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TITLE: Polysubstance use and misuse or abuse of prescription opioid analgesics: A multi-level analysis of international data

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INTRODUCTION

Over the last decade, increasing mortality and morbidity associated with opioid analgesics has led to concerns about misuse and abuse of these drugs, even when obtained via prescription. This has been most pronounced in the United States of America (USA) where dispensed prescriptions increased from 47 million in 2006 to 60 million in 2013 [11]. This was accompanied by increases in opioid-related overdose mortality and admission for treatment [22]. Policies designed to counter these trends have had some effect , with diversion, abuse, and attributable mortality reaching a plateau from 2011 [11]. However, concerns have been raised that misuse and abuse of opioid analgesics is not limited to those who access them via non-clinical routes, and has not been adequately addressed in individuals using them for legitimate medical needs [6,22,40].

A recent review of opioid analgesic use in chronic pain patients identified substantial levels of problematic use [37]. Three types of problematic use were defined using statements from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials and Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks [27,34]:

- *Misuse*: use contrary to the directed pattern of use, regardless of harm or adverse effects;
- *Abuse*: intentional use for a nonmedical purpose;
- *Addiction*: pattern of continued use with experience of, or demonstrated potential for, harm.

The authors estimated misuse was documented in 21-29% of patients, and addiction in 8-12%. Abuse could not be estimated due to insufficient data, but in the one suitable study

identified 8% of patients met abuse criteria. However, the authors noted that most studies reviewed were from the USA, and raised the question of whether problematic opioid analgesic use is "a problem that is somehow uniquely relevant to the US".

There is evidence of problematic opioid analgesic use outside the USA, particularly in Europe and Australia. Although heroin is the most frequently abused opioid in Europe, demand for treatment relating to problematic use of other opioids is increasing [13]. A 2012 review identified opioid analgesics as one of the most commonly misused medicines in Europe, although the authors also noted the limited available data [9]. A more recent study estimated the prevalence of prescription opioid abuse as 13.7 per 10,000 individuals for France, 11.0 per 10,000 for Germany, and 10.7 per 10,000 for the United Kingdom (UK), but less than 1 per 10,000 individuals for Spain and Italy [33]. Similar statistics are unavailable for Australia, but a substantial increase in opioid analgesic prescriptions and opioid-related hospitalisations and deaths has occurred over the past decade, suggesting increasing levels of misuse and abuse [8].

Using Global Drug Survey data from the USA, UK, France, Germany, and Australia we investigated whether misuse and abuse of opioid analgesics obtained via prescription varied between countries. As polysubstance use involving illicit drugs and/or benzodiazepines is among the few consistent, strong predictors of problematic opioid analgesic use [9,32,36], we also investigated whether the association between this predictor and misuse or abuse varied between countries.

METHODS

Sample

Data were drawn from the 2015 Global Drug Survey (GDS), an annual online anonymous cross-sectional survey of licit and illicit drug use which ran from November 9th 2014 to January 3rd 2015 (www.globaldrugsurvey.com). The GDS includes a core set of drug history and sociodemographic variables, with additional modules on specialist topics included or excluded each year. Starting with a universal drug screen, the web-based survey then adjusts to ensure only sections relevant to each persons' recent drug use experience are displayed. Further information on the range of topics covered is available at www.globaldrugsurvey.com/gds-surveys/survey-composition/. For the analyses presented, data were drawn from a specialist module on prescription drugs, and the sociodemographic and universal drug screen sections.

All participants confirmed they were aged ≥16 years and consented to analysis of the information they provided. Ethical approval was received from The Psychiatry, Nursing and Midwives Ethics subcommittee at Kings College, London. The survey was translated into 10 languages and promoted in partnership with a range of media outlets including *The Guardian, Zeit Online, la Repubblica*, and Fairfax Media, and also distributed through Facebook, Twitter, social news website Reddit and drug discussion forums. There are no exclusion criteria except being under the age of 16 years and thus it was open to any individual who wished to complete it. The 2015 GDS was available in English, Danish, Flemish, French, German, Greek, Hungarian, Italian, Portuguese, Spanish, and Slovenian and distributed via media partners in Australia, Belgium, Denmark, France, Germany, Greece, Hungary, Ireland, Mexico, the Netherlands, New Zealand, Poland, Portugal, Slovenia, Spain,

Switzerland, the UK, and the USA. However, as this was an online survey and it was advertised via social media, responses were also received from individuals residing in other countries. GDS therefore recruits a non-probability sample and is not designed to determine the prevalence of drug behaviours in the general population. GDS is, however, an efficient way of gaining in-depth understanding of stigmatized behaviors that may not be well captured in more representative surveys. Other publications provide further details on the utility, design, and limitations of the Global Drug Survey [4,7,26,39].

