

1 **Sales of over-the-counter products containing codeine in 31 countries,**
2 **2013-2019: a retrospective observational study**

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26

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29 sales data from IQVIA.

30

31

32 **ABSTRACT**

33 **Introduction**

34 Opioid prescribing trends have been investigated in many countries. However, the
35 patterns of over-the-counter purchases of opioids without a prescription, such as
36 codeine combinations, are mostly unknown.

37

38 **Objective**

39 We aimed to assess national sales and expenditure of over-the-counter codeine-
40 containing products purchased in 31 countries over six years.

41

42 **Methods**

43 We conducted a retrospective observational study using electronic point-of-sales data
44 from the human data science company, IQVIA, for Argentina, Belgium, Brazil,
45 Bulgaria, Canada, Croatia, Estonia, Finland, France, Germany, Greece, Ireland, Italy,
46 Japan, Latvia, Lithuania, Mexico, The Netherlands, Poland, Portugal, Romania, Russia,
47 Serbia, Slovakia, Slovenia, South Africa, Spain, Switzerland, Thailand, the UK, and the
48 USA. We calculated annual mean sales (units per 1000 of the population) and public
49 expenditure (GBP, £ per 1000) for each country between April 2013 and March 2019.
50 We quantified changes over time and the types of products sold.

51

52 **Results**

53 31.5 billion units of codeine, costing £2.55 billion, were sold over-the-counter in 31
54 countries between April 2013 and March 2019. Total sales increased by 3% (3025
55 units/1000 in 2013 to 3111 in 2019) and public expenditure doubled (£196/1000 in

56 2013 to £301/1000 in 2019). Sales were not equally distributed; South Africa sold the
57 most (31 units/person), followed by Ireland (24 units/person), France (16 units/person),
58 Latvia (15 units/person), and the UK (11 units/person). The types of products (n=569)
59 and formulations (n=12) sold varied.

60

61 **Conclusion and Relevance**

62 In many parts of the world, substantial numbers of people may be purchasing and
63 consuming codeine from over-the-counter products. Clinicians should ask patients
64 about their use of over-the-counter products and public health measures are required to
65 improve the collection of sales data and safety of such products.

66

67 **Study protocol pre-registration:** <https://osf.io/ay4mc>

68

69 **Key points**

- 70 • Total sales and public expenditure of over-the-counter products containing
71 codeine increased from April 2013 to March 2019 in line with increased trends
72 of global opioid use.
- 73 • There was substantial variation in mean sales of over-the-counter codeine
74 between countries.
- 75 • In countries with access to over-the-counter codeine, these sales data should be
76 reviewed to informed regulatory decisions and requirements for public health
77 measures to ensure safety.

78

79

80 **1 Introduction**

81 Prescribing patterns of opioids are documented in many countries [1–7]. However,
82 opioids such as analgesic combinations containing codeine can be purchased over-the-
83 counter (OTC) without a prescription or consultation with a doctor or prescriber in most
84 countries. As access to granular data on OTC sales has been limited, previous research
85 on the use of non-prescribed codeine has relied on case reports [8–10], self-reported
86 questionnaires [11–18], qualitative studies [19–22], and data from poisons centres,
87 hospital admissions, or coronial systems [23–27]. It is therefore unknown whether OTC
88 sales of codeine have followed trends similar to the use of prescribed opioids.

89
90 Codeine (3-methylmorphine) is used for its analgesic, antidiarrheal, and antitussive
91 effects [28–30]. It is often combined with other analgesics, such as paracetamol, and
92 non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. These
93 combinations have greater efficacy than codeine alone [28,31,32]. But most clinical
94 trials testing the efficacy of codeine have used high doses (25–90 mg), which are not
95 available OTC [31–33]. A Cochrane overview of systematic reviews on oral OTC
96 analgesics for acute pain found no studies or data that could be extracted on
97 combinations of analgesics containing low doses of codeine [33]. A systematic review
98 of the efficacy and safety of low-dose (≤ 30 mg) codeine included ten RCTs [34]. It
99 reported low- to moderate-quality evidence that combination products of low-dose
100 codeine provided little to moderate pain relief for acute and chronic pain conditions in
101 the short term [34]. In observational studies products containing codeine have been
102 associated with dependence, misuse, death, and collateral toxicity from combinations
103 with paracetamol and ibuprofen [9,25].

104

105 Access to codeine without a prescription can bolster the perception of safety, and in
106 some settings abuse of OTC codeine is normalised and encouraged. Mixing codeine
107 cough syrup with alcohol and or soft drinks has been popularised in rap music and by
108 American athletes, who make a drink called "purple drank" from codeine syrup and
109 soda [35]. OTC codeine has been used to manufacture illicit morphine and heroin and to
110 create a cheap heroin substitute called "krokodil" [36,37]. The use of "Krok" has been
111 reported in Russia, Europe, the UK, and North America, and its adverse effects from
112 intravenous use include damage to blood vessels, skin, muscles, and bones, multiorgan
113 failure, and death [36,38]. Thus, the growing opioid problem is incomplete without
114 evaluation of OTC sales of codeine.

115

116 Regulation of codeine-containing products varies across the world, making it difficult to
117 estimate how much they are used [39]. Under the 1961 Single Convention on Narcotic
118 Drugs, codeine is a Schedule III drug [40]. Drugs in this Schedule reportedly "are not
119 liable to abuse and cannot produce ill effects", and thus it is not mandatory to report
120 data on their consumption to the International Narcotics Control Board (INCB). In a
121 report presented at the WHO's Expert Committee on Drug Dependence in October
122 2019, reviewing codeine formulations listed in Schedule III, the INCB reported a 64%
123 increase in demand for codeine in the last decade [39].

124

125 However, governments can also mandate regulation of codeine. Minnesota (July 2013),
126 Manitoba (February 2016), France (July 2017), and Australia (February 2018) have
127 reclassified codeine to prescription-only [41–44]. A review of OTC codeine regulations

128 in the European Union showed that more than half of member countries did not permit
129 OTC sale of codeine as of March–August 2014 [45]. Despite variation in codeine's
130 regulatory status, studies have analysed consumption of OTC cough syrup containing
131 codeine in Taiwan [46] and the impact of rescheduling codeine to prescription-only in
132 Australia [47,48]. We aimed to assess national sales and public expenditure on OTC
133 codeine-containing products purchased in countries with available data.

134

135 **2 Methods**

136 **2.1 Design and data source**

137 We conducted a retrospective observational study using consumer health sales data
138 from *IQVIA* [49], which has previously been used in observational research on a range
139 of medications [46–48,50–53]. The data included products containing codeine in the
140 adult pain relief category, which were collected using scan track barcodes from
141 electronic point-of-sale (EPoS) store data in all countries that provided data, including
142 Argentina, Belgium, Brazil, Bulgaria, Canada, Croatia, Estonia, Finland, France,
143 Germany, Greece, Ireland, Italy, Japan, Latvia, Lithuania, Mexico, The Netherlands,
144 Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, South Africa, Spain,
145 Switzerland, Thailand, the UK, and the USA. *IQVIA* extracted the data on 16 September
146 2019 and provided quarterly sales from 1 April 2013 to 31 March 2019. *IQVIA*'s sample
147 of data is based on audits and covers a median of 73% (IQR: 58–86%) of
148 pharmaceutical markets (Table S1 in Supplement 1). Annual population statistics in
149 calendar years (2013 to 2018) were sourced from the World Bank [54].

150

151 **2.2 Data analysis**

152 We extracted details from the pack information and used descriptive statistics to
153 determine the numbers and types of products sold across the 31 countries. Data on
154 dosages were missing from the pack information for most countries, so we used
155 *IQVIA*'s standard units to account for liquid and solid dosage forms. We calculated the
156 total units sold over the study period and the totals for each year (e.g. from quarter two
157 in 2013 to quarter one in 2014). We also calculated the mean number of units sold over
158 six years, adjusted for population. We created an annual rate of units sold per 1000 of
159 each year's population for each country to examine trends over time.

