloxone, qualitative research, harm reduction, intravenous drug abuse

Introduction

Medicines, including those used to treat opioid dependence, have an important, legitimate role in medical practice, and can make an enormously positive contribution to the health and wellbeing of many patients (1). However, not all pharmaceuticals are used in accordance with doctors' directions. The injection of pharmaceutical products developed for oral or sublingual consumption has been well described in the literature, and this practice has been associated with a number of individual physical harms (2-6). Notably, the introduction of newer "abuse-deterrent" formulations may result in a range of serious and unanticipated harms. Two examples of this include the introduction of the gel cap formulation of Temazepam©, resulting in a range of injection related harms such as thrombophlebitis, abscesses and deep venous thrombosis (7), and the introduction of a less injectable oxycodone formulation in the US, leading to a significant drop in OxyContin injection, with a concurrent doubling in reported rates of heroin use in some populations (8).

Opioid substitution therapy (OST) for opioid dependence predominantly involves the use of methadone or buprenorphine, and has been found to be effective in reducing mortality, HIV transmission, crime, and other drug use (9-12). In Australia, OST is usually prescribed under the conditions of supervised dosing. Despite the high level of supervised dosing and, in the case of buprenorphine, the predominant use of the buprenorphine-naloxone (BNX) products, the diversion and injection of buprenorphine has been documented in both those receiving OST and also out of treatment populations (13-15). One Australian study estimated that approximately 9% of all 'supervised doses' of BNX are removed from clients' mouths at the dosing point (13), a proportion of which are later injected. Several international studies have also reported the nature, extent and consequences of injecting BPN (e.g. 3, 16, 17-22).

In late 2011, a new formulation of sublingual BNX registered as Suboxone Film, was introduced in Australia for the treatment of opioid dependence, with the main clinical rationale being to reduce aberrant use of BNX. Previous Australian research has highlighted the difficulties of effectively supervising sublingual BPN or BNX tablets, which usually take between 3 and 10

minutes for full dissolution of tablets (23). One randomised-controlled trial has found that BNX film adheres to the sublingual mucosa more rapidly and dissolves faster than BNX tablets, particularly at high doses (24). US data from 2011-2012 showed that "abuse and diversion" of BPN and BNX tablets exceeded that of BNX film (25). Given these characteristics, it was hoped in Australia that BNX film may be (a) quicker to supervise and (b) more difficult to remove from the mouth than BNX tablets, resulting in less removal of supervised doses from the dosing site and subsequent diversion or injection of supervised doses in comparison to BNX tablets.

The introduction of the BNX film formulation in Australia has presented a unique opportunity to examine the transmission of knowledge and behaviours between people who inject pharmaceutical opioids intended for oral or sublingual consumption. This study was undertaken as part of a larger mixed-methods post-marketing surveillance study to monitor the extent of diversion and injection of BNX film in Australia (26). To date, no qualitative studies have examined the context, extent and nature of BNX film injection. Given the potential for severe harms associated with the injection of pharmaceutical opioids intended for oral/sublingual consumption, understanding how information about injecting new formulations is learned and shared is crucial in understanding how best to disseminate harm reduction information and target interventions. Specifically, this study's aims were:

a. To examine how people who inject BNX film seek and share information about this practice, and
b. To document the methods used to prepare BNX film for injection and participants' experiences.

Method

This qualitative study was undertaken as part of a larger mixed-methods post-marketing surveillance study of the diversion and injection of BNX film (27). Qualitative research interviews with 16 people who reported injecting BNX film were conducted by trained interviewers during September 2012 to March 2013, approximately 12 months after the

introduction of the Film in Australia. Participants were recruited from among people currently in OST and recruited into the wider post-marketing surveillance studies of BNX film across three sites (Adelaide, Sydney, and Melbourne). Participants reflected the range of treatment settings and included a mix of public, private and general practice prescribers. Participants who indicated they had injected BNX film in the post-marketing surveillance interview and who indicated that they were willing to participate in another interview regarding BNX injecting were approached. All those approached consented to participate in the study which included a recorded face to face interview.

Measures

Participants were surveyed using a semi-structured interview schedule, with the interview recorded and then transcribed. Questions included commencement of injection of various OST medications, and more specifically questions focussed on BNX Film including: recent frequency of use, acquisition practices, preparation for injection, reasons for and experiences with injecting, sublingual use compared to injection, knowledge procurement, and concerns. These questions were designed to elicit narratives around injection of BNX film more generally.

Procedure

Eligible participants were invited to participate in an interview specifically relating to injection practices with BNX film. Interviews were conducted at cafes or in an office location (independent of OST services) and all participants provided informed consent to be interviewed and recorded. Participants were reimbursed either a $40 voucher (NSW, SA) or $40 cash (VIC) for their time and travel expenses, with interviews taking approximately 40 minutes.

