BRIEF REPORT

Treating codeine dependence with buprenorphine: Dose requirements and induction outcomes from a retrospective case series in New South Wales, Australia

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Abstract

Introduction and Aims. Codeine dependence is an emerging public health concern, yet no studies have specifically examined the treatment of codeine dependence. Given the lower potency of codeine it cannot be assumed that buprenorphine dose requirements for heroin dependence will generalise to codeine. This is the first study to examine buprenorphine treatment for codeine dependence.

Design and Methods. Retrospective case series of 19 codeine-dependent treatment entrants who received sublingual buprenorphine maintenance treatment through six specialist inpatient and outpatient treatment centres. Baseline codeine doses and buprenorphine dose at days 7 and 28 were collected, in addition to details on general demographics, pain and mental health, substance use and outcomes after 28 days of buprenorphine treatment.

Results. A significant linear relationship was found between initial codeine dose and dose of buprenorphine given at days 7 and 28 for the codeine dose range of 50–960 mg day\(^{-1}\) (mean: 564 mg; 95% confidence interval 431–696 mg). Median buprenorphine dose was 12.0 mg (interquartile range 9.5 mg, range 4–32 mg) at day 7 and 16.0 mg (interquartile range 13.5 mg, range 4–32 mg) at day 28. Buprenorphine doses received were markedly higher than estimated codeine doses based on standard dose conversion tables.

Discussion and Conclusions. With increasing presentations relating to codeine dependence, these findings provide important guidance to clinicians. Buprenorphine doses were consistently higher than doses estimated based on the dose of codeine consumed, and were comparable with doses used in the treatment of dependence with heroin and more potent prescription opioids. [Nielsen S, Bruno R, Murnion B, Dunlop A, Degenhardt L, Demirkol A, Muhleisen P, Lintzeris N. Treating codeine dependence with buprenorphine: Dose requirements and induction outcomes from a retrospective case series in New South Wales, Australia. Drug Alcohol Rev 2016;35:70–75]

Key words: codeine dependence, buprenorphine maintenance, induction, opioid analgesic.

Introduction

Codeine is the most commonly used opioid analgesic globally [1]. Severe harms have been reported with codeine use, particularly from consumption of high doses of combination products [2–7]. Growing numbers of patients with codeine dependence are attending general practice, hospital and specialist drug...
treatment services [7–10], and increasing codeine-related mortality is reported in multiple countries [11–13] highlighting the urgent need for effective codeine dependence treatment.

There is only a scant literature relating to treatment of codeine dependence. Buprenorphine is a treatment option for opioid dependence with a strong evidence base [14], predominantly in heroin users, with a small number of studies of prescription opioid users [15,16] and no studies specifically examining codeine-dependent people.

Previous research has identified that people experiencing codeine dependence differ from other opioid-dependent people on a number of important demographical and substance use characteristics [17,18]. Previous studies on buprenorphine dose in heroin and prescription opioid users have identified that demographical and drug use characteristics such as age, education, opioid type, route of opioid administration, other substance use, pain, withdrawal symptoms and craving are associated with buprenorphine dose [19,20]. As people who use codeine have been identified to differ from other opioid users on a number of these characteristics, it may be expected that required buprenorphine dose may differ as well. Additionally, codeine has a considerably lower potency than opioids such as heroin, morphine, oxycodone or methadone, and codeine-dependent people use lower doses of opioids when opioid dosages are compared in oral morphine equivalents [18]. It is uncertain if buprenorphine doses recommended for the treatment of opioid dependence (4–32 mg daily [21,22]) are safe or appropriate for the treatment of codeine dependence. For more potent opioids, low starting doses and slow induction are associated with poorer retention and more opioid use [14,23]. While less likely given the safety profile of buprenorphine, this must be balanced with the possibility of opioid overdose if the starting dose of buprenorphine is too high. The aim of this research was to address these opposing concerns by examining buprenorphine dose requirements for codeine-dependent people.

