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The challenge of complex drug use: Associated use of codeine containing medicines and new psychoactive substances in a European cross-sectional online population

Short title: The challenge of complex drug use

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Abstract

Objective

Misuse of codeine containing medicines in combination with new psychoactive substances (NPS) is inadequately described. This study characterises codeine consumption amongst NPS users and non-NPS users to provide warning of health issues.

Methods

Online survey conducted between July 2015 and March 2016.

Results

Out of 340 respondents, residing in a country in Europe and using codeine recently, 63.8% were female. Mean age: 34.9 years (SD = 12.4). Substance use included NPS (18.5%) and illicit controlled drugs (55.9%). Factors relating to codeine use found to significantly predict NPS use were consuming codeine extracted from combination tablets (OR = 16.79, 95% CI = 8.67–32.51), obtaining codeine from friends, family and acquaintances (OR = 3.98, 95% CI = 1.82–8.7), use of illicit controlled drugs (OR = 34.99, 95% CI = 8.39–145.94) and use of codeine to experience euphoria (OR = 6.41, 95% CI 3.42–12.04).

Conclusions

Amongst NPS users, codeine is less likely to be used daily, but more likely to be used for recreational purposes. Smaller populations engaging in high-risk use exist who take multiple drugs in high doses. Combinations of misused codeine and NPS highlight the need for policy to respond to a more complex drug situation.

Introduction

In the annual review of the European drug situation, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2016 Drug Report stated: '*Europe increasingly faces a more complex drug problem, in which stimulants, new psychoactive substances, misused medicines and problematic cannabis use all play a greater part*' (EMCDDA, 2016a). Separately, these substance classes create their own set of problems for public health: Diverted and misused prescription opioids causing fatal poisonings add complexity to the opioid problem in Europe (Office for National Statistics, 2016; Weisberg, Becker, Fiellin, & Stannard, 2014; Stannard, 2013); whilst a massive growth in the availability of new psychoactive substances (NPS) poses new challenges to regulators. At the same time, complex patterns are emerging where misused medicines, NPS and illicit controlled drugs are used together or in replacement of one another. Currently, gaps exist in our understanding of concurrent use of medicines and NPS and health risks posed.

Use and misuse of opioid analgesics

Use of opioid analgesics more than doubled in central Europe from around half a billion defined daily doses (DDD) per year in 2001-03 to about 1.6bn DDD per year in 2011-13 (Berterame et al., 2016). This has been accompanied by misuse, diversion, dependence and non-fatal and fatal overdoses (Weisberg et al., 2014; Office for National Statistics, 2016). This development has been registered in treatment services across Europe that are increasingly having to react to patients entering for misused medicines (EMCDDA, 2015a; Parry, Deluca, Cooper, & Van Hout, 2015). Whilst heroin remains a principal drug in drug-related deaths in Europe, other opioids have become more prominent in national data (EMCDDA, 2016b; Office for National Statistics, 2016). Tampering of medicines to enhance drug effects (Kimergård, Breindahl, Hindersson, & Deluca, 2016a) and transitions from weak to more toxic opioids and to heroin highlight unique concerns with misused medicines (Conroy & Hill, 2015).

NPS in Europe

Information from the EU Early Warning System show just how extensive the market for NPS has become. In the past five years alone, hundreds of new substances have appeared on the market (EMCDDA, 2015b; 2016a; 2016b). Sold as 'legal highs',

'bath salts', and 'research chemicals' on the Internet, and from marketplaces on the hidden web (Dolliver & Kuhns, 2016), global transportation networks offer prompt delivery of NPS worldwide. The emergence of some new substances has a strong link with their misuse as medicines (Brandt, King, & Evans-Brown, 2014). Fentanyl provides a good, albeit troubling example: Prescribed for severe pain caused by cancer and other debilitating and serious diseases, reports have highlighted the potential for fentanyl misuse associated with clusters of deaths (Mounteney, Giraudon, Denissov, & Griffiths, 2015). At the same time, fentanyl analogues have been identified on the illicit market since the late 1970s where α -methylfentanyl was first passed off as heroin substitutes in the US (Henderson, 1988; Kram, Cooper, & Allen, 1981). Since 2014, acetylfentanyl has been involved in hundreds of deaths in Europe, the US, Russia and elsewhere (DEA Office of Diversion Control, 2015; EMCDDA, 2016b; Melent'ev, Kataev, & Dvorskaya, 2015). Two years later, acrylfentanyl entered the market (Breindahl, Kimergård, Andreasen, & Pedersen, 2017) and has already been implicated in over 40 deaths (EMCDDA, 2017).

