

# The effect of transdermal opioid use on breakthrough opioid and sedative prescribing for rural patients with chronic pain in Northwest Tasmania: a longitudinal study

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**Purpose:** The aim of the study reported here was to determine the frequency of prescribing of immediate-release (IR) opioids, and benzodiazepines, with both oral sustained-release (SR) and transdermal (TD) opioid maintenance treatment, in a rural population with chronic non-cancer pain (CNCP).

**Subjects and methods:** A longitudinal study measuring IR opioid and benzodiazepine dispensed prescriptions (scripts) by route of maintenance opioid administration over time (monthly for 1 year). Subjects were opioid-treated CNCP patients from Northwest Tasmania. The outcome measures of mean monthly scripts were analyzed using generalized estimating equations with robust standard errors.

**Results:** Details of 12,191 dispensed scripts were obtained from 140 subjects over 12 months. Mean monthly IR scripts with oral SR opioid maintenance were 0.21 (95% confidence interval [CI] 0.10; 0.32). With TD opioid maintenance, this was nonsignificantly lower ( $P = 0.06$ ) at 0.04 (95% CI 0.00; 0.15). Mean monthly benzodiazepine scripts with oral SR opioids were 0.47 (95% CI 0.32; 0.62), and unchanged ( $P = 0.84$ ) for TD opioids at 0.45 (95% CI 0.28; 0.62).

**Conclusion:** There was a nonsignificant trend toward reduced prescribing of IR opioids with TD opioid-maintained, compared with oral SR opioid-maintained, CNCP rural patients. Benzodiazepine prescribing was similar for both groups. The rationale for use and the provision of breakthrough opioid analgesia for CNCP patients are complex, both for patients and their prescribers, while the regular use of benzodiazepines compounds the sedation from the subjects' maintenance opioid. The prolonged analgesic affect of TD opioids may benefit rural and remote CNCP populations and reduce the risk of diversion associated with oral opioids.

**Keywords:** benzodiazepines, rural health, drug diversion, chronic non-cancer pain

## Introduction

In 2005, transdermal (TD) buprenorphine in matrix form became available in Australia for "chronic severe disabling pain which is not responding to non-narcotic analgesics."<sup>1,2</sup> In 2006, the matrix version of TD fentanyl was introduced.<sup>3,4</sup> Between 2007 and 2010, longitudinal observational studies were conducted with opioid-treated chronic non-cancer pain (CNCP) subjects living in rural Northwest Tasmania, Australia.<sup>5,6</sup> They have demonstrated that the use of TD opioids, when compared with oral sustained-release (SR) opioids, significantly reduced the need for general practitioner contact and may have reduced total health care activity, while the personal time and expenses involved in accessing this health care were equivalent.

Many of the study subjects were additionally prescribed oral immediate-release (IR) opioids for breakthrough pain episodes and sedative benzodiazepine medicines for anxiety or insomnia. The rationale for use and the provision of breakthrough opioid analgesia for CNCP patients are complex both for patients and their prescribers, while the regular use of benzodiazepines compounds the sedation from the subjects' maintenance opioid.<sup>7,8</sup> This study measured the prescribing of oral IR opioids and benzodiazepines in this population. Differences between oral SR- and TD opioid-maintained subjects were investigated.

Northwest Tasmania is a rural area of 22,492 km<sup>2</sup> with a population in 2008 of 111,100 people, who mainly live on the northwest coastal strip.<sup>9,10</sup> Access to health care is often more difficult here than in metropolitan areas of Australia, due to the distance and the fewer specialist medical and allied health services that are available locally. The aim of this study was to determine whether the benefits of reduced health care utilization with TD opioids are negated by an increased use of oral IR opioids and/or benzodiazepines, when compared with oral SR opioid maintenance. If so, the value of TD opioid maintenance in these rural CNCP patients would be limited.

## Subjects and methods

### Subjects

Subjects were recruited from a longitudinal observational study of health care utilization by opioid-treated CNCP patients at completion (2010).<sup>5</sup> The inclusion criterion was consent to access of their Pharmaceutical Benefits Scheme (PBS) data for the most recently available calendar year (2008). The PBS is a Commonwealth of Australia scheme that provides approved medicines to all Australian residents at reasonable cost.<sup>11</sup>

The longitudinal observational study subjects were recruited from medical practices and hospital clinics in Northwest Tasmania via information posters placed in all patient waiting areas and from information provided by their general practitioners. Inclusion criteria were: having opioid-treated CNCP and being 18 years of age or older, able to complete a monthly self-report datasheet, and competent to give informed consent. The exclusion criteria were the converse.