160

161 For expenditure, *IQVIA* converted sales to pounds sterling (GBP, £) for each country on
162 the date of data extraction (16 September 2019). We calculated annual totals, mean
163 public expenditure for each country, adjusted for population, and a rate of GBP per
164 1000 to assess changes over time.

165

166 **2.3 Software and data sharing**

167 We used Stata v16 and Python v3 in Jupyter Notebooks with pandas [55], seaborn [56],
168 and matplotlib [57] libraries for analysis and figures. The commercial information we
169 used requires a fee to access. Thus, we cannot openly share the data, owing to
170 contractual agreements with *IQVIA*. However, we have openly shared our statistical
171 code at GitHub [58], preregistered [59] and published [60] our study protocol, and
172 shared all our study materials via the Open Science Framework (OSF) [61].

173

174 **3 Results**

175 31.5 billion units containing codeine were sold across 31 countries over the study period
176 (April 2013 to March 2019). Total sales increased by 2.8%, from 3025 units/1000 in
177 2013–14 to 3111 units/1000 in 2018–19. However, the distribution of sales between
178 countries was not uniform. Five countries represented 90% of all OTC codeine sales.
179 South Africa accounted for the greatest volume of sales (34%), followed by France
180 (20%), Japan (16.5%), the UK (14.5%), and Poland (5%). South Africa sold the most
181 (mean of 31 units/person, see Figure 1), followed by Ireland (24 units/person), France
182 (16 units/person), Latvia (15 units/person), and the UK (12 units/person).

183

184 [Figure 1 near here]

185

186 In the most recent year (April 2018–March 2019), South Africa sold the most (38
187 units/person), followed by Ireland (23 units/person), Latvia (16 units/person), the UK
188 (11 units/person), and Japan (10.7 units/person) (Table S2 in Supplement 1).

189

190 Over time, 48% of countries (15/31) had increased OTC codeine sales. For countries in
191 the top quartile of sales (Figure 2A), trends increased in South Africa (30%), Ireland
192 (8%), Latvia (11%), and Poland (19%), and sales fell in France (99%), the UK (7%),
193 Serbia (4%), and Croatia (17%). For countries in the second-largest quartile of sales
194 (Figure 2B), trends increased in Japan (1219%), Estonia (65%), Romania (10%), and
195 Bulgaria (18%), and sales fell in Switzerland (50%), Finland (22%), The Netherlands
196 (16%), and Slovenia (16%). Trends for countries in the bottom two quartiles are in
197 Figure S1 and S2 in Supplement 1.

198

199 [Figure 2 (Figure 2A and Figure 2B) near here]

200

201 The public spent £2.55 billion on OTC codeine-containing products in 31 countries over
202 six years; expenditure increased by 54%, from £196/1000 in 2013–14 to £301/1000 in
203 2018–19. Ireland had the largest mean public expenditure of £5.70 per person, followed
204 by the UK (mean of £1.60/person), South Africa (£1.26/person), Croatia (£1.25/person),
205 and Estonia (£1/person) (Figure 3). In April 2018 to March 2019, Ireland continued to
206 have the largest public expenditure (£6.60/person), followed by South Africa
207 (£1.64/person), the UK (£1.64/person), Japan (£1.47/person), and Estonia (£1.41)
208 (Table S2 in Supplement 1).

209

210 [Figure 3 near here]

211

212 Most countries (58%, 18/31) had increased public expenditure over time. There were
213 simultaneous increases (45%, 14/31) and decreases (39%, 12/31) in both sales and
214 expenditure in most countries, while other countries (16%, 5/31) had a discordance in
215 the direction of their sales and expenditure (Figure 4).

216

217 [Figure 4 near here]

218

219 There were 569 products and 12 formulations sold across 31 countries. Tablets were the
220 most common formulations sold, followed by syrups, soluble tablets, and coated tablets
221 (Figure S3 in Supplement 1). Products contained a median of three substances per
222 combination (IQR: 2–4, range: 1–16). Limited details were available in the pack

223 information: the dosages of codeine were available in 17% of products (98 of 569) in 15
224 countries.

225

226 **4 Discussion**

227 Many people are purchasing non-prescribed codeine in several parts of the world. Total
228 sales and public expenditure of OTC codeine products increased over time in line with
229 previous trends of global opioid use. However, sales were not equally distributed across
230 the 31 countries.

231

232 According to *IQVIA*'s data, South Africa consistently sold the greatest volume of OTC
233 codeine each year. In a study of opioid dependence in South Africa 5–8% of people in
234 addiction treatment facilities reported problems with OTC codeine medications and
235 cough mixtures as their primary or secondary drug of choice [62]. The availability of
236 non-prescribed codeine may also have ramifications for neighbouring countries that
237 restrict access. For example, there were reports in Zimbabwe that codeine-containing
238 cough syrup was being illegally smuggled in from South Africa and sold on the streets
239 after being outlawed in 2015 [63]. However, there are limited data in many countries on
240 the prevalence of such activities and the extent of codeine use and misuse.

241

242 Abuse of OTC codeine products has been encouraged and normalised on social media
243 and in hip-hop music [64–66], which is a growing public health concern. A scoping
244 review of the non-medical use of pharmaceuticals identified several ways in which
245 codeine was reportedly being abused, including mixtures with alcohol or soft drinks
246 (e.g. "purple drank") and in the production of home-made opiates (e.g. "krokodil") [67].

247 Public health interventions are needed to prevent abuse, misuse, and pharmacy shopping
248 of OTC codeine products, particularly in young adults. The hip-hop song titled "1-800-
249 273-8255", from the US suicide prevention lifeline, significantly increased public
250 awareness of and calls to the hotline [68]. Thus, hip-hop music can also be used as a
251 tool to tailor public health messages to young adults and counteract the glamourisation
252 of codeine misuse.

253

254 The growing recognition of codeine abuse and misuse has led governments in
255 Minnesota, Manitoba, France, and Australia to reclassify codeine to prescription-only
256 [41–44]. In South Africa, Canada, Switzerland, Ireland, and the UK, governments are
257 proposing or considering plans to reclassify codeine-containing products to
258 prescription-only [69–72]. Studies assessing the effect of rescheduling codeine to
259 prescription-only in Australia showed a reduction in all codeine-related poisonings and
260 no change in calls to poisons centres or sales of high-strength (>15 mg) prescribed
261 codeine after reclassification [47,73]. The success of Australia's rescheduling questions
262 whether governments worldwide should make codeine prescription-only. But since
263 many low- and middle-income countries experience barriers to accessing opioids [74–
264 76], the WHO recommends that codeine should not be upscheduled and for codeine to
265 be included in essential medicines lists [77]. If a consensus on the status of OTC
266 codeine products cannot be reached, data should be collected globally to monitor its use
267 and harms.

268

269 Changes to regulations of OTC codeine and differences in trade exemptions and
270 disclosures of commercial interests at the country level may explain some of the

271 variation in sales [39]. For example, in France, sales fell considerably after codeine
272 became prescription-only. In countries such as Canada, Germany, and the USA, which
273 had high rates of prescribed opioids [76], mean sales of OTC codeine products were
274 lower than countries without similar access to prescribed opioids. However, our figures
275 depended on coverage of data from *IQVIA* during this time. Thus, it is hard to determine
276 whether the variation in sales represents real differences between countries.

277

278 **Strengths and limitations**

279 We used *IQVIA*'s standard units to measure sales, which allows liquid and solid dosage
280 forms to be combined. The figures represent population-level sales and expenditure of
281 OTC codeine in 31 countries, providing the best available proxy for actual use. Sales
282 represented adult pain relief, although we calculated rates using population statistics for
283 all age groups, including children. Codeine-containing products may also be purchased
284 in large quantities from online pharmacies or the black market [78], not captured in
285 these data. *IQVIA*'s coverage and the completeness of data may have also affected sales
286 trends; they provided percentages on data coverage and converted expenditure to GBP
287 at single time points, which may not accurately represent changes to such metrics over
288 time.

