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RESEARCH REPORT

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A wastewater-based evaluation of the effectiveness of codeine control measures in Australia

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Abstract

Background and aim: From 1 February 2018, codeine was rescheduled from an over-the-counter (OTC) to a prescription-only medicine in Australia. We used wastewater-based epidemiology to measure changes in population codeine consumption before and after rescheduling.

Methods: We analysed 3703 wastewater samples from 48 wastewater treatment plants, taken between August 2016 and August 2019. Our samples represented 10.6 million people, 45% of the Australian population in state capitals and regional areas in each state or territory. Codeine concentrations were determined by liquid chromatography–tandem mass spectrometry and converted to per-capita consumption estimates using the site daily wastewater volume, catchment populations and codeine excretion kinetics.

Results: Average per-capita consumption of codeine decreased by 37% nationally immediately after the rescheduling in February 2018 [95% confidence interval (CI) = 35.3–39.4%] and substantially in all states between 24 and 51% (95% CI = 22.4–27.0% and 41.8–59.4%). The decrease was sustained at the lower level to August 2019. Locations with least pharmacy access decreased by 51% (95% CI = 41.7–61.7%), a greater decrease than 37% observed for those with greater pharmacy access (95% CI = 35.1–39.4%). Regional areas decreased by a smaller margin to cities (32 versus 38%, 95% CI = 30.2–34.1% versus 34.9–40.4%, respectively) from a base per-capita usage approximately 40% higher than cities.

Conclusion: Wastewater analysis shows that codeine consumption in Australia decreased by approximately 37% following its rescheduling as a prescription-only medicine in 2018. Wastewater-based epidemiology can be used to evaluate changes in population pharmaceutical consumption in responses to changes in drug scheduling.

KEYWORDS
Drug use evaluation, policy change, prescription opioid, regulation change, rescheduling, wastewater analysis

INTRODUCTION

Opioids are among the most widely used analgesic medicines globally, with more than 61 million people using them in 2018 [1]. Their misuse is responsible for two-thirds of all drug-related deaths; they have a high abuse potential and can produce dependence [2]. Codeine also accounts for one-third of all seizures of illegally trafficked or diverted pharmaceutical opioids globally, demonstrating its importance in drug policy [3].

Codeine has been the most widely used opioid in Australia. Its per-capita use steadily increased from three defined daily doses per day per 1000 people (DDD/d/1000) in 1990 to seven DDD/d/1000 in 2014 [4]. General population surveys showed in 2016 that approximately 88% of respondents reporting non-medical use of a pharmaceutical opioid were using codeine, with 75% of pain-killer misusers misusing an over-the-counter (OTC) codeine product [5]. Before February 2018, low-dose codeine (< 30 mg) formulations could be obtained OTC, often compounded with ibuprofen, antihistamines or paracetamol. This policy assumed that codeine posed a lower risk of abuse, dependence and overdose than more potent pharmaceutical opioids. However, the Therapeutic Goods Administration decided to reschedule codeine as a prescription-only medicine from 1 February 2018 in response to an increase in the numbers of people seeking treatment for codeine dependence and an increase in fatal opioid overdoses attributable to codeine [6–8], among other factors such as inappropriate use in pain treatment and potential for abuse.

We used wastewater-based epidemiology (WBE) to assess the impact of this change on the population level use of codeine. WBE provides a complementary approach to evaluate the effects of policy changes on the population consumption of licit and illicit drugs, including opioids [9]. It has recently evaluated the impact of minimum unit pricing on alcohol products in Northern Territory, Australia [10]. Wastewater-based studies collect representative samples of community urine from municipal sewage treatment plants and analyse levels of human metabolites of the target substances in the samples. Excretion factors can then be used to estimate the total amount of each parent substance consumed by people in the sewage catchment area. Repeated samples enable long-term monitoring of drug utilization in the population in near real time.

