The extent of misuse and diversion of medication for agonist opioid treatment: A review and expert opinions

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Summary

Introduction: Opioid dependence is a major global problem associated with negative health, social and economic outcomes. Agonist opioid treatment (AOT) is the prescription of opioid-containing medicines as a medication for illicit opioid drugs. AOT, as an intervention for opioid dependence, reduces illicit drug use and is proven to improve outcomes by preventing harm and mortality. Provision of access to AOT is associated with the misuse and diversion of opioid-containing medications. This misuse and diversion is a serious public health problem; it results in worsening outcomes with an increased risk to the individual’s health, a lack of progression in recovery and an increase in criminal activity.

Aim: The aim of this paper is to describe the extent of misuse and diversion of AOT medication. Methods: An assessment of the scale of the problem was made based on a defined process including analysis of evidence from a systematic review of published literature and experts’ practice. Results: Results describe rates of misuse of AOT medication ranging from 18 to 81%; diversion occurs in 23 to 39% of cases. Misuse and diversion of AOT is common and is associated with negative outcomes for individuals and society. Conclusion: Greater understanding of the extent and impact of misuse and diversion will assist in the development of strategies to reduce this problem and its significant consequences. As part of ensuring appropriate care for those with opioid dependence, addressing misuse and diversion must be considered an important priority.

Key Words: Extent; misuse and diversion; Agonist opioid treatment (AOT)

1. Introduction

Opioid dependence is a chronic condition associated with serious negative consequences to the individual and society. Untreated opioid dependence harms the individual and society through increased mortality, increased risk of blood-borne virus (BBV) transmission associated with injecting drug use, poor social functioning, loss of economic productivity and criminal justice expenditure [34]. Administration of Agonist Opioid Therapy (AOT) is a cornerstone in the treatment of opioid dependence. It reduces crime and illicit drug use, prevents the spread of blood-borne viruses and protects against overdose [33]. Such treatment is associated with improvements in health, recovery and social functioning and thus might represent a start in a rehabilitation process.

Methadone (MET) is used extensively in the
treatment of opioid dependence. Despite stringent access control, it is frequently diverted to the black market. Mono-buprenorphine (BPN) is associated with a lower risk of fatal overdose compared with MET, but also has significant potential for abuse. Buprenorphine/naloxone (BNX) was formulated to deter misuse while benefitting from the pharmacological advantages of mono-buprenorphine.

Diversion and misuse of AOT are major risks to opioid-dependent individuals and to society as a whole. Estimates of the annual costs of drug-related crime are significant [30].

Effective treatment is the best way of tackling the harm that drug dependency can cause, helping users overcome their addiction, reducing their involvement in crime, sustaining their recovery and enabling them to make a positive contribution to their family and community. Prisoners with a history of intravenous (IV) drug use, in particular, often have multiple and complex health needs, requiring a multi-disciplinary approach and specialized medical care. AOT is associated with sustained reductions in injecting behaviour [13].

For this review of the state of the field, a systematic review of published literature was carried out, and experts in the field of treatment of opioid dependence convened to discuss the extent of misuse and diversion with the aim of summarising evidence from published studies and contributing their experience to the overall picture.

2. Methods

The extent of the problems of misuse and diversion was assessed by a two-step process including review of evidence from a systematic search of published literature and expert recommendations. A systematic literature search was performed on PubMed and Google Scholar, covering the period from 1st January 1993 to 4th June 2014, to identify publications reporting diversion or misuse of buprenorphine- and methadone-containing medications. 135 publications were found describing buprenorphine diversion and 153 describing misuse. 126 publications were found describing methadone diversion and 231 describing misuse.

Two independent reviews of the initial literature search results were conducted, classifying publications based on relevance to this study. Of the total 645 sources identified, 530 were dismissed due to a lack of relevant study data found upon review of the title and abstract; 26 were judged not relevant due to “subjective comments”; 35 were dismissed due to a lack of relevant study data found on review of summary or entire article; 16 were judged not relevant due to duplicated data after the updated literature review. After these two rounds of review, 38 sources were identified as relevant for the discussion. Only those reporting study data on the extent of the problem are presented in this paper.