289

290 Better access to OTC sales data is required. Amendments to medicines legislation in the
291 UK show how such data could be collected. The Misuse of Drugs Regulation 2001, the
292 Medicines for Human Use (Administration and Sale or Supply) (Miscellaneous
293 Amendments) Order 2007, and the Medicines (Sale or Supply) (Miscellaneous
294 Provisions Amendment Regulations 2007) were updated to require pharmacies to

295 submit counts of private prescriptions for Schedule 2 and Schedule 3 controlled drugs to
296 the National Health Service (NHS) Prescription Services for analysis, audit, and
297 monitoring [79,80]. A similar system could be enforced through a public health
298 organisation such as the WHO or the International Narcotics Control Board (INCB),
299 which already collects governments' annual drug statistics on opioids [81]. Such data
300 could then be used by governments and researchers to monitor sales of OTC codeine
301 and measure the impact of regulatory changes.

302

303 **Conclusions**

304 Codeine is one of the most widely accessible and used opioids worldwide. However,
305 monitoring its use and preventing its misuse as an OTC product is a public health
306 challenge. Healthcare professionals should ask their patients about their use of OTC
307 products. Public health measures are needed to identify and prevent codeine misuse and
308 increase awareness and education of the harms of codeine, particularly in young adults.
309 Governments should review policies to improve the collection of sales data and safety
310 of products sold OTC containing codeine.

311

312

313

314 **Supplementary material**

315 Supplement 1: Supplementary tables and figures

316 Supplement 2: STROBE reporting checklist

317

318 **Declarations**

319 **Funding**

320 This research was supported by the Primary Care Research Trust of Birmingham and

321 Midlands Research Practices Consortium who provided the funding to purchase the

322 sales data from IQVIA.

323

324 **Competing interests**

325 GCR was financially supported by the National Institute for Health Research (NIHR)

326 School for Primary Care Research (SPCR), the Naji Foundation, and the Rotary

327 Foundation to study for a Doctor of Philosophy (2017-2020), but no longer has any

328 financial COIs. GCR is an Associate Editor of BMJ Evidence Based Medicine. JKA has

329 published articles and edited textbooks on adverse drug reactions and interactions and

330 has often given medicolegal advice, including appearances as an expert witness in

331 coroners' courts, often dealing with the adverse effects of opioids. BM works for NHS

332 England as a pharmacist adviser. BG has received research funding from the Laura and

333 John Arnold Foundation, the NIHR, the NIHR SPCR, the NIHR Oxford Biomedical

334 Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research

335 Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking

336 Foundation, Health Data Research UK (HDRUK), the Health Foundation, and the

337 World Health Organisation (WHO); he also receives personal income from speaking

338 and writing for lay audiences on the misuse of science. FDRH acknowledges part
339 support from the NIHR SPCR, the NIHR Applied Research Collaboration (ARC)
340 Oxford Thames Valley, and the NIHR Oxford OUH BRC. CH is an NIHR Senior
341 Investigator and has received expenses and fees for his media work, received expenses
342 from the WHO, FDA, and holds grant funding from the NIHR SPCR and the NIHR
343 SPCR Evidence Synthesis Working Group [Project 380], the NIHR BRC Oxford and
344 the WHO. On occasion, CH receives expenses for teaching EBM and is also paid for his
345 GP work in NHS out of hours (contract with Oxford Health NHS Foundation Trust).
346 CH is the Director of the CEBM. The views expressed are those of the authors and not
347 necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

348

349 **Availability of data and material**

350 Study materials are available on an open repository [61] (<https://osf.io/yt6bf/>). We
351 cannot openly share the data owing to contractual agreements with *IQVIA*, but the data
352 can be accessed directly from *IQVIA*, which will require a fee.

353

354 **Code availability**

355 Our statistical code is openly available at GitHub [58]
356 (https://github.com/georgiarichards/otc_codeine).

357

358 **Authors' contributions**

359 GCR devised the research question, designed the methods, wrote the protocol,
360 conducted a literature search, sourced the data, cleaned, managed, and analysed the
361 data, created the figures, and wrote the first draft of the manuscript. JKA and CH

362 reviewed the protocol and preliminary findings and provided supervisory support.

363 FDRH reviewed the protocol and facilitated the grant application. BM reviewed

364 preliminary findings and contributed to the interpretation of data. BG provided

365 supervisory support.

366

367 **Ethics approval**

368 Not applicable

369

370 **Consent to participate**

371 Not applicable

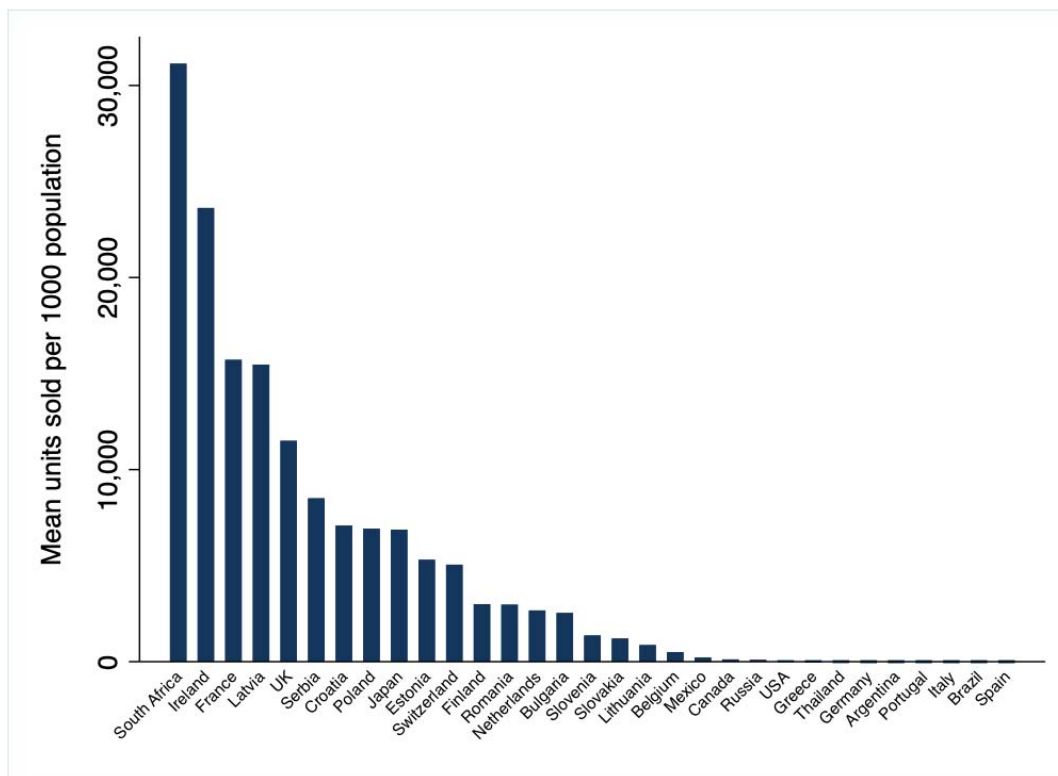
372

373 **Consent to publication**

374 All authors read and approved the final manuscript and consent to submit the

375 manuscript for publication.