The complexity of polysubstance use

Reports now highlight complex relationships between misused medicines and the use of NPS in place of and in addition to heroin and other illicit controlled drugs (EMCDDA, 2016a). An Australian study examining use of 'over-the-counter' codeine found an overlap between codeine use and recent use of heroin, methadone, and morphine amongst injecting drug users (Arora, Roxburgh, Bruno, Nielsen, & Burns, 2013). In a cross-European survey, 43% indicated non-medical prescription opioid use and use of illicit controlled drugs in the past year in the UK, 41% did so in Sweden, 30% in Germany, 24% in Denmark and 21% in Spain (Novak et al., 2016). Cannabis was the most frequently used illicit controlled drug in the survey. The Crime Survey for England and Wales found that 0.7% adults had used NPS in the past year (2015/16) (Lader, 2016). The survey estimated that 7.5% adults had taken a prescription opioid not prescribed to them, with 0.2% indicating that they took it for the 'feeling or experience' it gave them. Elliot & Evans (2014) performed a three-year review of NPS in post-mortem and criminal casework and found that 84% of cases with presence of NPS also contained other drugs, medicines or alcohol, underlining that polysubstance use affects levels of harm.

Misused codeine containing medicines

Codeine is currently one of the most used opioids globally (International Narcotics Control Board, 2015) and widely misused and associated with dependence in many countries in Europe (Cooper, 2013; Kimergård et al., 2017; Van Hout, Horan, Santlall, Rich, & Bergin, 2015; Roussin, Bouyssi, Pouché, Pourcel, & Lapeyre-Mestre, 2013). Regulations by medicine authorities to ensure legitimate supply and use of codeine containing medicines are in place at the international and national level across Europe. In many countries, codeine is supplied with a medical prescription. However, in several European countries, codeine formulations containing lower amounts of codeine can also be purchased 'over-the-counter' in licensed pharmacies (Foley et al., 2015). Studies have described misuse and dependence on codeine following use for appropriate medical reasons (Cooper, 2013; Kimergård et al., 2017). However, little is known about the role codeine plays in experimental use with additional research needed to investigate overlaps between misused codeine and the use of NPS. This present study focussed on people indicating recent use of codeine containing medicines. The study draws on a cross-sectional dataset obtained from an online survey with the aim of characterising codeine use amongst NPS users and non-NPS users across Europe. Identification of complex substance use patterns provide warning of health issues and demand created on treatment services.

Methods

The online survey was for adults, at least 18 years of age and residing in a country in Europe. Completion of the survey was targeted at those using or had used any type of codeine containing medicines in the last 3 months (prescription and 'over-the-counter'). The study was granted ethics approval by the Psychiatry, Nursing, and Midwifery Research Ethics Subcommittee (PNM RESC), King's College London. REC Reference Number: PNM/14/15-110.

Recruitment

Respondents were recruited to attract a broad sample of codeine users, including those using for medical and non-medical reasons. A survey link was advertised from a website dedicated to health and healthy living, offering information about the use of codeine. This site was chosen to recruit individuals with experience of problems and harms relating to codeine use. The survey was also advertised from websites, Facebook and Twitter accounts belonging to organisations and treatment services

offering support and treatment of opioid addiction. The moderator of a drug discussion forum was contacted and permission was obtained to post a survey link. It has been described how members of this forum share their personal knowledge and experiences from using a variety of substances including NPS (Davey, Schifano, Corazza, & Deluca, 2012; Soussan & Kjellgren, 2014). Finally, a link to the survey were passed on to students and staff at two universities (King's College London, UK and Waterford Institute of Technology, Ireland) via e-mail circulars and Twitter. The aim was to recruit young people as well as individuals who use codeine according to medical guidance.

