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ORIGINAL RESEARCH

How Resistant to Tampering are Codeine Containing Analgesics on the Market? Assessing the Potential for Opioid Extraction

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ABSTRACT

Introduction: Misuse of opioid analgesics, in combination with diversion, dependence, and fatal overdoses, presents a serious problem for public health, which affects many countries worldwide. Within this context, tampering with opioids has been associated with serious harm. The aim of the present study was to assess the tampering potential of codeine combination analgesics on the market (containing codeine/non-opioid analgesics) by the extraction of codeine.

Methods: Codeine was extracted from three combination formulations sold lawfully from licensed pharmacies without a medical prescription in Denmark and the UK. Extraction of codeine followed tampering procedures available on the Internet. The amounts of codeine and accompanying non-opioid analgesics in tampering products were analysed with liquid chromatography and tandem mass spectrometry (LC–MS/MS).

Results: LC–MS/MS showed recoveries of the total amounts of codeine in tampering products of 81–84% from Product 1 (codeine/acetylsalicylic acid); 61–67% from Product 2 (codeine/ibuprofen); and 42–71% from Product 3 (codeine/paracetamol). Recoveries of non-opioid analgesics ranged between: 57–73% acetylsalicylic acid; 5.5–8.5% ibuprofen, and 5.0–9.2% paracetamol.

Conclusion: With the tampering procedures used, high amounts of codeine were separated from the accompanying analgesics in some, but not in all of the codeine containing formulations. Evidence-based medicine regulation, treatment for opioid dependence, and information to minimise risks to the public are essential components of an effective public health strategy to address the harms of tampering and misuse.

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Keywords: Analgesics; Codeine; Internet; Opioids; Risk assessment; Tampering

INTRODUCTION

> *If you take too much paracetamol, it's going to kill you. So what I would do is I would put about 30 co-codamol tablets, 8 mg codeine over 500 mg paracetamol, into a bottle and fill it up with water. I would put that in the freezer until the paracetamol crystals formed. Then I poured out the liquid through a coffee filter so you ended up with pure codeine water.*
>
> *Patient (male, 34 years), in recovery-oriented drug treatment in the UK, reporting of tampering with codeine containing analgesics. (Interview conducted May 2015 by the first author with ethical approval granted by the NRES Committee London, London Bridge (REC reference: 15/LO/0107). Patient consent was obtained).*

Concerns have been growing in recent years amongst public health bodies, medicines regulators, and health professional groups in Europe over the increasing use of opioid analgesics and the associated risks of diversion, misuse, dependence, and fatal overdoses [1–5]. Misuse of opioids is not a homogeneous problem across Europe and the collection of data remains poor [5, 6]. Despite this, specific problems identified include the diversion of methadone and buprenorphine from opioid substitution treatment use [7–9] and diversion of fentanyl from the appropriate use as analgesics [2]. An increase in the rates of deaths involving controlled prescription opioids has been recorded in European countries in recent years [10–12], along with outbreaks of fentanyl-related deaths in the UK, Germany, Sweden, and Finland [2]. A 176% raise in deaths involving tramadol was recorded from 2009 to 2014 in the UK [13]. Data show a decline in new drug treatment demand from clients using heroin, yet over 10% of opioid clients entering services in 11 European countries in 2013 were entrants for prescription drugs such as methadone, buprenorphine, and fentanyl [14].

Against this background, tampering of medicines poses additional complications. There are now a growing number of reports that experimental users have found different ways of manipulating with various opioid analgesics to enhance their psychoactive effects, eliminate undesirable components (drugs and excipients), and bypass tampering-resistant formulations [7, 15–17]. Tampering has been linked to serious harm—for example, from snorting crushed buprenorphine tablets [18], intravenously injecting morphine and buprenorphine tablets dissolved in water [15, 18], and oral consumption of whole transdermal fentanyl patches [16, 17]. Misuse of and tampering with codeine has also been identified [19–22].

Codeine, an opioid used in treatment of pain, coughing, and diarrhoea, is supplied with a prescription, but is also sold lawfully from licensed pharmacies without a medical prescription ('over-the-counter') in European countries such as France, Denmark, Ireland, Bulgaria, Poland, and the UK [23, 24]. Formulations sold 'over-the-counter' contain a low amount of codeine in combination with a non-opioid analgesic, such as paracetamol or ibuprofen. An accompanying analgesic is included to achieve an increased effect on the relief of pain; however, adverse events from prolonged and excessive use of codeine combination analgesics have been reported,

including gastrointestinal disease and nephrotoxicity associated with ibuprofen and paracetamol consumption [25–28]. Because codeine is often misused through oral administration of combination tablets [19, 29, 30], tampering procedures which separate codeine from the accompanying analgesics appears to be gaining popularity amongst certain codeine taking populations, particularly in Internet savvy users [20, 22]. Often referred to as 'cold water extraction', the aim is to keep as much codeine as possible in the extracted tampering products, while at the same time reducing the amount of non-opioid analgesics to non-toxic levels.