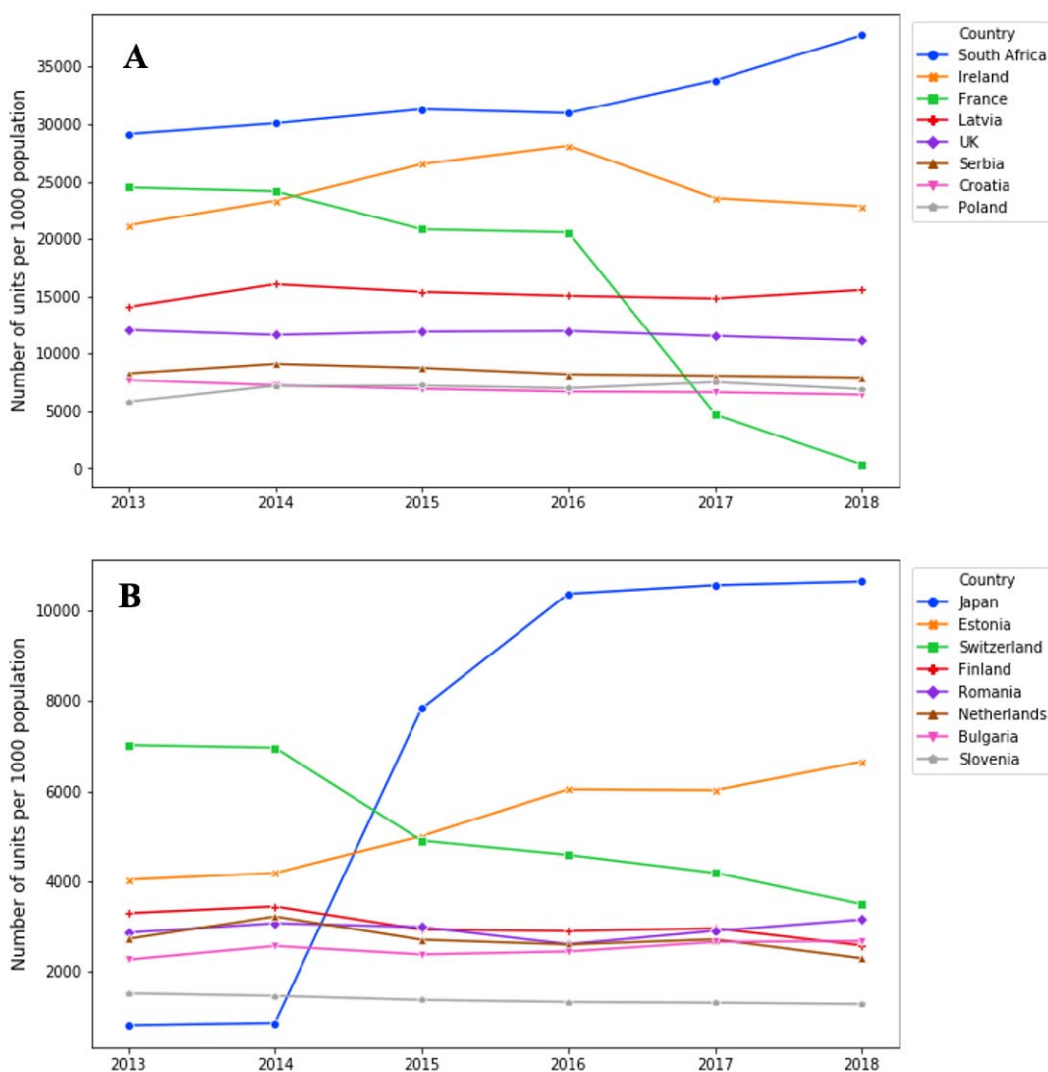
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377

378 **Figure 1:** Mean sales of over-the-counter (OTC) codeine-containing units sold over six
379 years in 31 countries with data in descending order

380



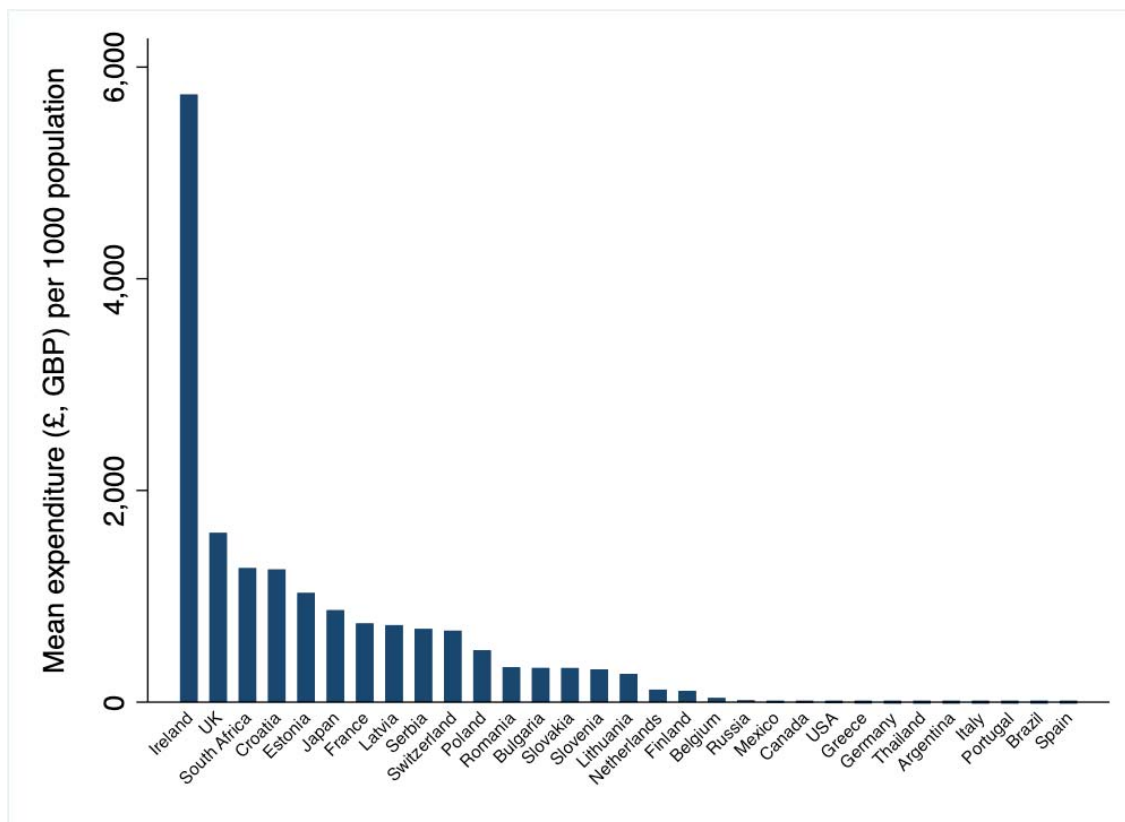
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382 **Figure 2:** Sales of over-the-counter (OTC) products containing codeine per 1000 of the

383 population starting in April 2013 to March 2014, and ending in April 2018 to March

384 2019, for countries in the top quartile (A) and second quartile (B) of sales

385



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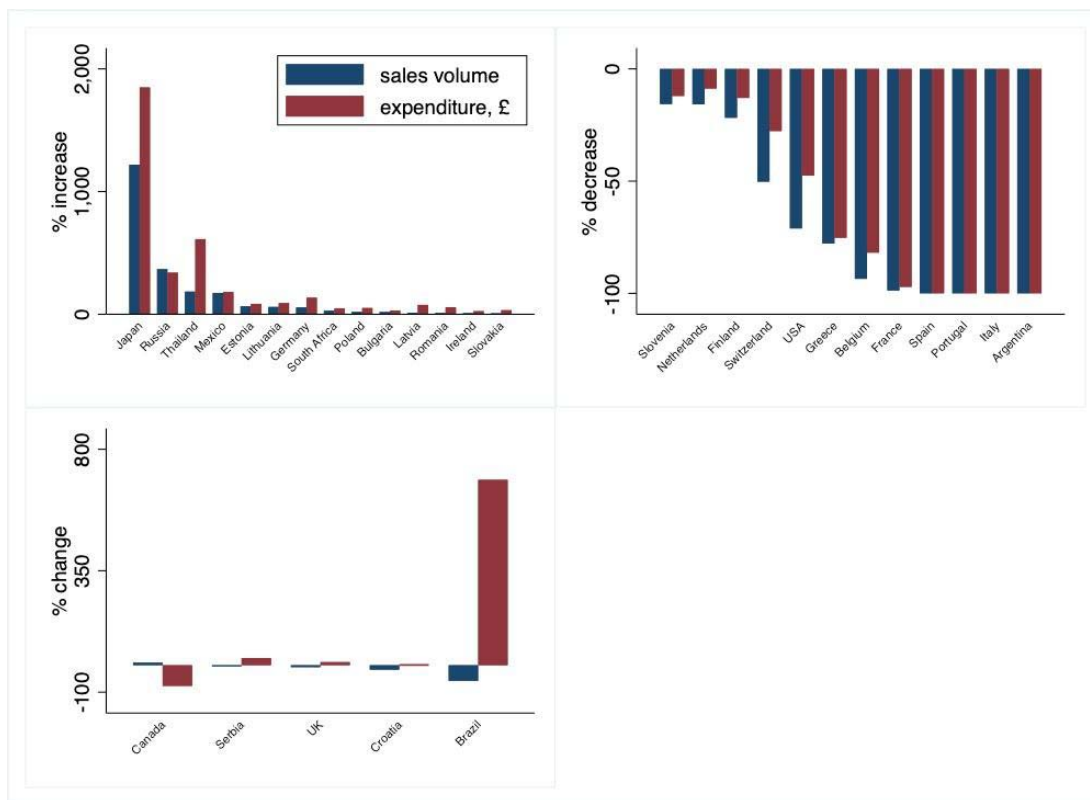
387 **Figure 3:** Public expenditure on over-the-counter (OTC) codeine-containing units sold