Measurements

The survey was created in BOS (Bristol Online Survey) and consisted of 49 closed and open-ended questions about demographics, codeine consumption and use of other substances (See Supplementary File). To identify recent use of codeine, respondents were asked to report the frequency of use during the last 3 months. Those who had not taken codeine at least once were asked not to complete the survey. Dose was measured in milligrams (mg) codeine consumed in a day on the last occasion of use. Instructions for how to report the dose in mg were provided.

Additional questions asked about codeine supply to identify sources of obtaining codeine. The responses were: (i) prescribed after a face to face consultation; (ii) purchased 'over-the-counter' in a pharmacy (no medical prescription required); (iii) shop on the Internet; (iv) from family, partner, friends or acquaintances. One question asked respondents about purchasing codeine from shops on the Internet selling codeine illegally.

The questionnaire included items from a scale designed to measure reasons for substance use (Boys, Marsden & Strang, 2001) to record medical and non-medical reasons to take codeine.

Respondents were asked if they had ever tampered with codeine containing medicines. In context of this study, tampering included methods used to enhance drug effects (Kimergård et al., 2016a), investigated through a series of questions constructed for the study about (i) drinking codeine cough syrups with soft drinks, juice, or alcohol; (ii) extracting codeine from tablets containing codeine and non-opioid analgesics like paracetamol or ibuprofen; (iii) taking codeine rectally; (iv)

snorting crushed codeine tablets; (v) injecting dissolved codeine tablets; (vi) consuming morphine or heroin manufactured from codeine.

The degree of psychological dependence on codeine was measured using the Severity of Dependence Scale. The scale has previously been used to assess codeine dependence (Kimergård et al., 2017; Nielsen, Cameron, & Lee, 2011). The scale is easy to administer due to its brevity and consists of five questions scored from 0 to 3 for a total score between 0 and 15. The higher the score, the higher severity of dependence (Gossop et al., 1995).

In the last section of the questionnaire, respondents were asked about using NPS and illicit controlled drugs. Respondents using NPS were asked to indicate the frequency of use over the past 3 months. Respondents were prompted to write in the names of the drugs they had taken.

Data analysis

Data was downloaded from BOS into SPSS (version 23). Descriptive statistics were reported as frequencies and means. Categorical variables were collapsed into binary variables for statistical testing. Codeine use was recoded to indicate consumption on a daily or non-daily basis. Consumption levels of codeine was captured as a continuous variable and re-coded as under or over 240 mg (the recommended maximum daily dose, according to the British National Formulary). Logistic regression models were used to investigate the association between independent variables and the use of NPS. Two groups were created consisting of non-NPS users and NPS users. The independent predictor variables were tampering of codeine containing medicines, risk behaviours relating to codeine use, main sources of obtaining codeine (including prescribed, 'over-the-counter', buying online or obtained from friends and family), use of illicit controlled drugs and medical and non-medical reasons to use codeine.

Results

Self-reported use of codeine, NPS and illicit controlled drugs were collected from 472 adult respondents (≥ 18 years) to an online survey, open between July 2015 and March 2016. When classified according to country, 340 respondents residing in a country in Europe remained in the final analysis. The mean age was 34.9 years (SD = 12.4). The number of female respondents was higher than males at 63.8%. Most

respondents resided in the UK (84.1%). A total of 54 respondents came from other countries in Europe (15.9%). Just over one-half were in gainful employment (58.2%), 14.1% received a student allowance, 6.8% depended on others as their main source of income and 6.2% received disability allowances. Only 12 respondents reported no income (3.5%).

Codeine use

In the last 3 months, a total of 273 respondents (80.3%) had used tablets that contained codeine in combination with a non-opioid analgesic, such as paracetamol, ibuprofen or acetylsalicylic. A lower proportion of 114 respondents (33.5%) had used tablets which contained codeine as the only active ingredient. About one out of eleven indicated use of codeine containing cough syrups (9.1%).

Codeine sourcing

Respondents had obtained codeine from several sources, including purchased 'over-the-counter' in a pharmacy (N = 180; 52.9%); prescribed from a professional after a face-to-face consultation (N = 164; 48.2%); obtained from family, partners, friends, and acquaintances (for free, purchased, or stolen) (N = 59; 17.4%); and, purchased from a shop on the Internet (N = 21; 6.2%).