### Study design

This longitudinal study measured the subjects' use of the PBS IR opioid and benzodiazepine dispensed prescriptions over time (monthly for 1 year). Subjects were free to change

their maintenance opioid medications (type, route, and dosage) throughout the study, as prescribed by their treating doctor(s). The study was approved by the Human Research Ethics Committee (Tasmania) Network (approval number: H0009695).

In Australia, for individual patient use, controlled SR and IR opioids are dispensed in packs of 20 doses. TD opioids are dispensed in packs for use over a period of 2 weeks. Benzodiazepines are supplied in packs of 50 doses.<sup>12</sup>

### PBS data

This data provided, by subject, the date of supply and the PBS item code of each prescription issued. Coding, using the World Health Organization Anatomical Therapeutic Chemical classification system, enabled identification of the subjects' maintenance oral SR or TD opioids, together with IR opioids and benzodiazepines<sup>13</sup> (Table 1). The PBS item code was used to determine the route and preparation of the opioid medications. All medicines were oral preparations apart from buprenorphine and fentanyl, which were TD.

### Statistical analysis

Longitudinal (panel) data consist of a panel variable and a time variable. Here, the panel variable was the subject and the time variable was the prescription month. Each subject's monthly prescriptions were uniquely identified by these two variables. The number of monthly oral IR opioid and benzodiazepine prescriptions, by the subjects' maintenance opioid group, was repeatedly compared over the study period. The variation in monthly prescriptions by an individual subject over time was less than that between subjects. This correlation was recognized and dealt with statistically.

The study outcome variables were the mean monthly IR opioid and benzodiazepine prescriptions. The predictor variable was the long-acting maintenance opioid group,

**Table 1** World Health Organization Anatomical Therapeutic Chemical (ATC) codes<sup>13</sup> and names used

	ATC code	ATC name
Opioids	N02AA01	Morphine (SR/IR)
	N02AA05	Oxycodone (SR/IR)
	N02AB03	Fentanyl (TD)
	N02AC	Methadone
	N02AE01	Buprenorphine (TD)
Sedatives	N05BA01	Diazepam
	N05BA04	Oxazepam
	N05BA12	Alprazolam
	N05CD02	Nitrazepam

**Abbreviations:** ATC, anatomical therapeutic chemical; IR, immediate release; SR, sustained release; TD, transdermal.

either oral or TD, with the most frequent being oral SR opioid maintenance. This was used to establish the reference mean of oral IR opioid and benzodiazepine monthly scripts (the intercept). The change in these means (the coefficient) that occurred if the predictor variable was present was calculated and converted to point estimates using linear combinations of estimators. Analysis was performed using Stata I/C (v 11; StataCorp, College Station, TX, USA) statistical software. The Hubert–White sandwich estimator was used to obtain robust standard errors that adjust for clustering on individual subjects.<sup>14</sup> A  $P$  value  $< 0.05$  was considered statistically significant.

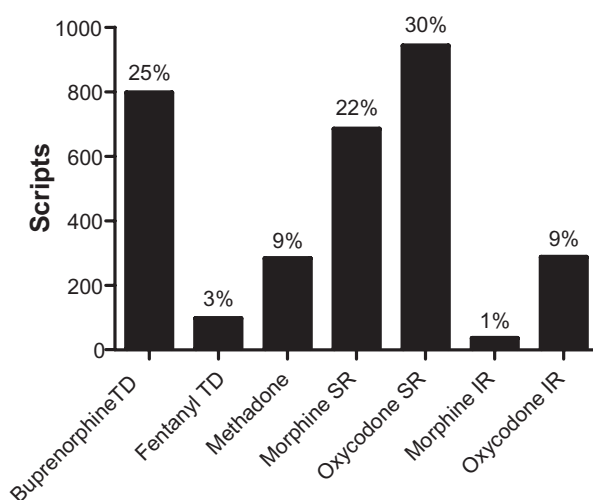
## Results

Of the 198 subjects who provided data to the observational studies previously described,<sup>5,6</sup> 148 (75%) consented to the release of their associated PBS data. Four of these received their medications through the Department of Veterans' Affairs and four had ceased opioids. This provided 140 (71%) available datasets, with details of 12,191 dispensed prescriptions for the study year.

There were 3133 controlled opioid prescriptions dispensed. For this study, methadone was included in the oral SR group, as twice daily dosing is recommended for CNCP therapy<sup>15</sup> (Figure 1). This produced 1254 subject months of data classified by maintenance opioid group (Figure 2).