We estimated per-capita codeine consumption in wastewater samples collected before and after the rescheduling from 48 wastewater treatment plants (WWTPs) in the capital cities of each state and jurisdiction of Australia and in several regional locations throughout Australia between August 2016 and August 2019 to evaluate the impact of the national rescheduling of codeine.

METHODS

Wastewater sampling

A total of 3703 samples of 24-hour composite influent wastewater were collected from 48 WWTPs throughout Australia, from August 2016 to August 2019. Five to 7 days of consecutively collected composite samples were collected in flow or time-proportional mode at the WWTP inlet. They were preserved at pH2 by adding 2 M HCl (1 ml per 100 ml sample), immediately frozen and shipped frozen to the laboratory by overnight delivery. Samples were stored at −20°C and analysed within 1 month of receipt. More information on the number of samples collected at each of the locations is provided in Supporting information, Table S1, as well as other site metrics such as population, wastewater volume, sampling mode and sampling frequency.

The sampling campaign included 19 locations in the Australian state and territory capital cities (Perth, Darwin, Adelaide, Brisbane, Sydney, Canberra, Melbourne and Hobart). Australia's eight capital cities contain more than two-thirds of the national population, with the remainder residing in regional areas. There were 29 regional locations outside the main capital cities (defined by the Australian Bureau of Statistics greater capital city statistical area), hereafter termed 'regional'. The service population of the WWTPs studied equated to 10.6 million inhabitants, approximately 45% of the Australian population (total population = 23 401 892 million in 2016, according to the Australian Bureau of Statistics [11]).

The sampling strategy included up to 6 weeks of collection per year on up to 7 consecutive days in every even month (February, April, June, August, October and December) for sites in the jurisdiction capitals and 3 weeks per year in April, August and December for regional sites. Sites in Tasmania and Northern Territory could not provide regular samples earlier in the campaign. Some locations in regional areas could not participate in each sampling period because of staffing issues, cyclones, flooding or bushfires. In a few sites in Tasmania, staff were not able to collect samples on Saturdays and Sundays. One site in Melbourne was excluded from the study as it contained a major opioid poppy processing facility within the catchment area and its per-capita mass loads of codeine were more than 10-fold higher than other locations. Further information can be found in Supporting information, Table S1.

Codeine was selected as the target biomarker for analysis. The samples were analysed by direct injection methods at the time (2016–19, soon after sample collection) for codeine as part of the analytical method for the National Wastewater Drug Monitoring Program (NWDMP) in Australia.

Sample preparation and analysis

Materials used in this study are listed in the Supporting information. Liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) analysis and quality assurance and quality control (QAQC) procedures were conducted according to the methods described in previous studies (see [12, 13]). Briefly, raw wastewater influent samples were spiked with isotopically labelled reference standard (Codeine D3), vortex-mixed, filtered and 7 µl injected onto a biphenyl column (2.1 × 100 mm, 3 µm) using a Shimadzu LC system coupled to a SCIEX 5500 mass spectrometer. Concentrations were calculated

using an isotope-dilution method by comparing the response ratio of the analytical standard and isotopically labelled standard in calibration samples against the response in wastewater samples. Calibration consisted of a 7-point calibration curve of increasing concentration of analytical reference standard and consistent concentration of isotopically labelled standard [0.05–100 parts per billion (ppb) native, 5 ppb internal standard]. The lowest limit of quantification (LLOQ) was 0.05 ppb and upper limit of quantification (ULOQ) was 100 ppb.

Statistics

Consumption estimates

Concentrations obtained by LC–MS/MS were used to calculate the per-capita consumption of codeine, using daily flow estimates provided by WWTP operators and population estimates generated by layering census information on wastewater catchment maps using methods published previously [14]. The equation to estimate codeine consumption (mg consumed/day/1000 people) is shown in equation 1.

$$codeine\ consumption = \frac{(concentration \times flow)}{population_{1000s}} \times \frac{1}{excretion}, \quad (1)$$

where *concentration* is the concentration in ng/l (ppt) of codeine in the sample, *flow* is the total volume of wastewater entering the WWTP in the corresponding 24 hours in megalitres (ML), *population* is the population of the WWTP in 1000s and *excretion* is the fraction of a dose of codeine which is eliminated into urine (0.638, e.g. 63.8%) [15]. Codeine was used to estimate codeine consumption. Normalizing wastewater concentrations to excretion, population and flow allows comparisons of consumption between locations of different population and size and over time.