A proportion of four respondents (1.2%) had purchased codeine from a shop on the Internet which they thought was selling codeine illegally. A further seven respondents (2.1%) indicated that they were unsure as to the legality of a shop from where they had purchased codeine. When prompted to write in why respondents thought the shop was selling codeine illegally, the most common answer was because the shop sold high-strength codeine tablets without asking for a medical prescription. Purchasing on the hidden web and paying with bitcoins were also reported in reply.

Codeine dependence

In the full sample of 340 respondents, 59 scored five or above on the Severity of Dependence Scale indicating possible dependence upon codeine. Mean SDS score was 2.2 (SD = 3.4).

Polysubstance use amongst respondents with recent codeine use

One in five (18.5%) had ever used NPS. The highest proportion of them stated that

they had not used NPS in the last 3 months (39.7%), 27% indicated that they had used NPS once or twice, 17.5% that they had used monthly and 14.3% that they had used weekly. Overall, 190 respondents (55.9%) reported life-time use of an illicit controlled drug. Of these, a majority indicated use of cannabis. Out of all the respondents, 61 (17.9%) reported life-time use of both NPS and illicit controlled drugs. Amongst those who exceeded the recommended maximum 24-h dose of 240 mg codeine on last occasion of use, 17 respondents (5%) had also used NPS and reported life-time use of illicit controlled drugs.

Tampering of codeine containing medicines

In the logistic regression model, tampering of codeine containing medicines were found to significantly predict the use of NPS (Table 1). Compared with non-NPS users, NPS users were more likely to consume codeine extracted from tablets containing codeine and a non-opioid analgesic (OR = 16.79, 95% CI 8.67–32.51), drink codeine cough syrups in a mixture with a soft drink or alcohol (OR = 8.02, 95% CI 4.09–15.72) and take codeine rectally to experience effects more intensely (OR = 4.82, 95% CI 1.63–14.29). No significant differences were found for other tampering behaviours between non-NPS users and NPS users.

Codeine risk behaviours

Those who had used NPS were less likely to report daily use of codeine (22%) than those who had never used NPS (39%) ($p < 0.05$). Codeine dependence did not significantly predict the use of NPS (Table 2). Obtaining codeine through a medical prescription was less likely amongst NPS users (22%) in comparison to non-NPS users (48%) ($p < 0.01$). Those reporting use of NPS were more likely to obtain codeine from family, partners, friends, and acquaintances (21%) than those not reporting use of NPS (6%) ($p < 0.01$). Buying codeine on the Internet was also higher in the NPS user group at 10%, compared to 2% in the non-NPS user group ($p < 0.01$). Compared with those with no use of NPS, NPS users were more likely to use illicit controlled drugs (97% compared to 47%, $p < 0.01$).

Reasons for codeine use in NPS and non-NPS users

Use of codeine for non-medical reasons were significant in predicting associations with the use of NPS (Table 3). Respondents with use of NPS were more likely to have used codeine to get stone or intoxicated (46%) compared to non-NPS users

(7%) ($p < 0.01$). The group using NPS had a higher proportion of respondents using codeine to feel elated or euphoric (43%) than the group that had not used NPS (10%) ($p < 0.01$). Users of NPS were more likely than non-NPS users to have used codeine to improve the effects of other substances (16% compared to 3%, $p < 0.01$) and to help ease the effects of other substances (14% compared to 4%, $p < 0.01$). Amongst those reporting use of NPS, 60% used codeine as treatment of pain, whereas 90% of those not reporting use of NPS used codeine for pain management ($p < 0.01$).

Discussion

The study identified a population engaging in complex substance use of a relatively young age (mean age = 34.9 years) where specific challenges in terms of identification, intervention and treatment exist. The findings of the study add to previous studies to underline the potential for misuse and dependence of codeine where use of prescribed and 'over-the-counter' products for genuine medical reasons transitions into problematic use (Cooper, 2013; Kimergård et al., 2017, Van Hout et al., 2015). However, our findings also describe codeine use for recreational purposes where high doses are consumed to induce opioid euphoria. As part of this experimental use, codeine is used in combination with NPS in patterns that also involves tampering of codeine containing medicines to experience opioid effects with greater intensity. Such ways of combining misused medicines, NPS and illicit controlled drugs pose a challenge for public health and highlight the need for policy and treatment to respond to a more complex situation than previously faced.