388

over six years in 31 countries with data in descending order

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390



391

392

Figure 4: Percentage changes in sales (units sold per 1000 of the population) and public

393

expenditure (£ per 1000) on products containing codeine sold over-the-counter (OTC)

394

in 31 countries between April 2013 and March 2019

395

396 **References**

- 397 1. Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid
398 prescribing trends and geographical variation in England, 1998-2018: a
399 retrospective database study. *Lancet Psych* [Internet]. The DataLab, Nuffield
400 Department of Primary Care Health Sciences, University of Oxford, Radcliffe
401 Observatory Quarter, Oxford, UK. Centre for Evidence Based Medicine, Nuffield
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403 2019;6:140–50. Available from: [http://dx.doi.org/10.1016/S2215-0366\(18\)30471-1](http://dx.doi.org/10.1016/S2215-0366(18)30471-1).
- 404 2. Davies E, Sewell B, Jones M, Phillips CJ, Rance JY. Examining opioid prescribing
405 trends for non-cancer pain using an estimated oral morphine equivalence measure:
406 a retrospective cohort study between 2005 and 2015. *BJGP Open* [Internet]. Royal
407 College of General Practitioners; 2020 [cited 2021 Jan 7];bjgpopen20X101122.
408 Available from:
409 <https://bjgpopen.org/content/early/2020/11/30/bjgpopen20X101122>.
- 410 3. Gomes T, Mamdani MM, Paterson JM, Dhalla IA, Juurlink DN. Trends in high-
411 dose opioid prescribing in Canada. *Can Fam Physician* [Internet]. Scientist at the
412 Institute for Clinical Evaluative Sciences; Assistant Professor at the Institute for
413 Health Policy, Management and Evaluation and the Leslie Dan Faculty of
414 Pharmacy at the University of Toronto; and Scientist at the Li Ka Shing Knowledge
415 ; 2014;60:826–32. Available from:
416 <https://www.ncbi.nlm.nih.gov/pubmed/25217680>.
- 417 4. Wagemakers FN, Hollingworth SA, Kreijkamp-Kaspers S, Tee EHL, Leendertse
418 AJ, van Driel ML. Opioid analgesic use in Australia and The Netherlands: a cross-
419 country comparison. *Int J Clin Pharm*. 2017;39.
- 420 5. Goodman-Meza D, Friedman J, Kalmin MM, Aguilar-Posada E, Seamans MJ,
421 Velazquez-Moreno S, et al. Geographical and socioeconomic disparities in opioid
422 access in Mexico, 2015–19: a retrospective analysis of surveillance data. *Lancet*
423 *Public Heal* [Internet]. Elsevier; 2021 [cited 2021 Jan 29];6:e88–96. Available
424 from: <https://linkinghub.elsevier.com/retrieve/pii/S2468266720302607>.
- 425 6. Kalkman GA, Kramers C, Van Dongen RT, Van Den Brink W, Schellekens A.
426 Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-
427 source database study. *Lancet Public Heal* [Internet]. 2019 [cited 2019 Oct

- 428 29];4:498–505. Available from: www.thelancet.com.
- 429 7. Krawczyk N, Greene MC, Zorzanelli R, Bastos FI. Rising trends of prescription
430 opioid sales in contemporary Brazil, 2009-2015. *Am J Public Health* 2018.
- 431 8. Dutch MJ. Nurofen Plus misuse: An emerging cause of perforated gastric ulcer.
432 *Med J Aust* [Internet]. Australasian Medical Publishing Co. Ltd; 2008 [cited 2020
433 Sep 7];188:56–7. Available from:
434 [https://www.mja.com.au/journal/2008/188/1/nurofen-plus-misuse-emerging-cause-](https://www.mja.com.au/journal/2008/188/1/nurofen-plus-misuse-emerging-cause-perforated-gastric-ulcer)
435 [perforated-gastric-ulcer](https://www.mja.com.au/journal/2008/188/1/nurofen-plus-misuse-emerging-cause-perforated-gastric-ulcer).
- 436 9. Frei MY, Nielsen S, Dobbin MDH, Tobin CL. Serious morbidity associated with
437 misuse of over-the-counter codeine-ibuprofen analgesics: A series of 27 cases. *Med*
438 *J Aust*. Australasian Medical Publishing Co. Ltd; 2010;193:294–6.
- 439 10. Lambert AP. Life-threatening hypokalaemia from abuse of Nurofen Plus. *J R Soc*
440 *Med* [Internet]. SAGE Publications; 2005 [cited 2020 Sep 7];98:21–21. Available
441 from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1079233>.
- 442 11. Roussin A, Bouyssi A, Pouché L, Pourcel L, Lapeyre-Mestre M. Misuse and
443 Dependence on Non-Prescription Codeine Analgesics or Sedative H1
444 Antihistamines by Adults: A Cross-Sectional Investigation in France. *PLoS One*
445 [Internet]. Public Library of Science; 2013 [cited 2020 Sep 24];8. Available from:
446 [/pmc/articles/PMC3789666/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC3789666/?report=abstract).
- 447 12. Carney T, Wells J, Parry CDH, McGuinness P, Harris R, Van Hout MC. A
448 comparative analysis of pharmacists’ perspectives on codeine use and misuse - A
449 three country survey. *Subst Abus Treat Prev Policy*. BioMed Central Ltd.; 2018;13.
- 450 13. Sproule BA, Busto UE, Somer G, Romach MK, Sellers EM. Characteristics of
451 dependent and nondependent regular users of codeine. *J Clin Psychopharmacol*
452 [Internet]. *J Clin Psychopharmacol*; 1999 [cited 2020 Sep 7];19:367–72. Available
453 from: <https://pubmed.ncbi.nlm.nih.gov/10440466>.
- 454 14. Wu Q, Yu J, Yang C, Chen J, Yang L, Zhang H, et al. Nonmedical use of cough
455 syrup among secondary vocational school students: A national survey in China.
456 *Med (United States)* [Internet]. Lippincott Williams and Wilkins; 2016 [cited 2021
457 Jan 18];95. Available from: <https://pubmed.ncbi.nlm.nih.gov/26962800>.
- 458 15. Kimergård A, Foley M, Davey Z, Dunne J, Drummond C, Deluca P. Codeine use,
459 dependence and help-seeking behaviour in the UK and Ireland: an online cross-