Data aggregation

Data were aggregated by state or territory, capita or regional and to the national level by population-weighting each catchment result within each jurisdiction. The codeine trend was presented at four levels: national, state or territory, capital or regional and for each individual site. The data were also aggregated by Pharmacy Access/Remoteness Index of Australia (PhARIA) codes, which is a measure of the accessibility of pharmacies in each of the geographic locations [16].

Interrupted time–series (ITS) analysis

A linear mixed-model was used to perform an ITS analysis that tested the effect of rescheduling on codeine consumption. Codeine consumption was regressed on time, rescheduling (before and after), states/territories, the two-way interaction between time and rescheduling, the two-way interaction between state and time, the two-way interaction between state and rescheduling and the three-way interaction between state, time and rescheduling (equation 2). Details of the interpretation of each individual term can be found in Chan *et al.* [17]. This model assesses the immediate effect of rescheduling on consumption and its effect on trends and differences between states in each of these changes. A random intercept was specified for sampling site to adjust for the dependence between repeated samples from the same site. The model also adjusted for the remoteness and months of the year. To facilitate interpretation, we estimated the marginal mean of consumption immediately before and after rescheduling and tested if the marginal mean of consumption at various time-points after rescheduling was different from that before rescheduling. We fully adjusted for the multiple comparisons of marginal means using Tukey's method:

$$\begin{aligned} codeine\ consumption = {} & regionality + state + pre/post\ rescheduling + time \\ & + month + time \times (pre/post\ rescheduling + time) \times (state + time) \\ & \times rescheduling \times (state + \mu_i + \epsilon_{ij}) \end{aligned} \quad (2)$$

where μ_i represents the random effect of site I and $\mu_i \sim N(0, \sigma_0)$, ϵ_{ij} is the error term for sample j from site I and $\epsilon_{ij} \sim N(0, \sigma_1)$.

The analysis plan of this study was not pre-registered, and the results should be considered exploratory.

RESULTS

Codeine was detected above the limit of quantification in all samples over the period (3703; August 2016 to August 2019) and back-calculated to produce consumption estimates as per equation 1. In total, 1606 samples were collected before February 2018 and 2097 from February 2018 to August 2019 (Supporting information, Table S2).

National changes in codeine consumption

Nationally, the population-weighted average codeine consumption decreased from 717 mg/day/1000 inhabitants to 449 mg/day/1000 inhabitants, a decrease of 37% [95% confidence interval (CI) = 35.3–39.4%] (Figure 1a and Supporting information, Tables S3 and S4). The seasonal difference between summer and winter periods after the rescheduling appeared to be smaller than before for some jurisdictions (Figure 1b and Supporting information, Table S5).

State/territory changes in codeine consumption

State or territory consumption estimates were calculated as the population-weighted average of all sites within each state. As

can be seen in Figure 2a,b, each jurisdiction observed a different pattern of use before and after the rescheduling and also exhibited a different magnitude of decrease (Supporting information, Table S7 and also shown in Supporting information, Table S6 broken into capital and regional). South Australia and Tasmania had the smallest decreases, with a 25% decrease (95% CI = 22.4–27.0% and 16.0–33.4%, respectively). This decrease was smaller in the regional areas than in capital cities (SA city: 25%, 95% CI = 22.0–27.5%; regional 19%, 95% CI = 10.9–26.9%; Tas city: 31%, 95% CI = 23.4–38.4%, regional 20%, 95% CI = 8.25–32.5%); Supporting information, Table S8. The Northern Territory had the greatest overall decrease of 51% (95% CI = 43.8–59.1%), with larger decreases observed in the NT regional area (55% decrease, 95% CI = 40.9–68.6%, with the NT capital site close behind with a 51% decrease, 95% CI = 41.8–59.4%). Differences were also observed between individual sites in each state, shown in Supporting information, Figs S3, S5–S12 and Tables S5 and S8.