In addition to the systematic literature review, the opinion of experts in the field was sought. Eight experts from the UK, Germany, Spain, Norway, Finland and Italy (the Faculty) were invited to express their opinion with regards to the extent of misuse and diversion in an online survey. The survey questions focused on the extent of the problem with the aim to generate an overall consensus. A meeting was subsequently held in Rome on 23rd June 2014. Each member of the Faculty reviewed the relevant publications and presented the current status and knowledge of misuse and diversion of medicines prescribed for opioid dependence care in their locality.

3. Results and Discussion

The identified relevant publications provided an overview of the current understanding of the extent of misuse and diversion of AOT. The approach employed by the Faculty confirmed that the data outlining the extent of misuse and diversion is very limited.

The majority of the clinical trials identified report on the safety profiles of AOT medication and generally describe the potential for misuse. Review of randomised clinical trials showed that BNX has a comparably better safety profile [12] and many misusers do not achieve a significant “high” when injecting BNX intravenously [6]. One multicentre trial reports that BNX, compared to BPN, was the agonist opioid treatment medication preferred by 54% of the study population [8]. Post-marketing surveillance reports show that BNX is more successful than BPN in treatment settings and has a better adherence rate [22].

Real world data on the extent of misuse in each locality is better defined in published surveys and interview reports. MET diversion and misuse have been reported extensively for many years in the USA [32] and Australia [15]. Significant problems exist in Scotland, where 47% of drug-related deaths in 2011 were attributable to MET misuse and diversion [21]. Interviews carried out with 513 AOT clients in Australia reported that 17% injected MET on top of their treatment medication, 23% injected BPN and 9% injected BNX. The report concluded that, compared to other
AOT treatments, BNX was injected less frequently and by fewer injecting drug users [9]. Interviews with 440 AOT clients in Australian pharmacies and clinics reported that 18% of participants admitted to having inhaled BPN. Most of these were people aged 35 or younger and had been previously incarcerated [14]. Another study carried out in New Zealand reported that 81% of a 98 patient sample admitted intravenously misusing BPN; 65% of the patients had BPN in their urine. These statistics were slightly lower for BNX—57% and 43% respectively [25]. A retrospective observational study of data collected in Australia reported that misuse of opioid replacement therapies represented less than 5% of all illicit opioid injections [31]. In Finland, mono-buprenorphine was the most frequently misused drug by injection among 73% of the opioid-dependent individuals surveyed, with most illicit supplies coming from France [3]. A study showed that homeless IDUs were more likely to have injected high-dose BPN than those who were not homeless (67% vs. 47%), and their injection behaviours were more likely to be unsafe. Homeless IDUs were less likely to receive medical follow-up care and were less well informed about the correct way of using high-dose BPN than non-homeless IDUs [5].

There are several motivations for misuse: Schuman-Olivier et al reported on 129 outpatient-based opioid treatment admissions in the USA, concluding that the associated decrease in illicit AOT use upon access to legal prescriptions indicates that misuse is primarily motivated by attempts to self-treat opioid dependence, pain and depression [27]. Another survey of 51 people in self-administered syringe exchange programmes reported that 76% admitted to obtaining BNX illicitly and the reasons for misuse varied: 66% aimed to stop using other opioids and 69% wanted to “get high” [4]. A survey in Germany revealed that the main reasons for misuse and diversion are insufficient medication dose, no heroin available, no physician available or low price. The same survey showed that 8% of patients in AOT have used non-prescribed medicine in the last 24 hours and 20% have done so in the last 30 days. 10% of AOT patients injected AOT medication [26]. Self-medication due to restricted access to treatment and sub-therapeutic dosing are frequent motivators for diversion and misuse, and this is consistent among global sources of data [36].

Diversion is equally difficult to describe, as there is a lack of real world data published. In Australia, a survey of 1278 authorised AOT prescribers highlighted uncertainties in assessing the diversion of AOT medication. It was reported that most prescribers perceive that patients adhere to AOT [17]. Additionally, interviews with 86 health care professionals in Sweden showed that diversion and illicit use of MET and BPN is not perceived to be a serious problem [24]. Interviews with 40 pharmacists and pharmacy technicians in community pharmacies, outpatient hospitals, and clinics in the USA reported that 85% of respondents indicated that patients did not cause problems at their pharmacies and expressed positive attitudes and perceptions about AOT patients treated with BNX [23].