In total, the 2015 GDS received responses from over 100,000 participants from 175 countries, with 31 countries contributing 100 or more responses. Our original intention was to analyse data from the USA, Australia, and the five European countries examined by Shei *et al.* [33] (UK, France, Germany, Spain, and Italy). However, we could only include countries with enough overall participants to ensure a sufficient sample of prescription opioid users for the multi-level analyses (described below). Unfortunately, less than 1,000 responses were received from participants resident in Italy and Spain so we could not include these countries in the analyses. Thus the analysis sample was defined as GDS on participants from Australia, France, Germany, the UK and the USA who had used prescription codeine, hydrocodone, oxycontin, or tramadol in the past 12 months. The relative frequency of prescribing of these opioid analgesics differs between countries: codeine and tramadol are more commonly prescribed in the UK, France, and Germany [1,16,31] whereas oxycodone and hydrocodone are more commonly prescribed in the USA [38]. In Australia, codeine is prescribed most frequently, followed by tramadol and oxycodone which are prescribed at similar frequencies [19].

Measures

Demographic covariates

Information was collected on gender, age, and highest educational qualification (high school, college diploma, undergraduate, postgraduate).

Drug use

Participants were asked "Have you used any of the following drugs in the last year?" and presented with a list of illicit drugs and licit drugs (including opioid analgesics and benzodiazepines). The following questions were revealed dynamically for each opioid analgesic for which they endorsed past-year use.

Methods of access

Participants were asked "Which of the following methods have you used to obtain it [specific medication]?" with the following options: Prescribed to you; Given to you by a friend; Bought by you from a dealer; Bought by you on the internet (multiple selections possible).

Ease of access to a prescription

Participants were asked “How easy would it be for you get it [drug] prescribed to you within the next 7 days?” selecting one option from: Very easy; Easy; Possible; Difficult; Very difficult. Responses were collapsed into a binary variable indicating “Very easy”" or “Easy”" responses versus other responses.

125

126 *Opioid analgesic misuse and abuse*

127 Misuse and abuse were defined following Vowles *et al*. [37]. In our data, misuse was coded
128 if participants endorsed one or more of the following responses to "If it [drug] was prescribed
129 to you in the last 12 months have you found yourself…":

130 - taking more than was prescribed;
131 - trying to get hold of extra medication;
132 - being unable cut down or stop using it;
133 - feeling physically and/or emotionally unwell when using less or stopping use;
134 - ever overdosed.

135 Abuse was coded if participants endorsed one or more of the following responses to the same
136 question:

137 - mixing it with other drugs to enhance the drug effect;
138 - mixing it with alcohol to enhance the drug effect.

139 Abuse was also coded if participants endorsed the option "getting high" when responding to
140 the question "In the last year have you taken this medication to achieve these desirable
141 objectives…".

142 Misuse and abuse variables were derived separately for each opioid analgesic, but as some
143 participants endorsed the use of more than one opioid analgesic, these data were also
144 combined to create two variables indicating misuse of at least one opioid analgesic and abuse
145 of at least one opioid analgesic.