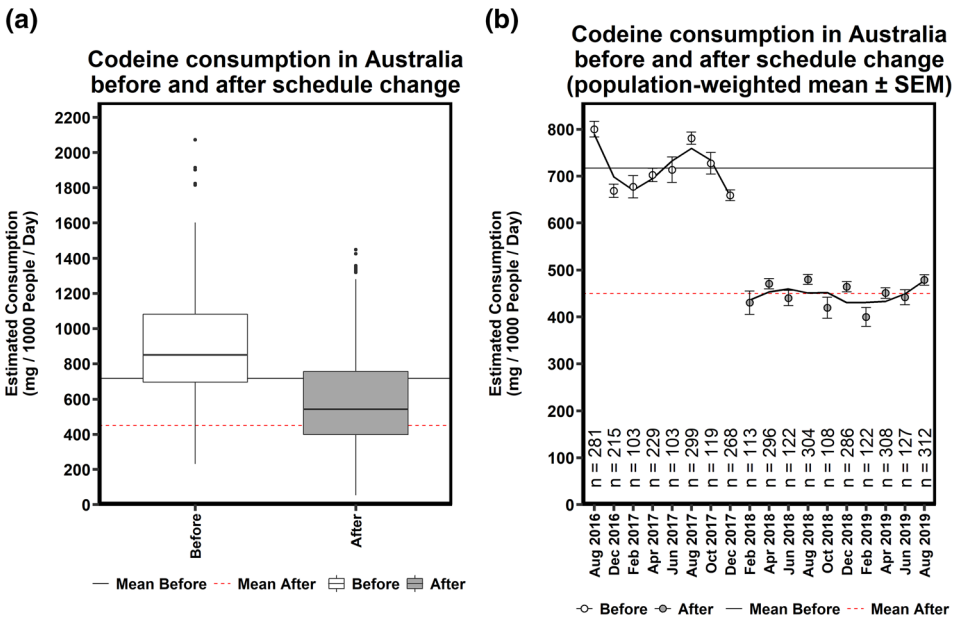

FIGURE 1 National-level changes in codeine consumption before and after codeine rescheduling in February 2018, by wastewater analysis: (a) box-plot showing all codeine data before and after (all samples from all sites individually) and (b) national population-weighted average trend [± standard error of the mean (SEM)] of all locations, by month. A suggested oral morphine equivalent dose of codeine is 20 mg codeine for every 1 mg morphine [18]