Ethical approval

Approval for the qualitative interviews of people who inject BNX film was provided by the Sydney Local Health District Human Research Ethics Committee (HREC), University of New

South Wales HREC, Alfred Hospital HREC and the University of Adelaide HREC. The study conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

Data Analysis

Data analysis was conducted using the NVivo10 program (QSR International.). To ensure consistency, a selection of early transcripts was reviewed independently by three researchers. The analysis involved the use of *qualitative description* (28) where participants' responses were coded by question responses, and subcategories of coded data were derived by grouping the experiences of the participants. Qualitative description does not involve interpretation of the data using themes rather it describes what the participant has stated during interviews, and allows for understanding of a topic from the participants' viewpoint and "entails a kind of interpretation that is low inference, or likely to result in easier consensus among researchers" (29). Content analysis of this nature allows an intense examination of language conducive to "classifying large amounts of text into an efficient number of categories that represent similar meanings" (30). This methodology is well-suited to research which seeks to examine health behaviours (31). Similarities and differences in participants' responses to the various questions posed were examined. Descriptive statistics are also provided for demographic characteristics and details of current opioid treatment.

Participants

Sixteen participants were interviewed. Most participants were male (n=13, 81%), with an average age of forty years (range 20-56 years). Participants were mainly unemployed (11 of 16, or 69%), spending an average of 10 years in education (range 7-12 years) and living in rental accommodation. The majority (n=13, 81%) were receiving opioid substitution treatment (OST) at the time of interview (twelve receiving BNX film and one receiving methadone). Participants prescribed BNX reported an average 16mg buprenorphine daily (range 8-32mg) at the time of interview.

Results

Frequency of injection

Six participants reported injecting BNX film daily (five reported >5 times a day), two reported weekly use, three participants reported occasional use (once per month or less), and five had injected at least once.

Knowledge Acquisition

Participants reported a variety of sources for learning how to inject the film with most (56%, n=9) through the injecting networks of friends and acquaintances, either through being told how to do so (P3, n=6), or by observing others' practices (P11, n=3).

> *I learnt from my mate how to do it, ah, not a mate as much an acquaintance and they, pretty much just said, what I do is basically the same drill as you would mix up you know anything* (P3).
>
> *I learnt through watching my friends, again, just they were using a lot more than I was.* (P11).

Five of the participants reported following the advice given, and as can be seen in the extract above one was told to continue with their usual practice (P3). One participant reported first watching friends and then one of those friends "*recommending that I not try a lot at once so they only cut a quarter off the film and gave it to me* (p11)." This person had just taken prescribed Methadone and reported going into precipitated withdrawal immediately after injecting BNX film.

Other participants (44%, n=7) cited experimentation (P13; n=3) and personal experience (P14; n=4) as their primary source of knowledge, for example:

> *I just tried it again, yeah, and put a lot of water with it because I tried to put a little bit of water with it but it went to like a jelly sort of thing so I put a bit extra water with it and Bob's your uncle* (P13).

> *Just personally through injecting pills and heroin and that, just sort of translated to that* (P14).

The Internet was also identified as a source of 'extra' information regarding injection of BNX film by two participants:

> *I was mainly checking* (the Internet) *to find out whether you could inject it you could say whether it was injectable or whether people had withdrawals, bad withdrawals from it ... The posts on the net could tell you whether you're able to do it* (P4).

Both participants who investigated intravenous use of BNX film via the Internet also asked friends (n=1), and used their own personal experience (n=1). One participant mentioned hearing through the 'grapevine', with another commenting that a number of people had approached him asking how to inject it.

Preparation of the BNX film for injection

Participants provided mixed accounts of the ease with which the film may be dissolved. The general impression given by participants is that BNX film dissolves quite readily in water, usually with a spoon or the syringe plunger to mix it up (75%, n=12), with comments such as "*dissolves quite readily, mix it with the plunger*" (P16), and "*Put into syringe add hot water and keep shaking until dissolved*" (P5) describing the process. There was consistency across the 8 participants who reported that BNX film becomes 'gluggy', or gelatine-like when wet, either in the mouth via the saliva or when water is added to inject. This included 4 participants who also reported it dissolved readily in water, with comments made such as "[The BNX film] *is like chewing gum*" (P14), "[the BNX film] *goes all yucky when wet/ turns into gel*" (P13) and "*bit more viscous than water/ orangey white solution*" (P16).

The majority of participants reported only injecting a 'dry' BNX film dose (never been in someone's mouth, 94%, n=15) rather than a 'wet' dose (removed from the mouth). A number of participants (60%, 9 of 15) reported either slightly heating the water or adding boiling water; six

(40%) used unheated water. One participant reported using lukewarm water when mixing 'wet' BNX film and unheated water when mixing with 'dry' BNX film. The temperature of the water did not appear to affect the gelatine-like nature of the film with: four (50%) of those participants reporting this phenomenon not heating the water; and, two (25%) of those who reported it mixed readily not heating the water.