146

147 *Polysubstance use*

148 Using the screening question "Have you used any of the following drugs in the past year?",
149 we identified participants who endorsed use of benzodiazepines (with or without a

150 prescription) or the following illicit drugs: cannabis (hydroponic, herbal, resin, or oil),
151 ecstasy (pills or powder), cocaine, crack, amphetamine, methamphetamine, mephedrone, or
152 heroin. For descriptive purposes, we used these data to create a categorical variable
153 indicating the following mutually exclusive patterns of substance use: no use of illicit drugs
154 or benzodiazepines in the past year; use of one or more illicit drugs only; use of
155 benzodiazepines only; use of one or more illicit drugs *and* benzodiazepines (combined use).
156 For analytical purposes we created two binary variables, one indicating use of illicit drugs in
157 the past year and other indicating use of benzodiazepines in the past year.
158
159 **Statistical analysis**
160 Sample characteristics were summarised using standard descriptive statistics. Multivariable
161 analyses were conducted using multi-level (i.e. mixed effects) binary logistic regression
162 models to allow for clustering of participants within countries, and estimation of the
163 variability in misuse and abuse due to country of residence. These models were used to
164 investigate the association between polysubstance use and (i) misuse of at least one
165 prescription opioid analgesic; (ii) abuse of at least one prescription opioid analgesic. Age,
166 gender, education level, and employment status were included as covariates.
167
168 Models included a random country-level intercept to allow for between-country variation in
169 risk of opioid analgesic misuse and abuse. The effect of country of residence was quantified
170 using the intraclass correlation and median odds ratio [24]. Illicit drug use and
171 benzodiazepine use were initially modelled as fixed effects with an interaction term; random
172 slope models were then fitted to evaluate whether the associations between misuse/abuse and
173 illicit drug use and benzodiazepine use varied by country of residence. The models provide
174 odds ratio (OR) estimates for the association between polysubstance use and misuse or abuse,

175 holding country of residence constant [15,17]. The covariates age, gender, education level,
176 and employment were included as fixed effects. Models were fitted via maximum likelihood
177 with difference in model fit evaluated using likelihood ratio chi-squared tests. As the
178 alternative hypotheses regarding variances are technically one-sided, halving the p-value for
179 these tests has been suggested [35]; we report the standard p-values but consider this
180 modification when interpreting results. Analyses were conducted in R version 3.3.1 (Bug in
181 Your Hair) [29] using the lme4 package for multi-level models, with 95% confidence
182 intervals (CI) for the final model parameter estimates obtained using bootstrapping with 4000
183 replicates per model [5].
184
185 **RESULTS**
186
187 **Sample description**
188 The analysis sample consisted of 5,670 participants who had used codeine, hydrocodone,
189 oxycontin, or tramadol in the past 12 months and had obtained it via a prescription (see Table
190 1). Overall, 45.8% of the sample were female with an average age of 33.2 years (standard
191 deviation 13.8 years). Participants were relatively evenly distributed across the education
192 categories: 24.9% reported highschool as their highest qualification, 22.2% reported a college
193 diploma, 28.7% reported an undergraduate degree, and 22.6% reported a postgraduate
194 degree. Almost two thirds (64.1%) were employed. The analysis sample differs from the
195 total sample of GDS participants from the five countries in that the full sample has a lower
196 percentage of women (37%), lower average age (30.0 years), fewer participants with a
197 postgraduate qualification (14.9%), and a lower level of employment (60.7%).
198

199 The analysis sample included similar numbers of participants from each of the five countries,
200 although there were slightly fewer from Germany. Use of particular opioid analgesics
201 differed by country of residence, as expected given regional differences in prescribing
202 practices. Codeine was the most frequently used drug by participants resident in Australia
203 (91.2%), France (90.6%), Germany (77.7%), and the United Kingdom (92.8%), while
204 hydrocodone was most commonly used by US participants (63.9%). Overall, 45.4% of the
205 sample had not used benzodiazepines or illicit drugs in the past year. Past-year illicit drug
206 use was reported by a further 42.3%, with 4.4% having used only benzodiazepines in the past
207 year, and 7.9% endorsing use of both benzodiazepines and illicit drugs. Of those who had
208 used illicit drugs in the past year more than half (57.0%) had only used cannabis, with ecstasy
209 (12.2%) and cocaine (10.0%) the next most frequently used single drugs. Only 2% (N=58) of
210 illicit drug users had used heroin in the past year. Of those who had used benzodiazepines in
211 the past year, 61.7% reported obtaining them via prescription.
212
213 **Access to opioid analgesics**
214 Obtaining a prescription for these opioid analgesics within seven days was perceived as being
215 easier for codeine (39.4% reported it would be "very easy" or "easy") and tramadol (46.4%),
216 compared to hydrocodone (18.4%) and oxycontin (25.1%). Obtaining any of these opioid
217 analgesics *without* a prescription, via a dealer or the internet, was very uncommon (see
218 Figure 1). Only about 1% of codeine and tramadol users reported obtaining these drugs via a
219 dealer or the internet. For hydrocodone and oxycontin the percentage of participants who
220 also reported obtaining the drug from a dealer was higher (7.0% and 5.7% respectively), but
221 the percentage buying these drugs via the internet was less than 1%. Being given these drugs
222 by friends was a more common route for obtaining them without a prescription (reported by
223 6.7% to 23.2% of participants, depending on drug).