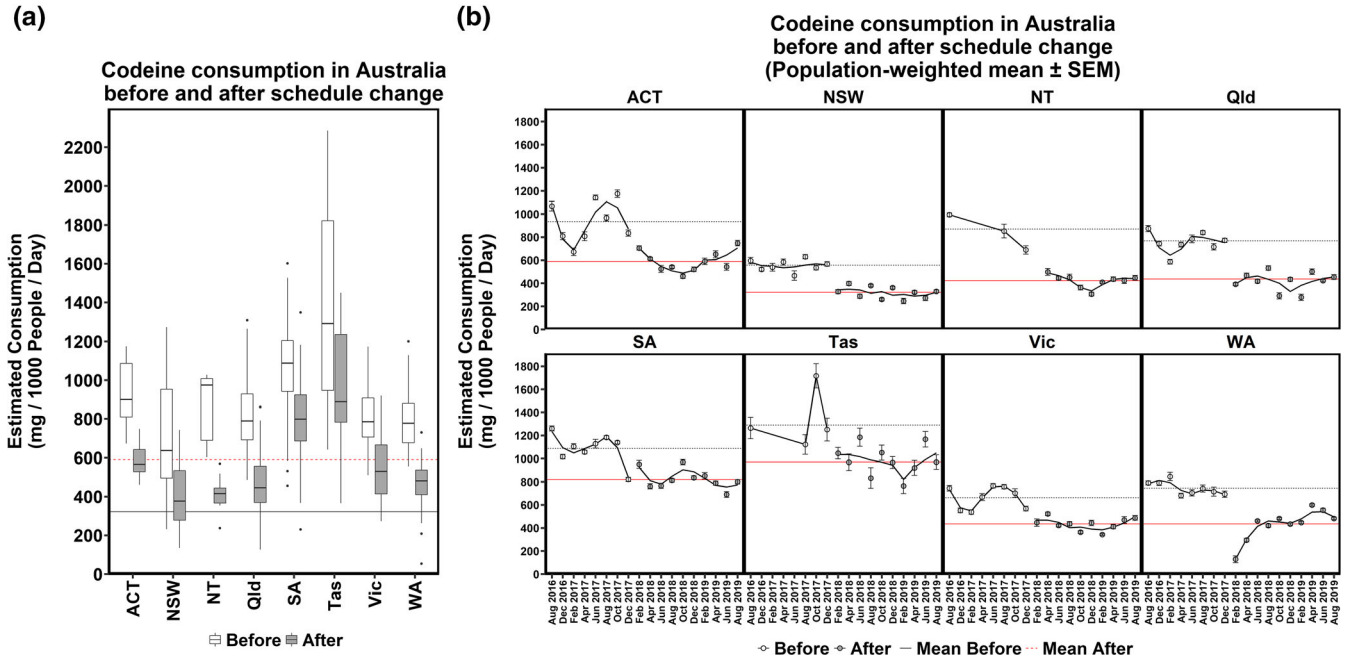

FIGURE 2 Codeine consumption estimates by state and territory before and after it was rescheduled: (a) box-plot showing before and after for each jurisdiction and (b) the population-weighted average consumption estimate trends [± standard error of the mean (SEM)] before and after rescheduling. A suggested oral equivalent dose of codeine is 20 mg codeine for every 1 mg morphine [18]

Capital or regional changes in codeine consumption

When the national data were aggregated by state capital cities and regional areas (outside state capitals), rates of use were approximately 25% higher in regional areas before the rescheduling (Supporting information, Fig. S1). The reduction in consumption was greater in the capital city areas (~38%, 95% CI = 34.9–40.4%, 700–440 mg/1000 people/day) than in the regional areas (~32%, 95% CI = 34.9–40.4%, 910–620 mg/1000 people/day), Table S4.

Changes in codeine consumption based on pharmacy access

The wastewater data were compared for the catchment's accessibility to pharmacies using the PhARIA codes (1 = highest accessibility of pharmacies; 6 = least accessible) [16] (Fig. S2). Catchments with the PhARIA codes indicating least access to pharmacies [5, 6] had higher proportional change (−55 and −52%, 95% CI = 40.9–68.6% and 41.7–61.7%) than the two PhARIA codes with greatest access to pharmacies [1, 2] (−37 and −44%, 95% CI = 35.1–39.4% and 37.4–49.8%).

ITS analysis

The ITS analysis demonstrated that mean and median codeine consumption were substantially lower after rescheduling in each Australian state or territory. The model coefficients from the linear mixed model were shown in Supporting information, Table S9. Figure 3 shows the model-based estimated marginal mean and the corresponding 95% confidence band of codeine consumption.

Table 1 shows the decrease immediately (February 2018), 6 months (August 2018), 12 months (February 2019) and 18 months (August 2019) after rescheduling. For all states/territories, there was a statistically significant drop immediately after rescheduling ($P < 0.001$). The decrease was largest in Western Australia (estimate = −724 mg/