**Design and Methods**

**Design**

A retrospective case series of patients that presented for treatment of codeine dependence transferred to sublingual buprenorphine maintenance treatment, as part of a larger study examining pharmaceutical opioid treatment presentations [18].

**Participants**

Cases where codeine was the principal drug of concern were drawn from patients who had presented to inpatient and outpatient specialist drug treatment services in metropolitan and regional New South Wales, Australia (The Langton Centre, Royal Prince Alfred Hospital, Concord General Repatriation Hospital, John Hunter Hospital, Newcastle Pharmacotherapy Service and the Calvary Mater Hospital). These represent services with specialist experience in the treatment of pharmaceutical opioid dependence, and as such, the clinical care provided by these experienced clinicians is considered to represent best practice. We included patients where maintenance sublingual buprenorphine (±naloxone) treatment was provided, and codeine dose prior to starting on buprenorphine, and buprenorphine dosing information for days 7 and/or 28 was available (in three cases, buprenorphine dose was available at only one time point). Cases where transdermal buprenorphine was prescribed ($n=2$), where no buprenorphine dose data were available ($n=2$), and one case where codeine was not the only opioid used were excluded.

**Procedures**

Data collection periods covered 12–24 months at each site, with all cases collected over the period March 2010 to November 2013. Data were extracted from medical records by two researchers (SN, PM) using a specifically designed data extraction form. Demographical information (age, gender), details of the presentation including opioid use, other substance (including non-opioid) use, previous drug treatment history, pain and other comorbidities reported, buprenorphine dose at days 7 and 28, and outcome of buprenorphine stabilisation including any complications, were reported. Oral morphine equivalent doses were calculated using initial codeine dose and standard dose conversion calculations [24]. Study procedures were approved by the Sydney Local Health District Ethics Review Committee.

**Analyses**

Codeine doses were calculated based on reported daily codeine consumption at treatment entry. Where patients reported a dose range, the mid-point of the dose range was used to calculate the dose. We created scatter plots of codeine dose prior to buprenorphine stabilisation versus buprenorphine dose at days 7 and 28. Linear and quadratic models were fit to the data. We tested for outliers based on the day 7 data and removed two cases with standard residuals greater than 2.2, removing these from analyses from both days 7 and 28 for consistency. Raw data (all cases) are presented in Table 1.
Table 1. *Actual and estimated buprenorphine doses at days 7 and 28*

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<tr>
<th>Codeine dose at treatment entry (mg per day)</th>
<th>Estimated BPN dose (mg day⁻¹) using standard dose conversion (OME) tables</th>
<th>BPN dose received day 7</th>
<th>Ratio: estimated OME dose to actual dose (%)</th>
<th>Estimated BPN dose using linear model</th>
<th>Ratio: linear model estimated dose to actual dose (%)</th>
<th>BPN dose received day 28</th>
<th>Ratio estimated OME dose to actual dose (%)</th>
<th>Estimated BPN dose by linear model</th>
<th>Ratio linear model estimated dose to actual dose (%)</th>
<th>Outliers removed from linear model analyses</th>
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*indicates outliers removed from analyses. BPN, buprenorphine; NA, buprenorphine dose not available at time point; OME, oral morphine equivalent.
Results

We report on 19 codeine-dependent people who received maintenance sublingual buprenorphine treatment. The cases included represent the majority of cases where sublingual maintenance buprenorphine was the treatment (86% or 19/22). Buprenorphine induction occurred in: hospital inpatient (n = 2), inpatient drug treatment (n = 3) and outpatient drug treatment setting (n = 14). Most (n = 16, 84%) were women, mean age of 41.2 (standard deviation 9.3) years, and a mean of 7.7 [95% confidence interval (CI) 4.2–11.3; median 3, range 1–25] years of codeine use. A significant minority reported current nicotine (42%) and benzodiazepine (42%) use, a third (32%) reported current problematic alcohol use. Most (63%) commenced opioid use for a pain condition. Four participants (25%) reported a heroin use history; none reported current heroin or stimulant use.