Reports regarding the volume of water required varied considerably across the sample. Several participants (5 of 8) noted that with low volumes of water the substance became 'gelatine like' requiring the addition of more water to dilute the mixture (e.g. around 80 to 100 units in total of water for 2-4mg film). However, participants also reported the BNX film dissolved readily using less water (e.g. 40-50 units in total for 2-4mg of film).

Twelve (75%) participants reported using a filter: either a cigarette filter (44%, n=7) or cotton wool (25%, n=4) and one did not mention the kind of filter used. It should be noted that all of those reporting gelatine like characteristics had used a filter of some form, whereas only 4 (50%) of those not reporting such characteristics using filters. The excerpt below was a typical description on the process of BNX Film preparation prior to injection:

> *I just put it in water, just like you would heroin or Suboxone or anything like that…used a filter to mix it around 'til it was a different colour, and mixed it around and then just sucked it up, filtered it with a cigarette filter and just shot it up…I didn't heat it at all. Just mix up by itself, it kind of goes like a chewing gum as you mix it* (P14).

Experiences with BNX film injecting

Participants were asked if they had noticed any differences between the experiences of using BNX film sublingually compared to injecting it. Around half of the participants who commented (57% or 8 of 14), reported that injecting BNX film provided a more rapid or immediate effect than sublingual use:

> *You feel it faster* [injecting BNX film], *you're not as sick as quickly, it makes you*

> *feel better quickly …it just makes you feel better a whole lot quicker because otherwise* [taking it sublingually] *you've got to wait an hour to two hours for it to kind of really make you feel better* (P15).

Half of those who reported rapid effects used BNX film daily, with others reporting occasional use (n=2), weekly use (n=1) and single use (n=1).

In the excerpt below, the participant stated that the medication works better when used sublingually or as directed (43%; or 6 of 14):

> *I think it might makes you hang out quicker* [When injected]…*Under my mouth it lasts longer and it's better…like I said after that though it wears out easier…'cause I'd wake up in the morning better fresher and I go get my dose easier if I had it under my tongue* (P8).

Five participants, of whom three had used daily, did describe feeling slightly different in their mood state or in their bodily experience after injection of BNX film. For example participants described getting a "*little perk, like more energy*" (P4), or a "*tingling sensation and motivate you in that sense*" (P5). Other participants (n=2) reported no physical difference between sublingual or intravenous administration of BNX film.

Adverse effects arising from injecting BNX film

Eleven participants (69%) reported some concerns (and some (n=4) reported more than one concern regarding physical health and veins issues) arising from injecting BNX film. Issues included problems with local injecting sites (55%, n=6); broader health concerns such as perceived heart disturbance and puffy hands (37%, n=4); precipitated withdrawal from injecting BNX film after using other opiates (e.g. *Within a short time my world was coming to end for all I knew I thought it was and I was terrified* (P11)(20%, n=3)); and, having a 'dirty hit' which was assumed to be the result of injecting a dose that had come from someone's mouth (13%, n=2). Those who reported local vein problems provided descriptions such as:

> *Destroys your veins, absolutely destroys your veins. Use a vein once and that's it, it has gone for two weeks, and then it's narrowed and it's clogging and if you use it too often it's gone completely. I have got no usable veins in my arms or hands at all*. (P1).

P1 had previously stated that injection of Subutex tablets had destroyed his veins. Of the six participants who reported local injecting site issues, five reported that they had also had previous veins issues when injecting Subutex.

Two participants who mentioned having vein problems also reported having chest pain after injecting BNX film with both providing similar narratives, for example:

> *I was worried for about one week because the section near my heart where I can actually feel, it feels like it's put a resin, a line, a gunky line going into the heart. I could actually feel that for the last 3 or 4 days …I'm assuming that it has worn off it's coming off my body which is very happy, because I was worried about having a heart attack or something* (P4).

Both participants reported frequent injection of BNX film (2-5 times a day). Neither of these participants sought help for their chest pain symptoms, nor did those who had been affected by precipitated withdrawal.

Discussion

This qualitative study examined the experiences of people who had injected BNX film across three Australian jurisdictions at a time when BNX film was being introduced. Our study found that, consistent with previous studies examining knowledge transfer (32, 33), friends and other people who inject drugs remained the most common source of knowledge regarding injecting new pharmaceutical preparations, either by verbal instruction or direct observation (34). Experimentation (35) and prior personal experience of injecting other substances were also drawn upon to inform injecting practices with the BNX film. Such self-experimentation may at

times be associated with the potential for harm – for example, nearly two-thirds of participants reported heating their film-water solution prior to injecting – yet recent laboratory findings suggest heating pharmaceutical opioids may result in greater particulate matter, and increase the risk of thrombosis or infection (36). The internet still does not appear to be a common source of such specific injecting information in this group of individuals.