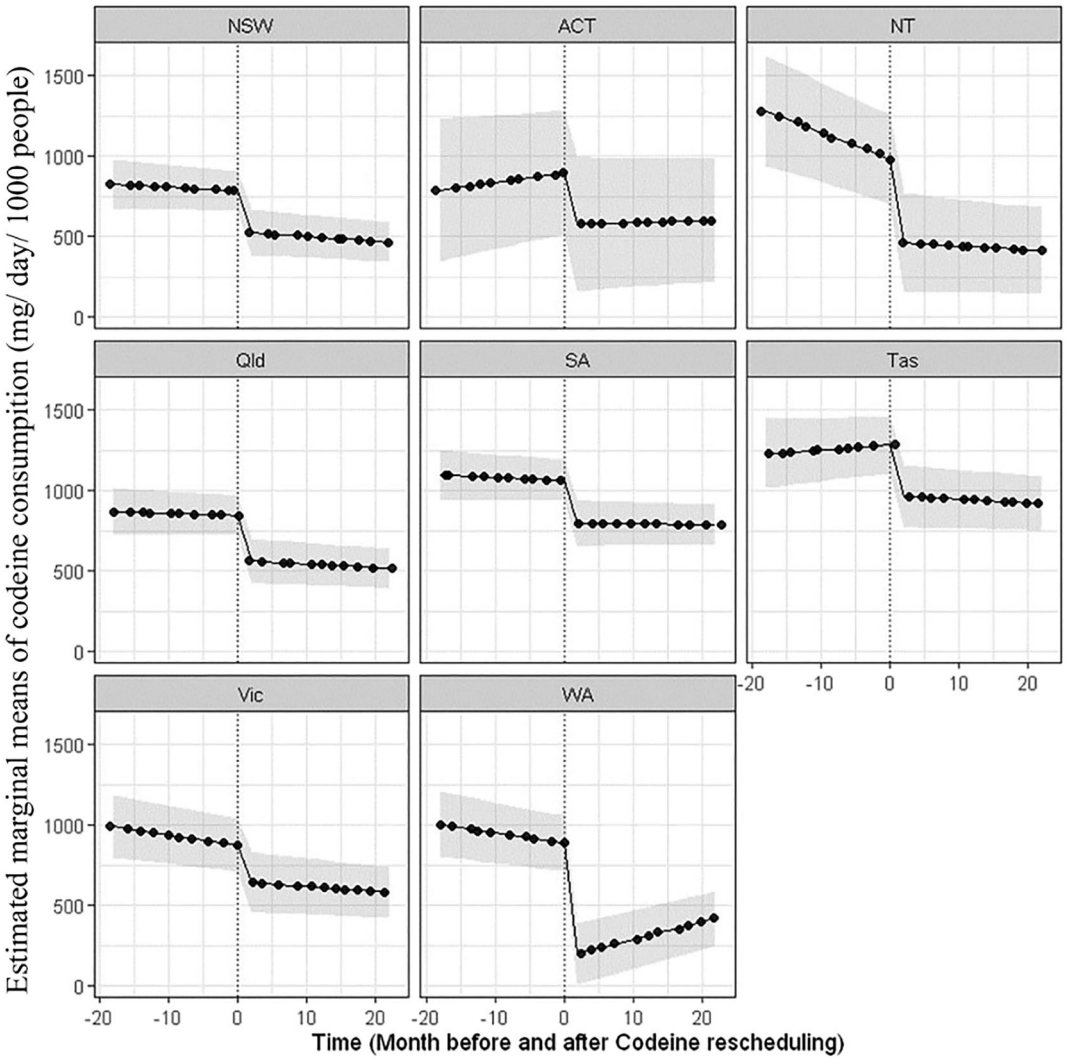

FIGURE 3 Interrupted time–series analysis. The estimated marginal means and the corresponding 95% confidence band of the estimated codeine temporal trend by States/Territories, over time. The rescheduling month is indicated by the vertical dotted line

TABLE 1 Decrease from the period immediately before (December 2017) codeine rescheduling. Units are the estimated marginal mean reduction in consumption (mg/day/1000 people) (95% confidence interval)