However, across various European countries, 16–39% of AOT patients have diverted their AOT medication [7]. A US cross-sectional, open-ended survey of 49 individuals entering opioid addiction treatment programs reported that all subjects had diverted BNX and 61% had obtained illicit drugs from an individual holding a legitimate prescription for BNX [20]. A French study reported that thefts and forged prescriptions were commonly utilised to divert prescription drugs. Of 11027 described substances in the study, 11% were illegally obtained [11]. Divers- ion is becoming a recognised problem in Norway, due to the increased incidence of MET attributed mortality and a corresponding halving of heroin attributed mortality [2]. Informal surveys show that the primary drivers of diversion in Norway are economic. A clinical trial carried out by Fudala and colleagues showed that opioid dependent subjects were not willing to spend significant amounts of money on BNX injections [12]; however, recent UK research reveals that the cost of diverted AOT medication in prisons is higher than that on the street, indicating that a lack of supply of illicit drugs may increase the desirability of diverted prescribed medication [35]. A survey by Alho et al [1] reports that 80% of the participants had experience with intravenous BNX; however, the street price of this medication is significantly lower than BNP (€12 and €28 respectively) [29]. Finally, a UK survey report states that the most common reason for diverting MET was to “help another substance user out” [10].

Schuman-Olivier et al reported a survey of 369 clinicians who examined the perceived danger from BNX diversion. 40% of clinicians believed that BNX diversion increases accidental overdoses [28]. A US post-marketing surveillance survey of physicians’ perceptions of BNX diversion and abuse states that 46% of the physicians believed that BNX was diverted, but 44% believed that illegal use was for self-management of withdrawal and 53% believed that the source of the medication was substance abuse
### Table 1: Typical results of extended review of literature: misuse of AOT medication

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Method</th>
<th>Evidence of extent of misuse</th>
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<tbody>
<tr>
<td><strong>Clinical trials</strong></td>
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<tr>
<td>Fudala P.J., et al [12]</td>
<td>1998</td>
<td>USA</td>
<td>Inpatient randomized double-blind trial, crossover design: 10 subjects were stabilized on morphine followed by injection of placebo, morphine, BPN, BNX, or naloxone</td>
<td>The trial showed that although the combination of buprenorphine with naloxone in a 4:1 ratio produced opioid antagonist-like effects, its potential for intravenous abuse by opioid addicts was limited.</td>
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<tr>
<td>Comer S.D., et al [6]</td>
<td>2010</td>
<td>USA</td>
<td>8-9 week inpatient trial of 12 intravenous heroin users maintained on each of three different sublingual buprenorphine doses</td>
<td>Study showed that IV BNX was self-administered less frequently than BPN and a low sublingual dose of BPN was used. BNX was less “liked” than BPN.</td>
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<tr>
<td>Daulouède J.P., et al [8]</td>
<td>2010</td>
<td>France</td>
<td>Prospective, open-label, multicentre trial compared preferences for BPN and BNX in 53 opioid-dependent patients stabilized on buprenorphine</td>
<td>At the end of the trial, 54% of patients preferred BNX, 31% preferred BPN, and 15% had no preference; most patients (71%) wished to continue treatment with BNX. Patients on BNX treatment were believed to be less likely to engage in harmful behaviour.</td>
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<tr>
<td><strong>Surveys/ interviews</strong></td>
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<tr>
<td>Alho H et al [1]</td>
<td>2007</td>
<td>Finland</td>
<td>Survey distributed to attendees at a Helsinki needle exchange program over 2-weeks in April, 2005</td>
<td>68% of the respondents had tried IV BNX and 66% of those who tried it, took it again or even regularly. 80% reported that they had a “bad” experience with the combination product, while less than 20% reported it “similar” to experiences with IV BPN. Respondents were willing to pay a significantly higher street price for BPN than for BNX.</td>
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<tr>
<td>Bazazi A.R., et al [4]</td>
<td>2011</td>
<td>USA</td>
<td>Survey was self-administered among 51 syringe exchange program and community outreach program injecting opioid users and 49 non-injecting opioid users in Providence, RI</td>
<td>76% of participants reported having obtained BNX illicitly. 86% reported the use of diverted BNX. 74% who had used BNX reported doing so to treat opioid withdrawal symptoms and 66% to stop using other opioids. 69% of non-IDUs reported using BNX to “get high”.</td>
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<tr>
<td>Degenhardt L., et al [9]</td>
<td>2009</td>
<td>Australia</td>
<td>Regular IDUs were interviewed about injecting behaviour annually in each Australian capital city (900 per year) and data for 2003-2007 were used</td>
<td>Injection of (17%) MET, (23%) BPN and (9%) BNX was more likely to occur among those injecting other on-top pharmaceutical opioids.</td>
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<tr>
<td>Horyniak D., et al [14]</td>
<td>2011</td>
<td>Australia</td>
<td>Cross-sectional sample of 440 AOT clients was recruited through pharmacies and clinics in 3 Australian jurisdictions, and interviewed face-to-face using a structured questionnaire</td>
<td>18% reported having ever inhaled BPN; these were more likely to: be aged 35 or younger, to have been in prison or to have ever injected BPN. Clients from New South Wales and Victoria were significantly less likely to have ever inhaled BPN than those from South Australia.</td>
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<tr>
<td>Robinson G.M., et al [25]</td>
<td>1993</td>
<td>New Zealand</td>
<td>Two surveys of 12 months duration were undertaken on opioid users presenting to the Wellington Alcohol and Drug Centre before and after the introduction of a combination BNX</td>
<td>81% of patients reported misuse with IV BPN and 65% of patients had BPN in the urine. In a follow up survey, 57% reported misuse of BNX and 43% had BNX in the urine. One-third of the patients who used IV BNX reported instances of withdrawal symptoms, and subjectively the drug was less attractive to misusers.</td>
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patients [16].