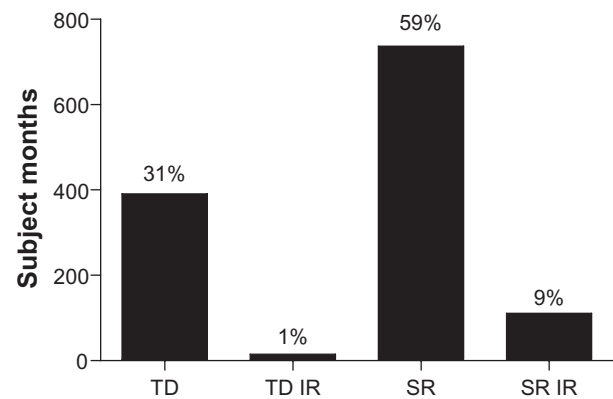
### Breakthrough IR opioid use

The generalized estimating equation population-averaged model of mean monthly IR opioid scripts adjusted for clustering on subjects was calculated. With oral SR opioids,



**Figure 1** Patient prescribed opioid scripts (n = 3133).

**Abbreviations:** IR, immediate release; SR, sustained release; TD, transdermal.



**Figure 2** Immediate-release (IR) opioid use by maintenance opioid group (n = 1254).

**Abbreviations:** SR, sustained release; TD, transdermal.

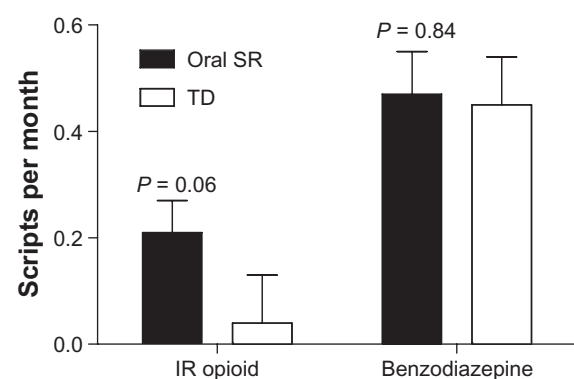
the subject would have 0.21 IR opioid scripts (equivalent to four tablets) dispensed per month. In contrast, with TD opioids, this was nonsignificantly lower at 0.04 scripts (equivalent to one tablet) (Figure 3). In more simple terms, 53 of the 61 TD subjects had no need for short-acting breakthrough opioids, while 23 of the 111 oral SR subjects required them.

### Benzodiazepine use

There were 802 benzodiazepine prescriptions (Figure 4). Both diazepam and nitrazepam are long-acting drugs (with half lives  $> 24$  hours). The generalized estimating equation model of mean monthly benzodiazepine scripts was calculated. For oral SR opioids, this was 0.47 scripts (equivalent to 23 tablets) and this was unchanged for TD opioids at 0.45 scripts (Figure 3).

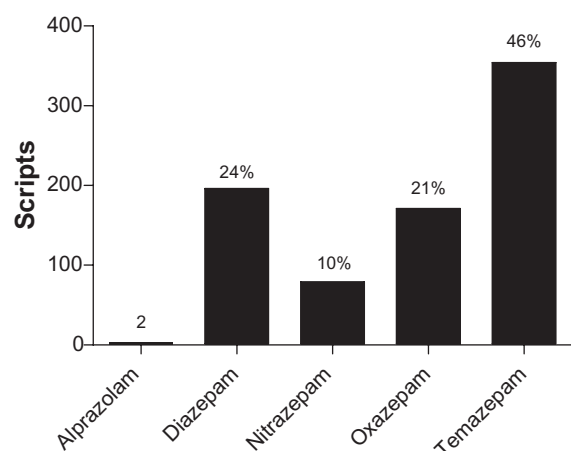
## Discussion

This study compared IR opioid and benzodiazepine use by opioid-treated CNCP rural patients from Northwest Tasmania.



**Figure 3** Immediate-release (IR) opioid and benzodiazepine use (n = 140), with mean, 95% confidence interval, and  $P$  values.

**Abbreviations:** SR, sustained release; TD, transdermal.



**Figure 4** Patient prescribed benzodiazepines (n = 804).

A trend toward less use of breakthrough IR opioids with TD opioid preparations was found. Although this result is not statistically significant, the 95% confidence interval is largely negative. The use of benzodiazepine medications was similar for both oral SR and TD opioids.

We have previously shown that in opioid-treated CNCP rural patients, the use of TD opioid preparations, with their prolonged analgesic effect, significantly reduces the number of general practitioner contacts and may reduce total health care activities, at no additional socioeconomic cost.<sup>5,6</sup> The present study may indicate reduced breakthrough IR opioid use with no additional benzodiazepine use by these subjects.

TD opioids are relatively simple and safe to use, both for prescribers and patients. As the population ages, there will be an increased requirement for safe and effective pain relief for both degenerative and malignant pain. With the development of these preparations, TD matrix opioids may open the door to the further relief of suffering and the living of fulfilled lives.