State or territory	February 2018	August 2018	February 2019	August 2019
NSW	−259 (−456, −62)	−277 (−444, −109)	−294 (−435, −153)	−311 (−430, −193)
ACT	−309 (−765, 146)	−303 (−690, 85)	−296 (−623, 31)	−289 (−567, −12)
NT	−547 (−978, −116)	−563 (−932, −193)	−578 (−892, −265)	−593 (−861, −326)
QLD	−283 (−467, −99)	−297 (−451, −142)	−310 (−438, −182)	−324 (−430, −218)
SA	−270 (−453, −87)	−273 (−429, −117)	−276 (−407, −144)	−279 (−390, −167)
TAS	−307 (−582, −32)	−321 (−555, −86)	−335 (−533, −137)	−349 (−517, −180)
VIC	−239 (−505, 27)	−257 (−482, −33)	−276 (−462, −89)	−294 (−447, −140)
WA	−724 (−961, −487)	−658 (−859, −457)	−592 (−759, −424)	−525 (−666, −384)

day/1000 people, 95% CI = −961, −487) and smallest in Victoria (estimate = −239 mg/day/1000 people; 95% CI = −505, −27). Consumption trends were largely flat after rescheduling except in Western Australia, where there was a larger decrease followed by a re-equilibration of the trend (i.e. see Figure 2). In Western Australia a substantial decrease was observed immediately after rescheduling, while 18 months after rescheduling, the difference narrowed to −525 mg/day/1000 people (95% CI = −666, −384, compared to December 2017, which was immediately before rescheduling).

DISCUSSION

Changes in codeine consumption before and after rescheduling

After codeine was rescheduled to a prescription-only medicine on the first of February 2018, the population-weighted average consumption of codeine dropped immediately and significantly (∼37%). In 2013, the proportion of OTC codeine products was estimated at 40.1% on a mass basis (4967 kg of the 12 376 kg sold) [19]. This proportion is closer to the wastewater data (where both record data in mass of codeine) than sales data which are based on number of packs sold. For example, sales of codeine at the national level during the study period were not as close to our estimates, showing a combined ∼50% decrease in total packs of codeine sold nationally, constituting a reduction in high-strength codeine (−37%) and low-strength codeine (−80%) [20]. Some discrepancy between the reductions may also be expected owing to differences in the type of data. Bulk sales into pharmacies (sales data) indicate the volumes purchased at the pharmacy or hospital level and may not reflect community consumption because they do not take account of compliance or delays in consumption due to stockpiling) Similar reductions were observed in monthly calls to poison call centres relating to intentional codeine poisonings, which decreased by approximately 50% [20].

The colder climate states of ACT, VIC and TAS appeared to have a greater winter–summer variance in codeine consumption before rescheduling than the jurisdictions with a more moderate, subtropical climate (NT, NSW, QLD and SA). After the rescheduling, Western Australia observed a larger immediate decrease before the baseline re-equilibrated, a trend mainly driven by two of the three inner-city sites in Perth.

South Australia was the only jurisdiction where the decrease in response to the rescheduling occurred in December 2017 rather than February 2018. This change was observed mainly in Adelaide city sites and not in regional areas. There were variations in the changes after rescheduling in each location, with some showing gradual declines while others had step decreases or more varied fluctuations. A few sites had similar consumption estimates before and after the change, suggesting a minimal change (Figs S5–S12).

Consumption of codeine in regional sites was higher than in major cities. This finding is in line with a codeine utilization study that found the highest utilization rates of codeine were in the most remote areas [19]. There are generally fewer health services in the more regional and remote areas outside larger urban centres, and treatment options may be limited so patients may self-manage pain with products such as codeine [21]. However, when the data were aggregated based on capital cities or regional areas, the reduction in codeine use was slightly lower in regional areas compared with cities (32% in regional areas versus 37% in capitals). The smaller decreases observed in the more regional areas may be based on our definition of regional (everything outside state or territory capital cities), which includes large regional centres. When PhARIA codes were applied to assess general access to first-line services across the sites for a more granular definition, the greatest decrease in codeine consumption was observed in areas with the least access to pharmacies, most of which were regional. The PhARIA describes general access to a key first-line medical service, suggesting that a greater proportion of codeine use in the most remote areas may have been obtained OTC, because OTC sales ceased post-rescheduling.