Overall, it is considered that inadequate dosing, treatment time limitations, and concomitant polydrug abuse are indicators of poor treatment results. External determinants of misuse and diversion include demographic, treatment and community factors, such as accessibility of treatment, while internal determinants are most commonly self-medication, pleasure, source of funding and relationships with other users. There are important potential differences between different types of therapy in relation to the likelihood of users engaging in criminal activity. Including abuse-
deterrent medications like BNX in AOT has been demonstrated to reduce the likelihood of misuse by injection and diversion. The clinical evidence so far surrounding MET, BPN and BNX suggests that some opioid agonist pharmacotherapies are more suitable for unsupervised therapy than others, which should be an important consideration when implementing regulations on treatment delivery [19].

Although further work is required to obtain conclusive evidence of the epidemiology of the misuse

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<tr>
<td>Monte A.A., et al [20]</td>
<td>2009</td>
<td>USA</td>
<td>Cross-sectional, open-ended survey was administered to 51 individuals entering opioid addiction treatment programs in two New England states. The authors obtained formative information about the knowledge, attitudes, beliefs, practices, and street economy of BNX diversion</td>
<td>49 subjects had diverted BNX to modulate opiate withdrawal symptoms arising from attempted “self-detoxification,” insufficient funds to purchase preferred illicit opioids, or inability to find a preferred source of drugs. High proportion of individuals in the study locations who sought treatment for opioid addiction self-reported the purchase and use of diverted BNX.</td>
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<tr>
<td>Raisch D.W., et al [23]</td>
<td>2005</td>
<td>USA</td>
<td>Pharmacists and technicians participated in a clinical trial of opioid dependence treatment using BNX.</td>
<td>Most pharmacy personnel (77.5%) involved with this study were not more concerned about theft or break-ins and would be willing to participate in opioid dependence treatment as the medication became available commercially (70%). The majority of respondents (85%) indicated that patients did not cause problems at their pharmacies.</td>
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<tr>
<td>Richert T., et al [24]</td>
<td>2013</td>
<td>Sweden</td>
<td>Study based on surveys and structured interviews on drug use among various populations of young people, in addition to qualitative interviews with 86 informants who encounter adolescents who are using illicit drugs</td>
<td>Illicit use of MET and BPN is rare among young people in Sweden. According to high school surveys, less than 0.1% have tried these substances. However, several informants expressed concern that MET and BPN may cause fatalities among young drug users without an opioid tolerance.</td>
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<tr>
<td>Schuman-Olivier Z., et al [28]</td>
<td>2013</td>
<td>USA</td>
<td>Participants (n = 369) completed a 34-item survey in 2010 during two national symposia on opioid dependence. Multivariable regression was conducted, examining the relationship of perceived danger from BNX diversion with clinician characteristics and their beliefs about BNX treatment and diversion</td>
<td>The belief that BNX diversion increases accidental overdoses in the community was strongly associated with perceived danger from BNX diversion. Clinicians with greater BNX patient experience were more likely to believe that treatment access barriers are the major cause of BNX diversion.</td>
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<tr>
<td>Duffy P et al [10]</td>
<td>2014</td>
<td>UK</td>
<td>Questionnaires completed with 886 past year users of MET recruited in and out of prescribing agencies. Topics covered included current prescribing, obtaining/providing MET, reasons for using illicit MET and other substance use.</td>