224

225

226 **Level of misuse and abuse of opioid analgesics**

227 Between 8% and 22% of participants who had not used any illicit drugs or benzodiazepines
228 in the past year reported misuse or abuse of codeine, hydrocodone, oxycontin, or tramadol
229 (see Table 2). Overall, compared to those who had not used any other substances,
230 approximately twice as many participants who had used illicit drugs only, or benzodiazepines
231 only, reported misuse of any opioid analgesic (26.8% and 33.5% respectively compared to
232 14.7%). Three times as many participants who engaged in polysubstance use reported misuse
233 (45.7%). Participants who only used illicit drugs, or only used benzodiazepines, were
234 approximately three times as likely to report abuse of opioid analgesics compared to those
235 who used no other substances (23.9% and 27.8% respectively compared to 8.8%). Almost
236 five times as many participants who endorsed polysubstance use reported abuse of opioid
237 analgesics (43.7%). The percentage of participants reporting misuse and abuse differed by
238 country of residence; Australian participants were the least likely to report misuse and abuse
239 (17.0% and 12.5% respectively), while participants from the USA were most likely (28.2%
240 and 27.7% respectively). Similar percentages of participants from France and the UK
241 reported misuse (21.5% and 21.0% respectively) and abuse (15.6% and 16.6% respectively).
242 German participants reported a level of misuse similar to participants from the USA (27.5%),
243 but were less likely to report abuse (20%).

244

245 **Association between polysubstance use and misuse/abuse of prescription opioid**
246 **medications**

247 We first fitted "empty" multi-level models to investigate how much variability in misuse and
248 abuse of opioid analgesics could be explained by participant country of residence [25]. For

both models, likelihood ratio tests comparing fixed effects and random intercept models indicated that there was significance variance explained by the between-country effect on misuse (χ_1^2=34.98, p <0.0001) and abuse (χ_1^2=73.53, p <0.0001). However, the intraclass correlations and median odds ratios for both models were small. The percentage of variance in misuse explained by country of residence was only 1.5% and the median odds ratio was 1.12, while the percentage of variance in abuse explained was 2.8% and the median odds ratio was 1.34.

For the opioid analgesic misuse model, allowing the effects of illicit drug use and benzodiazepine use to vary by country of residence did not significantly improve model fit (χ_5^2=8.53, p = 0.13) and they were therefore included as fixed effects in the full multivariable model. Based on the full multivariable model (see Table 3), use of both illicit drugs and benzodiazepines was associated with over four-fold greater odds of opioid analgesic misuse compared to not using any additional substances (OR 4.36, 95% CI 3.29 – 5.93), while use of benzodiazepines only was associated with three-fold greater odds (OR 3.37, 95% CI 2.25 – 5.25). However, both were more strongly associated with misuse than use of illicit drugs only (OR 1.79, 95% CI 1.41 – 2.37).