Implications of codeine rescheduling

Our analysis showed that for all sites in all states and territories, there was a substantial decline in codeine consumption after rescheduling. The size of the decline varied between states, but all showed a decline in codeine consumption.

Our findings are consistent with the findings of studies that have investigated the impacts of the Australian codeine rescheduling on codeine-related harms [20, 22], sales [23, 24], prescriptions [25, 26], patients [27], medical professionals [28–30] and the utilization of other opioids [31]. Studies using pharmaceutical sales data also showed a significant 50% reduction in national codeine sales after rescheduling. During the same period, by contrast, the total amount of codeine prescribed under the Pharmaceutical Benefits Scheme (PBS) showed negligible change [25]. This suggests that the majority of the decrease in consumption was probably due to the removal of OTC codeine after rescheduling. There was no increase in prescriptions of stronger opioids [25], as was observed after a change in codeine regulation in Italy [32]. While many of these studies assessed the change at the national level, our study indicates that there were some differences in the proportional decrease between states and territories. All these results suggest that rescheduling codeine to prescription-only produced an immediate and substantial decrease in codeine consumption in all regions of Australia.

The main data sources for drug utilization research are generally sales or prescription data. Counterfeit/illicit pharmaceuticals is a US $4.4 billion industry globally, with a recent INTERPOL operation, Pangea XV, spanning 94 countries, collectively making 7800 seizures of illicit/counterfeit pharmaceuticals or medical products (3 million units) [33]. In addition, a recent 11-kg seizure of illicit fentanyl (a potent opioid) was detected in Melbourne, Australia (equivalent to 55 million doses of 0.2 mg) [34]. WBE could also help to bridge the gap in drug utilization research between prescription/sales data and the total consumption of pharmaceuticals where there is a substantial illicit pharmaceutical market.

Our results also suggest that WBE can be used to evaluate changes in population consumption after changes in pharmaceutical scheduling of opioids. A similar approach could be applied to evaluating scheduling changes for other drugs. The advantage of the wastewater-based approach is it can be implemented at community scale to assess changes in smaller, discrete areas, particularly for localized interventions. It can also cover data shadows—areas that are generally not captured representatively in many data sets, such as regional and remote areas. The scale of existing wastewater collections in many regions of the globe (especially for current COVID-19 monitoring) affords national-scale assessments, as demonstrated in this study.

CONCLUSION

The WBE approach was used to evaluate codeine consumption patterns before and after a national rescheduling of low-dose codeine from OTC to a prescription-only medicine. Results showed that codeine consumption decreased substantially nationally, with some variations in the size of reduction between capital cities, states and territories. In addition, locations with lower access to pharmacies showed larger decreases than areas with greater pharmacy access. This is the first study to evaluate a national drug policy change via wastewater, demonstrating that WBE is a viable way of assessing the effects of pharmaceutical regulatory interventions on population consumption of pharmaceuticals or other drugs.

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DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Ben Tscharke: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing-original draft; writing-review and editing. **Jake O'Brien:** Conceptualization; funding acquisition; writing-review and editing. **Fahad Ahmed:** Data curation; writing-review and editing. **Lynn Nguyen:** Data curation; writing-review and editing. **Maulik Ghetia:** Data curation; writing-review and editing. **Gary Chan:** Data curation; formal analysis; investigation; supervision; visualization; writing-review and editing. **Phong Thai:** Conceptualization; funding acquisition; methodology; supervision; writing-review and editing. **Cobus Gerber:** Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; writing-review and editing. **Richard Bade:** Investigation; writing-review and editing. **Jochen F Mueller:** Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; writing-review and editing. **Kevin V. Thomas:** Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; writing-review and editing. **Jason White:** Funding acquisition; project administration; writing-review and editing. **Wayne D Hall:** Investigation; supervision; writing-original draft; writing-review and editing.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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