Mean dose of codeine at baseline was 564 mg (95% CI: 431–696 mg). Median buprenorphine dose was 12.0 mg (interquartile range 13.5 mg, range 4–32 mg) at day 7 and 16.0 mg (interquartile range 13.5 mg, range 4–32 mg) at day 28 (Figure 1). A significant linear relationship was found between initial codeine dose and buprenorphine dose at day 7: β = 0.013, t(14) = 3.63, P = 0.03, adjR² = 0.45) and day 28, β = 0.015, t(13) = 4.69, P = 0.05, adjR² = 0.21, with no evidence of significant quadratic relationships (all P > 0.21). Comparisons of buprenorphine doses received were compared with estimated buprenorphine doses calculated with standard dose conversion tables (Table 1). Calculated doses were considerably smaller than the actual dose received at days 7 and 28.

All participants were retained in maintenance treatment at 1 month following buprenorphine induction. Most cases reported no additional opioid use; unsanctioned use of over-the-counter codeine and/or oxycodone was documented in four cases. Sedation was reported in one case, with the dose then reduced by 20%. There was no indication in other cases that doses were too high, and no adverse events such as overdose were reported in the 28-day period.

Discussion and Conclusions

This is the first report on buprenorphine dosing for the treatment of codeine dependence. The findings are striking in two important ways. Firstly, estimated doses of buprenorphine calculated using accepted references differed by a mean of 10-fold from the actual buprenorphine doses that patients received. This means that clinicians using standard opioid dose conversion calculations, as is common practice in some areas of medicine [25], are at risk of grossly underestimating the buprenorphine dose that patients may need. This has the potential to contribute to poor clinical outcomes, as previously demonstrated with lower induction doses and slower induction speeds for dependence to more potent opioids [14,23]. The second important finding is that high-dose buprenorphine (up to 32 mg daily) appears to be safe and well tolerated in this group of codeine-dependent patients. Consistent with current guidelines [21], most patients achieved a ‘maintenance’ dose by day 7. There was one case of reported sedation, necessitating a 20% dose reduction, with no other complications documented in relation to buprenorphine dose.

The dose ranges of buprenorphine observed in this study are comparable with standard doses used in the treatment of heroin dependence, and within dose ranges in national guidelines [21]. These findings suggest that despite the lower potency of codeine and the identified demographical and substances use differences in codeine-dependent populations [7,17], the buprenorphine doses received by these codeine-dependent patients are remarkably similar to other opioid users. A possible explanation for this finding is the high codeine doses, combined with the long use histories, which may result in similar levels of opioid neuroadaptation, despite the use of a weaker opioid. Considerable inter-individual variability was observed,
highlighting the importance of individual dose titration as best practice [21]. This variability may be partially explained by the known genetic CYP2D6 polymorphism in codeine metabolism, where much higher or lower amounts of morphine are metabolised from a given dose of codeine in different individuals [26,27]. Additionally, this sample had a number of characteristics that may impact on the buprenorphine dose, such as pain, alcohol misuse and benzodiazepine use [20,21].

The central message for clinicians, who are increasingly seeing codeine-dependent patients, is that despite the lower potency of codeine, these codeine-dependent patients receive buprenorphine doses that are similar to other opioid-dependent people, and consistent with current guidelines. This is consistent with previous research with more potent prescription opioids [28].

There are caveats to this research using a retrospective case series, including possible selection bias and the lack of a comparator control group. Data in patient files may be missing or inconsistently recorded. Further, the size of the sample is small, preventing examination of other potential covariates such as pain history. The variation in prescribing practice between treatment settings may have contributed to variations in dose. These represent important areas of future work to better understand dosing practices with buprenorphine. Finally, we do not know how well these 19 patients represent codeine-dependent people more generally and recommend caution in extrapolating these findings.

Despite these caveats, this study effectively demonstrates that these codeine-dependent patients receiving sublingual buprenorphine maintenance treatment for opioid dependence appear to have buprenorphine doses that are consistently higher than doses estimated based on the doses of codeine consumed, and which are comparable with the dose ranges observed in the treatment of opioid dependence more generally.

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