Allowing the effects of illicit drug use and benzodiazepine use to vary by country of residence did significantly improve the fit of the model for opioid analgesic abuse (χ_5^2=13.26, p = 0.02). The effect of illicit drug use on abuse varied considerably more between country of residence than the effect of benzodiazepine use (see Table 3). Covariance with the intercept was negative for both illicit drug use and benzodiazepine use, suggesting the association of polysubstance use with abuse is weaker in countries with higher levels of abuse. The fixed effects estimates for the relationship between polysubstance use and opioid

274 analgesic abuse were stronger than those for misuse, but displayed the same pattern. The
275 odds of opioid analgesic abuse were highest for participants using both illicit drugs and
276 benzodiazepines compared to those not using any additional substances (OR 6.49, 95% CI
277 4.0 – 10.48), over four-fold higher for those using benzodiazepines only (OR 4.79, 95% CI
278 2.70 – 8.95), and over two-folder higher for those using only illicit drugs (OR 2.46, 95% CI
279 1.75 – 3.60).
280
281 **DISCUSSION**
282
283 In this sample of individuals from the USA, UK, France, Germany, and Australia who had
284 used opioid medications obtained via prescription in the past year, 1 in 4 individuals reported
285 misuse of any opioid analgesics, and approximately 1 in 5 individuals reported abuse.
286 Although these data come from a non-probability sample, this level of opioid medication
287 misuse is similar to that obtained from a recent systematic review of misuse, abuse, and
288 addiction in chronic pain patients [37], and represents one of the few available estimates of
289 level of abuse of these drugs. Misuse and abuse differed between those who had and had not
290 used illicit drugs and/or benzodiazepines in the past year; approximately 1 in 7 non-users
291 reported misuse and 1 in 11 reported abuse, compared to approximately 1 in 3 users reporting
292 misuse or abuse.
293
294 The multi-level models fitted indicated that country of residence only accounted for a small
295 proportion of the variance in opioid analgesic misuse and abuse. Holding the effect of
296 country of residence constant and adjusting for sociodemographic factors, combined use of
297 illicit drugs and benzodiazepines was associated with four-fold greater odds of opioid
298 analgesic misuse and six-fold greater odds of abuse compared to not using either drug. There

299 were no significant between-country differences in the effect of either illicit drug use or
300 benzodiazepine use on misuse. However, the association between both types of
301 polysubstance use and opioid analgesic abuse varied by country of residence, with this being
302 more pronounced for illicit drug use. Thus, although these results provide limited support for
303 the idea that misuse and abuse of these opioid analgesics is a phenomenon specific to the
304 USA, we did find evidence that the relationship between some risk factors and opioid
305 analgesic abuse may differ between countries.
306
307 The importance of benzodiazepine use in the context of problematic use of opioid analgesics
308 is perhaps unsurprising given that the combined use of these drugs is well documented [21]
309 and benzodiazepine use is a risk factor for opioid misuse [9] and overdose [20,41]. As those
310 using both opioids and benzodiazepines are at increased risk of fatal overdose, this finding
311 highlights the need for clinicians to be vigilant in identifying risk behaviours in those in
312 receipt of both medication classes. Despite most clinical guidelines cautioning against
313 concomitant prescription, there may be genuine indications such as managing co-existent
314 anxiety or augmenting analgesic effects [18]. In our sample of prescription opioid users, just
315 over 60% of benzodiazepine users reported also obtaining this drug via a prescription.
316 However, prescription opioids and benzodiazepines are two of the drugs most commonly
317 obtained via "doctor shopping" [20,23], so it is possible that in many cases a prescription for
318 one drug was obtained without the clinician knowing the patient already held a prescription
319 for the other. Regional differences in family doctor registration and prescription drug
320 monitoring programmes, which can help prevent doctor shopping, could account for some of
321 the between-country variation we observed in the association between polysubstance use and
322 prescription opioid abuse [2].
323