- 460 sectional survey. *QJM An Int J Med* [Internet]. Oxford University Press; 2017
461 [cited 2021 Jan 18];110:559–64. Available from:
462 <https://academic.oup.com/qjmed/article/110/9/559/3098674>.
- 463 16. Agaba E, Agaba P, Wigwe C. Use and abuse of analgesics in Nigeria: a community
464 survey. *Niger J Med* [Internet]. 2004 [cited 2021 Jan 29];13:379–82. Available
465 from: <https://pubmed.ncbi.nlm.nih.gov/15523865>.
- 466 17. Orriols L, Gaillard J, Lapeyre-Mestre M, Roussin A. Evaluation of abuse and
467 dependence on drugs used for self-medication: A pharmacoepidemiological pilot
468 study based on community pharmacies in France. *Drug Saf* [Internet]. *Drug Saf*;
469 2009 [cited 2020 Sep 11];32:859–73. Available from:
470 <https://pubmed.ncbi.nlm.nih.gov/19722729>.
- 471 18. Kontogiorgis C, Nena E, Berberoglou E, Moschoni K, Polyzois S, Tselempis A,
472 et al. Estimating Consumers' Knowledge and Attitudes Towards Over-The-Counter
473 Analgesic Medication in Greece in the Years of Financial Crisis: The Case of
474 Paracetamol. *Pain Ther*. 2016;5.
- 475 19. Cooper RJ. "I can't be an addict. I am." Over-the-counter medicine abuse: a
476 qualitative study. *BMJ Open* [Internet]. British Medical Journal Publishing Group;
477 2013 [cited 2020 Oct 6];3:2913. Available from: <http://bmjopen.bmj.com>.
- 478 20. Lee E, Cooper RJ. Codeine addiction and internet forum use and support:
479 Qualitative netnographic study. *J Med Internet Res* [Internet]. *Journal of Medical*
480 *Internet Research*; 2019 [cited 2020 Oct 6];21. Available from:
481 [/pmc/articles/PMC6658256/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/34811111/).
- 482 21. Van Hout MC, Rich E, Dada S, Bergin M. "codeine Is My Helper": Misuse of and
483 Dependence on Codeine-Containing Medicines in South Africa. *Qual Health Res*.
484 2017;27.
- 485 22. Kinnaird E, Kimergård A, Jennings S, Drummond C, Deluca P. From pain
486 treatment to opioid dependence: A qualitative study of the environmental influence
487 on codeine use in UK adults. *BMJ Open* [Internet]. BMJ Publishing Group; 2019
488 [cited 2021 Jan 12];9:e025331. Available from: <http://bmjopen.bmj.com>.
- 489 23. Roxburgh A, Hall WD, Burns L, Pilgrim J, Saar E, Nielsen S, et al. Trends and
490 characteristics of accidental and intentional codeine overdose deaths in Australia.
491 *Med J Aust*. Australasian Medical Publishing Co. Ltd; 2015;203:299.e1-299.e7.

- 492 24. Hopkins RE, Dobbin M, Pilgrim JL. Unintentional mortality associated with
493 paracetamol and codeine preparations, with and without doxylamine, in Australia.
494 *Forensic Sci Int* [Internet]. Elsevier Ireland Ltd; 2018 [cited 2020 Jul 2];282:122–6.
495 Available from: <https://pubmed.ncbi.nlm.nih.gov/29182956>.
- 496 25. Schifano F, Zamparutti G, Zambello F, Oyefeso A, Deluca P, Balestrieri M, et al.
497 Review of deaths related to analgesic- and cough suppressant-opioids; England and
498 Wales 1996-2002. *Pharmacopsychiatry*. Pharmacopsychiatry; 2006. p. 185–91.
- 499 26. Cairns R, Brown JA, Buckley NA. The impact of codeine re-scheduling on misuse:
500 a retrospective review of calls to Australia’s largest poisons centre. *Addiction*
501 [Internet]. Blackwell Publishing Ltd; 2016 [cited 2020 Sep 7];111:1848–53.
502 Available from: <https://pubmed.ncbi.nlm.nih.gov/27177599>.
- 503 27. Mill D, Johnson JL, Cock V, Monaghan E, Hotham ED. Counting the cost of over-
504 the-counter codeine containing analgesic misuse: A retrospective review of hospital
505 admissions over a 5 year period. *Drug Alcohol Rev* [Internet]. Blackwell
506 Publishing; 2018 [cited 2020 Sep 7];37:247–56. Available from:
507 <https://pubmed.ncbi.nlm.nih.gov/28925091>.
- 508 28. Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for
509 acute postoperative pain in adults. *Cochrane Database Syst Rev* [Internet]. Wiley;
510 2010 [cited 2021 Jan 18]; Available from:
511 <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008099.pub2/full>.
- 512 29. Omar MI, Alexander CE. Drug treatment for faecal incontinence in adults
513 [Internet]. *Cochrane Database Syst. Rev.* John Wiley and Sons Ltd; 2013 [cited
514 2020 Sep 3]. Available from:
515 <http://doi.wiley.com/10.1002/14651858.CD002116.pub2>.
- 516 30. Molassiotis A, Bailey C, Caress A, Tan JY. Interventions for cough in cancer
517 [Internet]. *Cochrane Database Syst. Rev.* John Wiley and Sons Ltd; 2015 [cited
518 2020 Sep 4]. Available from:
519 <http://doi.wiley.com/10.1002/14651858.CD007881.pub3>.
- 520 31. Derry S, Karlin SM, Moore RA. Single dose oral ibuprofen plus codeine for acute
521 postoperative pain in adults [Internet]. *Cochrane Database Syst. Rev.* John Wiley
522 and Sons Ltd; 2015 [cited 2020 Sep 4]. Available from:
523 <http://doi.wiley.com/10.1002/14651858.CD010107.pub3>.

- 524 32. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol
525 (acetaminophen) with codeine for postoperative pain in adults [Internet]. Cochrane
526 Database Syst. Rev. John Wiley and Sons Ltd; 2009 [cited 2020 Sep 4]. Available
527 from: <http://doi.wiley.com/10.1002/14651858.CD001547.pub2>.
- 528 33. Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L. Non-prescription
529 (OTC) oral analgesics for acute pain - an overview of Cochrane reviews [Internet].
530 Cochrane Database Syst. Rev. John Wiley and Sons Ltd; 2015 [cited 2020 Sep 3].
531 Available from: <http://doi.wiley.com/10.1002/14651858.CD010794.pub2>.
- 532 34. Abdel Shaheed C, Maher CG, McLachlan AJ. Efficacy and Safety of Low-dose
533 Codeine-containing Combination Analgesics for Pain. *Clin J Pain* [Internet]. 2019
534 [cited 2019 Dec 14];35:836–43. Available from:
535 <http://insights.ovid.com/crossref?an=00002508-201910000-00005>.
- 536 35. Agnich LE, Stogner JM, Miller BL, Marcum CD. Purple drank prevalence and
537 characteristics of misusers of codeine cough syrup mixtures. *Addict Behav*
538 [Internet]. *Addict Behav*; 2013 [cited 2021 Jan 18];38:2445–9. Available from:
539 <https://pubmed.ncbi.nlm.nih.gov/23688907>.
- 540 36. Soares JX, Alves EA, Silva AMN, De Figueiredo NG, Neves JF, Cravo SM, et al.
541 Street-Like Synthesis of Krokodil Results in the Formation of an Enlarged Cluster
542 of Known and New Morphinans. *Chem Res Toxicol* [Internet]. American Chemical
543 Society; 2017 [cited 2021 Jan 18];30:1609–21. Available from:
544 <https://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.7b00126>.
- 545 37. Bedford KR, Nolan SL, Onrust R, Siegers JD. The illicit preparation of morphine
546 and heroin from pharmaceutical products containing codeine: “homebake”
547 laboratories in New Zealand. *Forensic Sci Int* [Internet]. *Forensic Sci Int*; 1987
548 [cited 2021 Jan 18];34:197–204. Available from:
549 <https://pubmed.ncbi.nlm.nih.gov/3666623>.
- 550 38. Oliver T, Gheevarghese SJ, Gandhi U, Bhat ZY, Pillai U. “Krokodil”-A menace
551 slowly spreading across the Atlantic [Internet]. *Am. J. Ther.* Lippincott Williams
552 and Wilkins; 2015 [cited 2021 Jan 18]. p. 231–3. Available from:
553 <https://pubmed.ncbi.nlm.nih.gov/25756471>.
- 554 39. WHO. Pre-Review Report: Preparations of codeine listed in Schedule III of the
555 1961 Single Convention on Narcotic Drugs [Internet]. Geneva; 2019 Oct. Available