In the study, approximately one in five codeine users had used NPS and illicit controlled drugs. In a qualitative interview study conducted in Australia, Nielsen, Cameron, & Pahoki (2013) found that only few users of 'over-the-counter' codeine reported significant histories of other substance use. However, polysubstance use appears far more common in other populations, such as those posting on online drug discussion forums. In one study, more than half of those reporting current non-medical use of prescription opioids on online drug discussion forums were also indicating use of other substances, including NPS (Chiauzzi, DasMahapatra, Lobo, & Barratt, 2013).

Respondents who were NPS users were more likely to have obtained codeine from

friends, family and acquaintances and from buying on the Internet and less likely to obtain codeine from a medical prescription, compared to those who had not used NPS. Doses exceeding medicine regulators' recommendations are typically needed to experience a codeine 'high', possibly explaining why codeine was obtained from multiple and unauthorised sources. Respondents who had used NPS were less likely to consume codeine daily than those who had not used NPS. This indicates a pattern of less frequent use, but in excessive doses, with the primary aim of inducing euphoria and intoxication.

In this study, NPS users were more likely than non-NPS users to consume codeine extracted from combination tablets (codeine/non-opioid analgesics) and to drink codeine cough syrups mixed with soft drinks or alcohol. Codeine extraction has been described amongst members of drug discussion forums (Cone, 2006; Foley, Breindahl, Hindersson, Deluca, & Kimergård, 2016). One study found that extracting codeine with the use of simple techniques and household appliances can yield different amounts of codeine and non-opioid analgesics in the extracted mixtures making it difficult to control the doses (Kimergård, Deluca, Hindersson, & Breindahl, 2016b). Understanding risk factors associated with medicine tampering may help implement harm reduction interventions and deliver treatment to specific populations of polysubstance users where the risk of harm is disproportionately great (Kapitány-Fövényi et al., 2015; Kimergård et al., 2016a; Talu et al., 2010).

Our findings suggest a number of possible explanations for concomitant NPS and codeine use: Whilst disruptions to the NPS market may result in delays or obstructions in supply, codeine can be obtained relatively easy, including from 'over-the-counter' sales in many European countries (Cooper, 2013; Foley et al., 2015), suggesting that codeine is used as a substitute when access to other drugs is restricted. Another possible explanation is that codeine is used to ease the after effects of other drugs, such as stimulants, as indicated by 14% of NPS users in the study. Finally, studies have found that codeine is used non-medically to feel elated and intoxicated (Arora et al., 2013; Cooper, 2013; Nielsen et al., 2013), which compares favourably to findings of the present study. Still, further research should examine in detail the reasons for why NPS and opioid analgesics are used together with or in replacement of one another.

There is a need to make health professionals aware of the emerging trends of

combining misused medicines with NPS. Whilst heroin continues to pose a significant burden on emergency departments in Europe due to acute drug toxicity, data suggest that the mean number of drugs taken per patient has increased in many countries (EMCDDA, 2016c). For many new substances, knowledge and data can be limited and health professionals may have to respond to symptoms without knowing about the drugs taken (Wood, Ceronie, & Dargan, 2016; Guirguis et al., 2015). Overdoses caused by a combination of opioid analgesics, heroin, alcohol and new synthetic opioids can pose a difficult challenge for health professionals because of severe toxicity.

Limitations

One limitation of online research designs is that certain characteristics of the study sample are unknown. This is due to the survey link being posted on the Internet amongst (partly) anonymous populations with varying use of codeine and other substances. The sample comprised respondents from drug discussion forums, where users are known to engage in experimental drug use, but it also included individuals recruited from general health forums and from university e-mail circulars where use was predominantly within accepted medical guidance.

Online research will often include respondents from different countries, where the availability of codeine and NPS varies. Hence, relating the results to specific populations and countries should be done with consideration. Recruiting a greater number of respondents could explore national variation in codeine misuse and use of NPS.