324 The interplay between illicit drugs, benzodiazepines, and opioid analgesics is less well
325 characterised. As only 2% of those who had used illicit drugs in the past year were heroin
326 users it is unlikely that the results were driven by use of opioid analgesics as a substitute for
327 heroin. For 57% of participants using both illicit drugs and opioid analgesics, cannabis was
328 the only illicit drug they had used in the past year. Cannabis use has been identified as a risk
329 factor for opioid analgesic misuse in chronic pain patients [30], and previous research
330 identified a pattern of polysubstance use involving cannabis and both opioid analgesics and
331 benzodiazepines which was associated with increased risk of mental illness, another risk
332 factor for opioid misuse and abuse [10,12,26,32]. However, efforts to develop risk prediction
333 models for problematic opioid analgesic use have generally grouped all substance use
334 disorders together [10,12]. More research is needed to investigate the interaction between
335 different illicit drugs and benzodiazepines to better understand how use of these drugs
336 increases risk of problematic opioid analgesic use.
337
338 One limitation of these results is that we used data on past year drug use, which is not
339 necessarily the same as simultaneous use within a short time frame (e.g. 24 hours), although
340 Quek *et al*. [28] found that most people reporting use of multiple drugs in the past year also
341 reported simultaneous use of those drugs. The other main limitation is that these data were
342 collected via an anonymous online survey using a non-probability sampling strategy. It is not
343 possible to estimate response rates for this type of sampling strategy and it cannot be
344 considered to provide a representative sample of individuals from the countries included, so
345 the results should not be generalised to the broader populations from which they are drawn.
346 Participants in this type of study are likely to be younger, male, urban-dwelling, endorse use
347 of illicit drugs, and have completed more years of formal education than participants from a
348 representative sample [3]. However, although the recruitment strategy may not provide a

349 representative sample, the fact that it was anonymous and did not involve a participant's
350 clinical care provider may mean that people were more likely to disclose both misuse and
351 abuse of opioid analgesics, and use of illicit drugs. Additionally, this data set provided a
352 large sample of individuals who had obtained opioid analgesics via a prescription across
353 several countries. Given the noted scarcity of data on problematic use of opioid analgesics
354 from outside the USA [9,33,37], these data are useful for exploring this phenomenon and
355 generating new research questions. Regardless, the findings presented here should be
356 investigated further in representative samples from the USA, UK, France, Germany, and
357 Australia.
358
359 In conclusion, levels of opioid analgesic misuse and abuse appear to be higher in those who
360 engage in polysubstance use involving illicit drugs and/or benzodiazepines, but there are
361 substantial numbers of individuals who are not polysubstance users and engage in misuse
362 and/or abuse. Policies and interventions have been developed on the assumption that there
363 are two distinct populations of people, one that uses only medication prescribed to them and
364 are compliant with dosing instructions, and another group who obtain prescription opioids via
365 non-clinical routes, use other licit and/or illicit drugs, and engage in misuse and abuse. This
366 distinction does not accurately reflect the reality of prescription opioid use, and highlights the
367 importance of universal approaches to patient education, prescription and patient
368 monitoring. While doctors remain the major source for these drugs, they will need to be
369 targeted and engaged as the pivotal sites for change. Differences between the USA and other
370 developed countries in relation to healthcare regulatory systems, patient expectations, and
371 direct-to-consumer advertising have contributed to the substantially greater magnitude of
372 problematic opioid analgesic use in the USA [2,14,38]. However, the issue of misuse and

abuse amongst those who are prescribed opioid analgesics appears to be a problem that warrants attention on an international scale.

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***Figure 1**: Venn diagrams showing sources for obtaining (a) codeine, (b) hydrocodone, (c) oxycontin, (d) tramadol. Given numbers indicate that participants obtained prescription opioid analgesics from family and/or friends.*