The prescribing of TD opioids may particularly benefit CNCP patients in rural and remote areas where there is a relative shortage of doctors.<sup>16</sup> The long-acting analgesia provided by TD opioids, particularly buprenorphine preparations, and the simplicity of their application enables many rural patients to function largely independently of their health care providers. This increased self-efficacy may improve their overall quality of life.

This longitudinal (cohort) study had inherent strengths and weaknesses. The major strength was being able to follow these categories of medication use by opioid-treated CNCP subjects over 12 months with data from over 12,000 prescriptions recorded objectively. The main potential

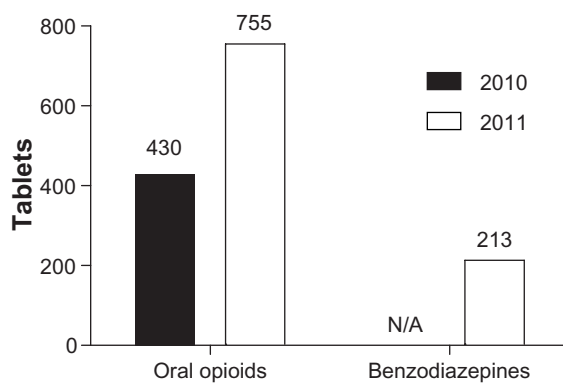
weakness is in the area of self-selection (recruitment) bias. The previous observational studies provided recruitment information for all opioid-treated CNCP patients in Northwest Tasmania, who, by regulatory necessity, are required to attend their prescribing doctor at least quarterly. The subjects (75%) who allowed access to their PBS prescription data were self-selected from that group.

It was not possible to ascertain the subjects' adherence to or diversion of their dispensed opioid and/or benzodiazepine medications. However, none of the subjects had their opioid access restricted by the Pharmaceutical Services Branch of the Tasmanian Health and Social Services Department, the State's opioid regulator.

These opioid medicines incur an additional layer of regulatory control above prescription-only medications, primarily to prevent diversion to the community for non-therapeutic purposes, as oral opioids are readily diverted. The Tasmanian Drug Trends 2011 report of the National Drug and Alcohol Research Centre (NDARC) found that, for injecting drug users (IDUs), heroin was difficult to access, while MS Contin<sup>TM</sup> and OxyContin<sup>TM</sup> (both Purdue Pharma, Stamford, CT, USA) were the predominant opioid formulations that were diverted from therapeutic purposes.<sup>17</sup> OxyContin is a modified-release preparation with a biphasic action. One-third of the oxycodone is in the enteric coating and is immediately available. The remainder is within the matrix and is gradually released.<sup>18</sup>

TD matrix opioid preparations included in this study are not mentioned by the IDUs in the NDARC report. They may be diverted and the opioid may be injected but this is not an easy task with matrix preparations. The New Zealand Drug Intelligence Bureau concluded that "the buprenorphine transdermal patch, is not considered to be of significant potential for diversion or misuse for illicit purposes," while the NDARC found that "diverted fentanyl does not yet appear to pose a major threat to IDUs in Australia."<sup>19,20</sup> The Tasmanian Police's May 2012: Corporate Performance Report indicated a substantial increase in seized oral opioids and benzodiazepines in Northwest Tasmania, with evidence that some individuals were legitimately obtaining prescription drugs and then on-selling them or trading prescription drugs for other drugs or property<sup>21</sup> (Figure 5).

If the risk of opioid diversion is a consideration in prescribing for CNCP patients, then, at present, TD opioids may be safer option. If this leads to a reduction in the prevalence of opioid diversion in Northwest Tasmania, there are considerable economic benefits, both from a reduction in self-harm and from reduced drug enforcement costs.



**Figure 5** Seized oral opioid and benzodiazepine tablets (Northwest Tasmania).<sup>21</sup>  
**Abbreviation:** N/A, not available.

Benzodiazepines have a limited role in pain management and should only be considered for short-term use.<sup>22</sup> They compound the sedation from the patients' maintenance opioids, which may compromise patients' cognitive function and inhibit their activities of daily living.

## Conclusion

The rationale for use and the provision of breakthrough opioid analgesia, for opioid-treated CNCP patients are complex, both for patients and their prescribers. This study in rural Northwest Tasmania has shown that CNCP subjects maintained with TD opioids may use less breakthrough opioid medication. Their use of benzodiazepines was similar to those patients maintained with oral SR opioids. This may strengthen the case for more widespread use of TD opioids and the reduced use of oral SR opioids in rural and remote areas where health care access is often difficult. In addition, a reduction in oral opioid prescribing may help reduce the problem of opioid diversion. The continuing development of these TD systems is to be welcomed.

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## Disclosure

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