Only people with access to the Internet could complete the survey, possibly excluding certain populations such as people in prison where high levels of medicine misuse and NPS use have been recorded (Kirby, 2016).

Another limitation is that the use of NPS and illicit controlled drugs may have been underreported due to fear of prosecution and stigmatisation, although the levels of both misused codeine, illicit controlled drug use and NPS use were high for this type of study. Respondents were asked about their use of NPS, which may have resulted in under or over-reporting depending on respondents' understanding and knowledge of which drugs are classified as NPS. Respondents were prompted to write in the names of drugs they had used, which did provide detailed insight into the abundance

of drugs used, but this item had a lower response rate.

Conclusions

Few studies have previously investigated recreational codeine use amongst NPS and non-NPS users. Amongst NPS users, codeine is less likely to be used daily, but more likely to be used for non-medical reasons, than amongst non-NPS users. Codeine is obtained from several sources to consume high doses to experience opioid euphoria and intoxication. It is a challenge to ensure availability of medicines for patients in pain, whilst reducing diversion and harm from recreational use. Many people who use NPS obtain information on the Internet from online drug discussion forums where users' experiences of misusing medicines can be found. As such, the Internet may provide opportunities to engage with polysubstance users and disseminate harm reduction advice when this is available concerning tampering of codeine containing medicines. A small group was identified in the study's findings who take multiple drugs in high doses, highlighting need for treatment of acute drug toxicity, but also long-term drug addiction. More research should be done to identify and characterise high-risk user groups.

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Tables

Table 1. Tampering of codeine containing medicines.

	Non-NPS users n = 277	NPS users n = 63	
	%	%	OR (95% CI)
Consumed codeine extracted from combination tablets	8%	60%**	16.79 (8.67–32.51)
Drinking codeine cough syrups with a soft drink, juice or alcohol	8%	40%**	8.02 (4.09–15.72)
Taken codeine rectally to experience opioid effects more intensely	3%	11%**	4.82 (1.63–14.29)
Snorted crushed codeine tablets	1%	11% ^a	a
Taken morphine/heroin manufactured from codeine	0.4%	8% ^a	a

** P < 0.01; ^a not calculated due to sample size; OR, odds ratio; CI, confidence interval.

Table 2. Codeine use and risk behaviours.

	Non-NPS users n = 277	NPS users n = 63	
	%	%	OR (95% CI)
Risk behaviours			
Codeine dependence ^a	17%	17%	1 (0.49–2.08)
Daily use of codeine	39%	22%*	0.45 (0.24–0.86)
Primary source of codeine			
Buying on the Internet	2%	10%**	5.73 (1.69–19.41)
From family, partner, friend, acquaintance	6%	21%**	3.98 (1.82–8.7)
‘Over-the-counter’ codeine	43%	44%	1.05 (0.60–1.82)
Prescribed following a consultation with a doctor	48%	22%**	0.31 (0.16–0.58)
Other substance use			
Life-time use of illicit controlled drugs	47%	97%**	34.99 (8.39–145.94)

* P < 0.05; ** P < 0.01; OR, odds ratio; CI, confidence interval.

^a Indicated by a score of ≥5 on the Severity of Dependence Scale.

Table 3. Reasons for codeine use in non-NPS users and NPS users.

	Non-NPS users	NPS users	
	n = 277	n = 63	
	%	%	OR (95% CI)
To get stoned or intoxicated	7%	46%**	10.96 (5.6–21.48)
To improve the effects of other substances	3%	16%**	7.28 (2.65–19.98)
To feel elated or euphoric	10%	43%**	6.41 (3.42–12.04)
To help relax	20%	56%**	4.93 (2.77–8.78)
To stop worrying about a problem	9%	33%**	4.83 (2.49–9.35)
To help ease the effects of other substances	4%	14%**	4.45 (1.73–11.47)
To feel better when down or depressed	14%	43%**	4.44 (2.44–8.11)
To ease withdrawal symptoms of opioids	4%	13%**	3.88 (1.47–10.29)
To help sleep	21%	41%**	2.65 (1.49–4.74)
To treat pain	90%	60%**	0.16 (0.09–0.31)

** P < 0.01; OR, odds ratio; CI, confidence interval.