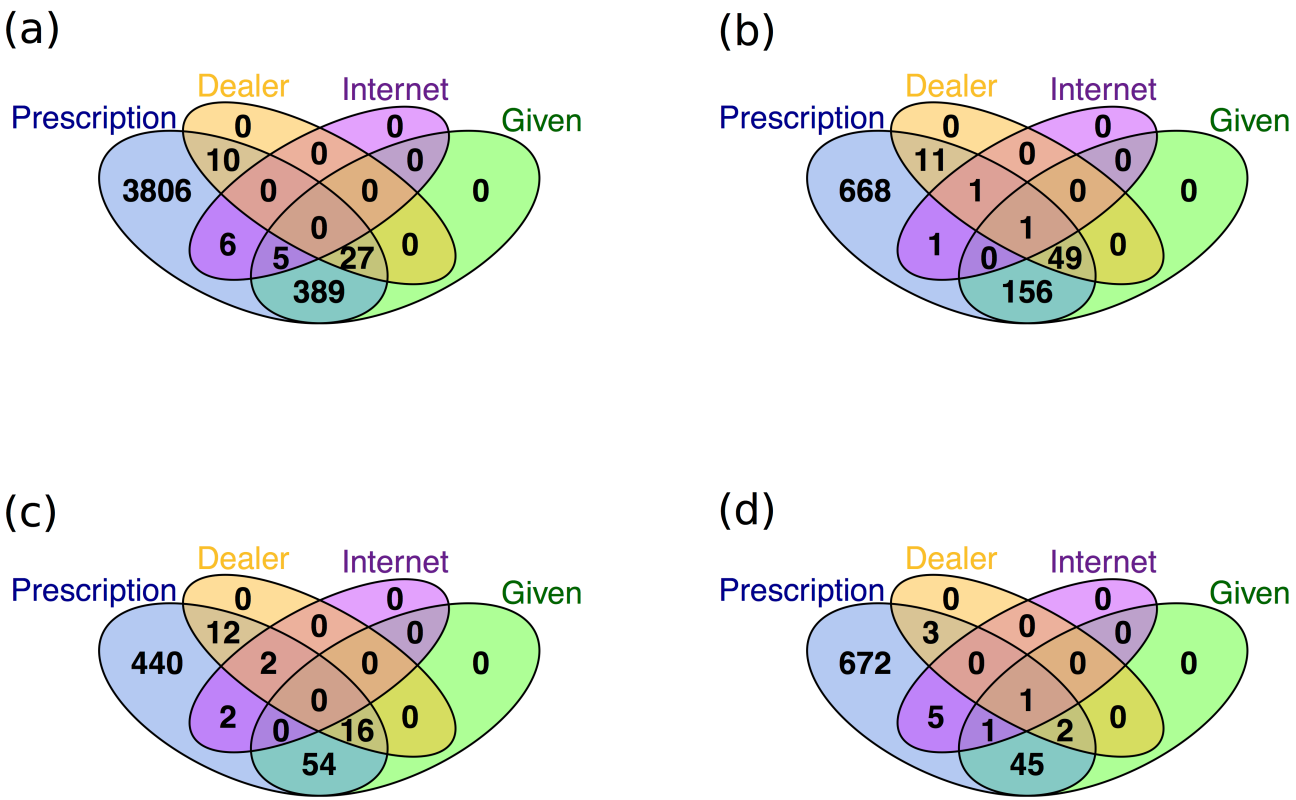

Table 1: Socio-demographic characteristics and patterns of drug use of analysis sample

Variable	Categories	Total (N = 5670)		Australia (N = 1013)		France (N = 1258)		Germany (N = 866)		United Kingdom (N = 1199)		United States (N = 1334)	
		N/mean	%/S.D.	N/mean	%/S.D.	N/mean	%/S.D.	N/mean	%/S.D.	N/mean	%/S.D.	N/mean	%/S.D.
Sex	Female	2598	45.8	459	45.3	597	47.5	354	40.9	486	40.5	702	52.6
	Male	3072	54.2	554	54.7	661	52.5	512	59.1	713	59.5	632	47.4
Age	Mean	33.2	13.8	39.1	14.7	29.1	10.2	32.2	12.8	34.0	13.0	32.6	15.8
Education	Highschool	1410	24.9	293	28.9	181	14.4	242	27.9	225	18.8	469	35.2
	College diploma	1256	22.2	145	14.3	315	25.0	276	31.9	279	23.3	241	18.1
	Undergraduate	1626	28.7	291	28.7	234	18.6	256	29.6	421	35.1	424	31.8
	Postgraduate	1280	22.6	271	26.8	511	40.6	82	9.5	256	21.4	160	12.0
	Missing	98	1.7	13	1.3	17	1.4	10	1.2	18	1.5	40	3.0
Employment	Yes	3635	64.1	722	71.3	728	57.9	545	62.9	791	66.0	849	63.6
	No	1993	35.1	281	27.7	518	41.2	314	36.3	402	33.5	478	35.8
	Missing	42	0.7	10	1.0	12	1.0	7	0.8	6	0.5	7	0.5
Opioid analgesic	Codeine	4243	74.8	924	91.2	1140	90.6	673	77.7	1113	92.8	393	29.5
	Hydrocodone	887	15.6	8	0.8	5	0.4	8	0.9	14	1.2	852	63.9
	Oxycontin	526	9.3	152	15.0	6	0.5	55	6.4	11	0.9	302	22.6
	Tramadol	729	12.9	82	8.1	203	16.1	168	19.4	166	13.8	110	8.2
Polysubstance use	None	2575	45.4	576	56.9	448	35.6	519	59.9	595	49.6	437	32.8
	Illicit only	2398	42.3	272	26.9	704	56.0	285	32.9	504	42.0	633	47.5
	Benzodiazepine only	248	4.4	82	8.1	43	3.4	23	2.7	30	2.5	70	5.2
	Combined	449	7.9	83	8.2	63	5.0	39	4.5	70	5.8	194	14.5