- 556 from: <https://www.who.int/medicines/access/controlled->
557 substances/Final_codeine.pdf.
- 558 40. United Nations. United Nations Single Convention on Narcotic Drugs, 1961
559 [Internet]. 1961 [cited 2021 Jan 20]. Available from:
560 [https://www.emcdda.europa.eu/drugs-library/single-convention-narcotic-drugs-](https://www.emcdda.europa.eu/drugs-library/single-convention-narcotic-drugs-1961_en)
561 1961_en.
- 562 41. Office of the Revisor of Statutes. 2020 Minnesota Statutes [Internet]. Minnesota
563 Legis. 2020 [cited 2020 Jan 24]. Available from:
564 <https://www.revisor.mn.gov/statutes/cite/152.02>.
- 565 42. College of Pharmacists of Manitoba. Exempted codeine changes [Internet]. 2016
566 [cited 2021 Jan 24]. Available from:
567 <https://mpa.in1touch.org/site/exemptedcodeine?nav=public>.
- 568 43. Wilkes D. France restricts dextromethorphan and codeine [Internet]. OTC Toolbox.
569 2017 [cited 2021 Jan 24]. Available from: [https://www.otctoolbox.com/industry-](https://www.otctoolbox.com/industry-news/france-restricts-dextromethorphan-and-codeine)
570 news/france-restricts-dextromethorphan-and-codeine.
- 571 44. Kirby T. The end of over-the-counter codeine in Australia. *Lancet* [Internet]. 2018
572 [cited 2019 Dec 13]; Available from: www.thelancet.com/psychiatry.
- 573 45. Foley M, Harris R, Rich E, Rapca A, Bergin M, Norman I, et al. The availability of
574 over-the-counter codeine medicines across the European Union. *Public Health*.
575 Elsevier; 2015;129:1465–70.
- 576 46. Lo MY, Ong MW, Lin JG, Sun WZ. Codeine consumption from over-the-counter
577 anti-cough syrup in Taiwan: A useful indicator for opioid abuse. *Acta Anaesthesiol*
578 *Taiwanica* [Internet]. Elsevier Taiwan LLC; 2015 [cited 2021 Jan 20];53:135–8.
579 Available from: <https://pubmed.ncbi.nlm.nih.gov/26646544>.
- 580 47. Cairns R, Schaffer AL, Brown JA, Pearson S, Buckley NA. Codeine use and harms
581 in Australia: evaluating the effects of re-scheduling. *Addiction* [Internet].
582 Blackwell Publishing Ltd; 2020 [cited 2020 May 17];115:451–9. Available from:
583 <https://onlinelibrary.wiley.com/doi/abs/10.1111/add.14798>.
- 584 48. Gisev N, Nielsen S, Cama E, Larance B, Bruno R, Degenhardt L. An ecological
585 study of the extent and factors associated with the use of prescription and over-the-
586 counter codeine in Australia. *Eur J Clin Pharmacol* [Internet]. Springer Verlag;
587 2016 [cited 2020 Jul 7];72:469–94. Available from:

- 588 <https://link.springer.com/article/10.1007/s00228-015-1995-8>.
- 589 49. Consumer Health - IQVIA [Internet]. [cited 2020 Jun 12]. Available from:
590 <https://www.iqvia.com/solutions/industry-segments/consumer-health>.
- 591 50. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption
592 of oral antibiotic formulations for young children according to the WHO Access,
593 Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70
594 middle-income and high-income countries. *Lancet Infect Dis*. Lancet Publishing
595 Group; 2019;19:67–75.
- 596 51. Suchard MA, Schuemie MJ, Krumholz HM, You SC, Chen RJ, Pratt N, et al.
597 Comprehensive comparative effectiveness and safety of first-line antihypertensive
598 drug classes: a systematic, multinational, large-scale analysis. *Lancet*. Lancet
599 Publishing Group; 2019;394:1816–26.
- 600 52. Guy GP, Haegerich TM, Evans ME, Losby JL, Young R, Jones CM. Vital Signs:
601 Pharmacy-Based Naloxone Dispensing — United States, 2012–2018. *MMWR*
602 *Morb Mortal Wkly Rep* [Internet]. NLM (Medline); 2019 [cited 2020 Jun
603 12];68:679–86. Available from:
604 http://www.cdc.gov/mmwr/volumes/68/wr/mm6831e1.htm?s_cid=mm6831e1_w.
- 605 53. Smith B, Culligan C, McFarlane A, Rickwood S, Clark C. The changing dynamic
606 of the UK retail pharmaceutical market [Internet]. 2018. Available from:
607 [https://www.iqvia.com/-/media/iqvia/pdfs/uk/the-changing-dynamic-of-the-uk-](https://www.iqvia.com/-/media/iqvia/pdfs/uk/the-changing-dynamic-of-the-uk-retail-pharmaceutical-market.pdf)
608 [retail-pharmaceutical-market.pdf](https://www.iqvia.com/-/media/iqvia/pdfs/uk/the-changing-dynamic-of-the-uk-retail-pharmaceutical-market.pdf).
- 609 54. The World Bank. Population data [Internet]. 2019 [cited 2020 May 28]. Available
610 from:
611 [https://data.worldbank.org/indicator/SP.POP.TOTL?end=2018&start=1960&view=](https://data.worldbank.org/indicator/SP.POP.TOTL?end=2018&start=1960&view=chart)
612 [chart](https://data.worldbank.org/indicator/SP.POP.TOTL?end=2018&start=1960&view=chart).
- 613 55. PANDAS Development Team. *pandas-dev/pandas: PANDAS*. Zenodo; 2020.
- 614 56. Waskom M. *mwaskom/seaborn*. Zenodo; 2020.
- 615 57. Hunter J. Matplotlib: a 2D graphics environment. *Comput Sci Eng*. 2009;9:90–5.
- 616 58. Richards G. *georgiarichards/otc_codeine* [Internet]. GitHub. 2020 [cited 2021 Apr
617 3]. Available from: https://github.com/georgiarichards/otc_codeine.
- 618 59. Richards G. Sales of over-the-counter (OTC) codeine-containing products in 31
619 countries, 2013-2019 [Internet]. OSF Regist. 2020 [cited 2021 Apr 3]. Available