<td>Missing appointments (prescription pick-up or reviews) were the most common reasons for use of diverted MET but the most common course of action in these circumstances was to use other street-sourced substances. Topping up dosage levels was also a common reason for obtaining illicit MET.</td>
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<tr>
<td>Johanson C.E., et al [16]</td>
<td>2012</td>
<td>USA</td>
<td>Applicants to substance abuse treatment and physicians certified to prescribe BPN were surveyed about their perceptions of BNX diversion and abuse</td>
<td>46% of the physicians believed that BNX was diverted, but 44% believed illegal use was for self-management of withdrawal and 53% believed the source of the medication was substance abuse patients. Measures of diversion and abuse of BNX increased from 2005 to 2009.</td>
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</table>
and diversion of AOT across all countries, it is clear that misuse and diversion are complex and increasing challenges for healthcare professionals and legislators. Specific actions that might reduce some of the potential harm of misuse and diversion include improving access to treatment and optimizing dosing practices; although there is no clear correlation between dosing and misuse in the available evidence, it is evident that AOT medication is commonly misused due to self-medication and/or seeking relief from withdrawal symptoms. In fact, a study comparing individuals misusing street MET in Italy with users whose primary drug of abuse was heroin differentiated street MET use from heroin use and indicated that methadone use could constitute a form of harm reduction [18]. Therefore, it is important that access to opioid addiction treatment is not restricted, but that potential strategies to reduce the health problems related to misuse and the criminality rates related to diversion, such as the use of the most abuse-deterrent forms of agonist opioid medication, are implemented. All relevant papers describing misuse and diversion are summarised in Table 1 and Table 2.

4. Conclusion

Misuse and diversion of opioid pharmacotherapy remain significant worldwide public health issues. Adverse consequences may include overdose fatalities, poor treatment outcomes and compromised public support for medicalization of opioid dependence as a chronic condition that requires long-term opioid prescribing. The use of abuse-deterrent formulations or “safe forms” of AOT may present an opportunity to minimise the risks of diversion and misuse while supporting broad treatment access, patient safety and long-term recovery.

There was an overall strong consensus between the experts that the problem of misuse and diversion requires more attention from the treatment community. Experts recognise the need for greater understanding of extent and impact of misuse and diversion, which could lead to improvements in the delivery of opioid dependence care and better regulations for treatment. Concerns about diversion and misuse cannot be ignored in the development of more efficient treatment systems designed to support patient recovery and enhance public health outcomes. Treatment policy makers and stakeholders in the treatment community should consider additional methods, informed by further relevant studies, for optimization of the treatment delivery system.

References

5. Dale-Perera A., Goulão J., Stöver H. (2012): OPPIDUM is an annual national study performed via anonymous questionnaires at specialized care centres that included subjects presenting a drug dependency or under AOT. In 2008, 5542 subjects were included and described the consumption of 11 027 psychoactive substances, of which 63.8% were prescription drugs. Among them, 11% were illegally obtained. The different illegal acquisition ways were ‘street market’ (77.6%), ‘gift’ (16.6%), ‘theft’ (2.3%), ‘forged prescription’ (2.3%), and ‘internet’ (0.7%).


an interim report by professor John Strang, chair of the expert group.


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Contributors
All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest
All authors have no conflict of interest.