Table 2: Levels of opioid analgesic misuse and abuse by polysubstance use. Percentages are shown for each opioid analgesic and for misuse or abuse of at least one.

Variable	**Opioid analgesic**	**Total**		**No substance use**		**Illicit only**		**Benzodiazepines only**		**Combined**	
		N	%	N	%	N	%	N	%	N	%
Misuse	Codeine	838	19.8	265	12.9	409	23.3	54	32.0	110	41.7
	Hydrocodone	253	28.5	48	17.1	122	29.5	20	38.5	63	44.4
	Oxycontin	148	28.1	29	14.1	67	32.2	16	43.2	36	48.0
	Tramadol	239	32.8	65	22.6	121	39.8	12	20.7	41	51.9
	Any	1308	23.1	378	14.7	642	26.8	83	33.5	205	45.7
Abuse	Codeine	641	15.1	159	7.7	335	19.1	46	27.2	101	38.3
	Hydrocodone	249	28.1	24	8.6	135	32.7	16	30.8	74	52.1
	Oxycontin	132	25.1	21	10.2	65	31.3	13	35.1	33	44.0
	Tramadol	180	24.7	40	13.9	98	32.2	10	17.2	32	40.5
	Any	1064	18.8	226	8.8	573	23.9	69	27.8	196	43.7

Table 3: Estimates from multi-level models of associations between opioid analgesic misuse and abuse, polysubstance use, and sociodemographic characteristics. 95% confidence intervals (C.I.) were obtained via bootstrapping.

Variable	**Value**	**Misuse**			**Abuse**		
		Beta	95% C.I.	P	Beta	95% C.I.	P
Fixed effects							
Illicit drug use	No	Ref.			Ref.		
	Yes	0.58	0.35 to 0.87	<0.0001	0.90	0.57 to 1.29	<0.0001
Benzodiazepine use	No	Ref.			Ref.		
	Yes	1.22	0.81 to 1.66	<0.0001	1.57	1 to 2.2	<0.0001
Illicit x benzodiazepine interaction		-0.33	-0.96 to 0.31	0.08	-0.59	-1.6 to 0.3	0.004
Age		-0.33	-0.45 to -0.22	<0.0001	-0.47	-0.63 to -0.32	<0.0001
Sex	Female	Ref.			Ref.		
	Male	0.31	-0.07 to 0.72	<0.0001	0.59	0.06 to 1.12	<0.0001
Education	Highschool	Ref.			Ref.		
	College diploma	-0.20	-0.49 to 0.14	<0.001	-0.21	-0.45 to 0.01	0.04
	Undergraduate degree	-0.33	-0.57 to -0.05	<0.001	-0.31	-0.6 to -0.09	0.002
	Postgraduate degree	-0.40	-0.7 to -0.1	<0.001	-0.47	-0.88 to -0.14	<0.001
Employment	No	Ref.			Ref.		
	Yes	-0.21	-0.39 to -0.06	0.002	-0.27	-0.57 to -0.03	<0.001
Random effects							
Intercept variance		0.03	0 to 0.08		0.03	0.01 to 0.19	
Illicit drug variance		N/A			0.14	0.01 to 0.35	
Benzodiazepines variance		N/A			0.004	0.01 to 0.16	
Intercept - illicit covariance		N/A			-0.02	-0.17 to 0.05	
Intercept - benzodiazepines covariance		N/A			-0.01	-0.11 to 0.04	
Illicit - benzodiazepines covariance		N/A			-0.01	-0.12 to 0.08	