We also found that participants across sites reported similar preparation techniques, with dissolution in water (either heated or unheated) and filtering using cigarette or cotton filters. Our finding that wheel filters were not commonly used represents one opportunity to target harm reduction messages to those who inject BNX film, as a double filtering process including a wheel filter has previously been shown to be optimal for other pharmaceutical opiates (30). Half of the participants noted that when mixing the BNX film preparation it became 'gelatine like.' This finding is not surprising considering the BNX film consists of hydroxypropyl methylcellulose, a thickener which is soluble but viscous in cold water, and virtually insoluble in a mixture of hot water and alcohol (37). There were however many and varied accounts of the effects of different volumes of water on the solution such that it is difficult to establish a reliable pattern. The findings from this study, taken in context of the existing evidence suggesting that a greater volume of water may reduce morphine crystallisation, indicates that harm reduction messages should include specific information about volume of water and temperature of water when preparing BNX film for injection (30).

Most participants reported injecting the film to enhance its immediate effects, either for more rapid onset, or greater intoxication, but participants generally reported that sublingual administration provided longer-lasting effects. These are consistent with expected pharmacokinetic effects of different routes of administration (38). Over two thirds of participants reported experiencing problems with injecting BNX film including vein issues, precipitated withdrawal, heart concerns and dirty hits. None of those reporting cardiac symptoms or precipitated withdrawal sought medical assistance, and importantly, participants reported a reticence to seek medical assistance when experiencing what they described as serious physical

symptoms. This provides further evidence for concerns raised about the barriers to seeking help for people who inject drugs, especially those who inject their own take-away prescribed OST (34-36).

These findings reinforce the important role of peer-based education strategies in reducing potential harms associated with injecting the BNX film and a need to disseminate this information to users (33, 39, 40). Although the safest route of administration is sublingual, information needs to be tailored to those who inject BNX film. Such advice could include using only cold water and double filtering to minimise the injection of the 'gelatine-like' texture, microbes and other particulate matter. Low threshold services such as needle and syringe programs and peer based services provide opportunities to deliver harm reduction advice to this target group (39, 40). In some countries, injectable opioid treatment options are available for those clients unable or unwilling to cease injection (37, 38).

A limitation of this study was the small sample size and exploratory in nature of the study, and the heterogeneity of prescribing practice across the jurisdictions; that is, each jurisdiction was in a different phase of rolling out BNX film as an OST alternative to buprenorphine-naloxone tablets. One jurisdiction, advanced in this process, therefore yielded the majority of data. Within the sample there was considerable agreement among the narratives across the recruitment sites, indicating that the sample size in this study, while small, was appropriate for this exploratory nature of this work

Conclusion

Understanding how knowledge is acquired about injecting new pharmaceutical formulations that are intended to reduce injection is crucial in developing more effective harm reduction strategies. The data illustrate different practices in preparing the film that do not reflect the best evidence, with respect to heating of water and use of wheel filters. Participants reported peer-networks as a source of knowledge around these preparation practices, highlighting the opportunities for using these existing networks to help transfer knowledge about reducing harm with new

formulations. Recommendations arising from the data gathered in this study include: further qualitative work on knowledge acquisition of injecting practices when new preparations of pharmaceutical opioids are introduced; and the specific ways in which peer-networks can be harnessed for the dissemination of harm reduction messages when novel preparations such as the film are introduced. Although we are well aware of the harms resulting from intravenous use of tablets this study has described such use with a new formulation with an unusual texture that may result in a variety of harms not seen with injection of tablets and as such it is important to continue to monitor this behaviour.

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Declaration of Interest

Briony Larance, Louisa Degenhardt, Nick Lintzeris, and Robert Ali have received untied educational grants from Reckitt Benckiser (RB) for the post-marketing surveillance of buprenorphine-naloxone tablets (2006-2008 and 2012-2013), the development of an opioid-related behaviour scale (2010), and a study of opioid substitution therapy uptake among chronic non-cancer pain patients. Suzanne Nielsen is and has previously been an investigator on untied education grants form Reckitt-Benckiser. Robert Ali has received untied educational grants from Reckitt Benckiser for educational activities and to examine the influence of genetics on treatment outcomes. Nicholas Lintzeris and Robert Ali have received untied educational grants from RB for research on transferring from methadone to buprenorphine, and an RCT evaluating Suboxone

Film. The study design and conduct as well as the interpretation of findings are the work of the investigators - Reckitt Benckiser had no role in the current study.

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