- 620 from: <https://osf.io/ay4mc>.
- 621 60. Richards GC, Mahtani KR, Goldacre B, Heneghan C. 135 Trends and variation in
622 the sales of over-the-counter analgesics: a protocol for a retrospective database
623 study and policy review. *BMJ Evidence-Based Med* [Internet]. BMJ; 2018 [cited
624 2021 Jan 5]. p. A63.2-A64. Available from:
625 https://ebm.bmj.com/content/23/Suppl_2/A63.2.
- 626 61. Richards GC, Hobbs R, Aronson JK, Heneghan C. Sales of over-the-counter (OTC)
627 codeine-containing products in 31 countries, 2013-2019 [Internet]. OSF. OSF; 2021
628 [cited 2021 Jan 4]. Available from: <https://osf.io/yt6bf>.
- 629 62. Weich L, Perkel C, van Zyl N, Rataemane S, Naidoo L. Review Article: Medical
630 management of opioid dependence in South Africa. *South African Med J* [Internet].
631 2008 [cited 2021 Jan 31];98. Available from:
632 <https://www.ajol.info/index.php/samj/article/view/13959>.
- 633 63. VICE Video. Zimbabwe's Codeine Cough Syrup Epidemic [Internet]. 2018 [cited
634 2021 Feb 1]. Available from: [https://video.vice.com/en_uk/video/vice-zimbabwes-](https://video.vice.com/en_uk/video/vice-zimbabwes-codeine-cough-syrup-epidemic-1-104/5c373790be407707904345c1)
635 [codeine-cough-syrup-epidemic-1-104/5c373790be407707904345c1](https://video.vice.com/en_uk/video/vice-zimbabwes-codeine-cough-syrup-epidemic-1-104/5c373790be407707904345c1).
- 636 64. Cherian R, Westbrook M, Ramo D, Sarkar U. Representations of codeine misuse
637 on instagram: Content analysis. *J Med Internet Res* [Internet]. JMIR Publications
638 Inc.; 2018 [cited 2021 Jan 19];20. Available from:
639 <https://pubmed.ncbi.nlm.nih.gov/29559422>.
- 640 65. Tettey N-S, Siddiqui K, Llamoca H, Nagamine S, Ahn S. Purple Drank, Sizurp, and
641 Lean: Hip-Hop Music and Codeine Use, A Call to Action for Public Health
642 Educators. *Int J Psychol Stud* [Internet]. Canadian Center of Science and
643 Education; 2020 [cited 2021 Jan 19];12:42. Available from:
644 <http://www.ccsenet.org/journal/index.php/ijps/article/view/0/42126>.
- 645 66. Peteet B, Roundtree C, Dixon S, Mosley C, Miller-Roenigk B, White J, et al.
646 'Codeine crazy:' a content analysis of prescription drug references in popular
647 music. *J Youth Stud* [Internet]. Routledge; 2020 [cited 2021 Jan 19]; Available
648 from: <https://www.tandfonline.com/doi/abs/10.1080/13676261.2020.1801992>.
- 649 67. Van Hout MC. Kitchen chemistry: A scoping review of the diversionary use of
650 pharmaceuticals for non-medicinal use and home production of drug solutions
651 [Internet]. *Drug Test. Anal.* John Wiley and Sons Ltd; 2014 [cited 2021 Jan 28]. p.

- 652 778–87. Available from: <https://pubmed.ncbi.nlm.nih.gov/24619569>.
- 653 68. Torgerson T, Swayze C, Sanghera S, Cooper C, Beaman J, Hartwell M, et al.
654 Public awareness of the National Suicide Prevention Lifeline following the release
655 of a hip-hop song. *BMJ Evidence-Based Med* [Internet]. BMJ; 2021 [cited 2021
656 Feb 12];[bmjebm-2020-111509](https://ebm.bmj.com/content/early/2021/01/28/bmjebm-2020-111509). Available from:
657 <https://ebm.bmj.com/content/early/2021/01/28/bmjebm-2020-111509>.
- 658 69. de Villiers J. Here are the over-the-counter medicines you may need a prescription
659 for in future - including Adcodol and Nurofen Plus [Internet]. *Bus. Insid. SA*. 2020
660 [cited 2021 Jan 25]. Available from: [https://www.businessinsider.co.za/codeine-](https://www.businessinsider.co.za/codeine-containing-medicines-in-south-africa-to-be-affected-by-south-african-health-products-regulatory-authoritys-up-scheduling-move-2020-1)
661 [containing-medicines-in-south-africa-to-be-affected-by-south-african-health-](https://www.businessinsider.co.za/codeine-containing-medicines-in-south-africa-to-be-affected-by-south-african-health-products-regulatory-authoritys-up-scheduling-move-2020-1)
662 [products-regulatory-authoritys-up-scheduling-move-2020-1](https://www.businessinsider.co.za/codeine-containing-medicines-in-south-africa-to-be-affected-by-south-african-health-products-regulatory-authoritys-up-scheduling-move-2020-1).
- 663 70. Ridley D. Swiss experts advise codeine reverse-switch [Internet]. LinkedIn. 2018
664 [cited 2021 Jan 25]. Available from: [https://www.linkedin.com/pulse/swiss-experts-](https://www.linkedin.com/pulse/swiss-experts-advise-codeine-reverse-switch-david-ridley)
665 [advise-codeine-reverse-switch-david-ridley](https://www.linkedin.com/pulse/swiss-experts-advise-codeine-reverse-switch-david-ridley).
- 666 71. MHRA. UK regulator strengthens opioid warnings [Internet]. *Vigil. Saf. alerts*
667 *Guid*. 2020 [cited 2021 Jan 20]. Available from:
668 <https://www.gov.uk/government/news/uk-regulator-strengthens-opioid-warnings>.
- 669 72. Government of Canada. Forward Regulatory Plan 2019-2021: Regulations
670 Amending the Narcotic Control Regulations under the Controlled Drugs and
671 Substances Act to make all products containing codeine available by prescription
672 only while ensuring access to these medications [Internet]. 2019 [cited 2021 Jan
673 28]. Available from: [https://www.canada.ca/en/health-canada/corporate/about-](https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/codeine-prescription.html)
674 [health-canada/legislation-guidelines/acts-regulations/forward-regulatory-](https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/codeine-prescription.html)
675 [plan/plan/codeine-prescription.html](https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/codeine-prescription.html).
- 676 73. Schaffer AL, Cairns R, Brown JA, Gisev N, Buckley NA, Pearson SA. Changes in
677 sales of analgesics to pharmacies after codeine was rescheduled as a prescription
678 only medicine. *Med J Aust*. John Wiley and Sons Inc.; 2020;212:321–7.
- 679 74. Fadhil I, Lyons G, Payne S. Barriers to, and opportunities for, palliative care
680 development in the Eastern Mediterranean Region. *Lancet Oncol*. Lancet
681 Publishing Group; 2017. p. e176–84.
- 682 75. Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, et al. Use of and
683 barriers to access to opioid analgesics: A worldwide, regional, and national study.

- 684 Lancet. 2016;387.
- 685 76. Richards GC, Aronson JK, Mahtani KR, Heneghan C. Global, regional, and
686 national consumption of controlled opioids: a cross-sectional study of 214 countries
687 and non-metropolitan territories. *Br J Pain* [Internet]. SAGE Publications Ltd; 2021
688 [cited 2021 Jun 11]; Available from: <https://doi.org/10.1177/20494637211013052>.
- 689 77. Richards GC, Aronson JK, Heneghan C, Mahtani KR, Koshiaris C, Persaud N.
690 Relation between opioid consumption and inclusion of opioids in 137 national
691 essential medicines lists. *BMJ Glob Heal*. 2020;5:1–8.
- 692 78. Marsh S. “I could get 500 tablets a month”: the ease of buying opiates online
693 [Internet]. *Guard*. 2019 [cited 2021 Jan 24]. Available from:
694 [https://www.theguardian.com/society/2019/apr/26/i-could-get-500-tablets-a-month-](https://www.theguardian.com/society/2019/apr/26/i-could-get-500-tablets-a-month-ease-of-buying-opiates-online)
695 [ease-of-buying-opiates-online](https://www.theguardian.com/society/2019/apr/26/i-could-get-500-tablets-a-month-ease-of-buying-opiates-online).
- 696 79. NHS England. The Controlled Drugs (Supervision of Management and Use)
697 Regulations 2013 [Internet]. Single Oper. Model. 2013 [cited 2021 Apr 19].
698 Available from: [https://www.england.nhs.uk/wp-content/uploads/2013/11/som-](https://www.england.nhs.uk/wp-content/uploads/2013/11/som-cont-drugs.pdf)
699 [cont-drugs.pdf](https://www.england.nhs.uk/wp-content/uploads/2013/11/som-cont-drugs.pdf).
- 700 80. PSNC. Controlled Drug prescription forms and validity [Internet]. *Pharm. Serv.*
701 *Negot. Comm*. 2020 [cited 2021 Apr 19]. Available from:
702 [https://psnc.org.uk/dispensing-supply/dispensing-controlled-drugs/controlled-drug-](https://psnc.org.uk/dispensing-supply/dispensing-controlled-drugs/controlled-drug-prescription-forms-and-validity)
703 [prescription-forms-and-validity](https://psnc.org.uk/dispensing-supply/dispensing-controlled-drugs/controlled-drug-prescription-forms-and-validity).
- 704 81. INCB. Narcotic Drugs — Estimated World Requirements for 2020 — Statistics for
705 2018 [Internet]. Vienna; 2019. Available from:
706 [https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-](https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf)
707 [2019.06-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf).
- 708