Whilst the number of individuals who routinely extracts codeine is unknown, use of 'cold water extraction' procedures have been reported by individuals from drug treatment services [31, 32], hospitals [33], and online communities [20, 22]. Detailed descriptions of 'cold water extraction' can be found on drug discussion forums on the Internet, such as Erowid and Bluelight, but have also found their way onto mainstream sites like YouTube where some videos of codeine extraction have more than 500,000 views [34]. Tampering of codeine appeals to recreational users consuming high amounts of codeine to induce opioid euphoria, to codeine dependent concerned with the toxicity of non-opioid analgesics, and to those unable to obtain potent prescription opioids who may turn to codeine to prevent withdrawal and cravings [35]. Information on dependence upon codeine is sparse, however, case reports and research studies have identified what seems to be a growing number of codeine dependent across Europe [19, 21, 29, 36–38]. Furthermore, an increase of nearly 50% in the distribution of codeine to the retail link between 1994 and 2013 [39], combined with 'over-the-counter' sales, is associated with widespread use of codeine. In this landscape of availability, individuals seeking to tamper with codeine can obtain multiple packages relatively unproblematic, such as from 'pharmacy shopping' [29, 36, 40].

Misuse of prescription opioids has brought into focus the risks of tampering. Sellers et al. [41] examined the attractiveness of different opioids for tampering amongst users. In another study, users were asked to tamper with prescription opioid tablets to assess whether tablets could be converted into forms amenable for snorting or injecting [42]. One study investigated the chemical synthetic pathways utilised in the illicit manufacturing of morphine and heroin from codeine formulations in 'underground labs' and measured the quantitative yields of such production [43]. The consequences of tampering with codeine are potentially wide-reaching, yet poorly researched. One 2003 study investigated the use of Internet procedures for codeine extraction [44], but included only one codeine formulation (codeine/paracetamol). A study from 1993 also examined the degree of separation after tampering with a single tablet of three different formulations with the use of laboratory equipment [45]. Important as the results of this study might be, they do not necessarily apply to the current situation because users typically extract codeine from 20 to 40 tablets at a time, using kitchen utensils and common household appliances [20]. Thus, the aim of the present study was to assess the tampering potential of codeine combination analgesics on the market in Denmark and the UK by the extraction of codeine. 'Cold water extraction' procedures from the Internet were used to extract codeine [46–48]. High-performance liquid chromatography with tandem mass spectrometry (LC–MS/MS)

measured the amounts of codeine and accompanying non-opioid analgesics in tampering solutions.

METHODS

Selection of 'Cold Water Extraction' Procedures

The words 'cold water extraction' and 'codeine' were used to search the Internet for methods of tampering. One search was conducted on known drug discussion forums; another was conducted with the use of a web search engine (Google). For each identified procedure, screenshots captured the mains steps involved in codeine extraction. The screenshots were then used to select procedures that (1) recently had been commented on by forum or website users, which is likely to provide a measure of current use; and (2) made reference to specific formulations—brands or generics—in order to match specific tampering procedures with specific codeine combination analgesics. Three 'cold water extraction' procedures from the Internet were chosen for the study [46–48] and matched with three different formulations.

Selection of Codeine Containing Analgesics

Out of an array of low-strength codeine formulations authorised for sale without a medical prescription in Denmark and the UK, three were chosen for this study: One sold in Denmark, two sold in the UK (Table 1). The Danish product contained 9.6 mg codeine phosphate hemihydrate, 500 mg acetylsalicylic acid, and 150 mg magnesium oxide (Product 1). Current regulation permits the sale of this product from pharmacies without a prescription, but also from retail outlets, such as supermarkets and petrol stations, without the supervision of a pharmacist. The products sold in the UK contained 12.8 mg codeine phosphate hemihydrate and 200 mg ibuprofen (Product 2), and 8 mg codeine phosphate hemihydrate and 500 mg paracetamol (Product

Table 1 Codeine containing analgesics used toward codeine extraction

Product number	Product sold in (Denmark/UK)	Amount of codeine phosphate hemihydrate/tablet[a] (mg)	Amount of codeine free-base/tablet (mg)	Amount of accompanying analgesics/tablet[a]	Number of tablets used for extraction	Total amounts of codeine free-base available for extraction (mg)
1	Denmark	9.6	7.07	500 mg acetylsalicylic acid, 150 mg magnesium oxide	16	113.2
2	UK	12.8	9.43	200 mg ibuprofen	12	113.2
3	UK	8	5.89	500 mg paracetamol	19	112.0

[a] As reported by the drug manufactures on the packaging and in the patient-information leaflets

3). The codeine/paracetamol formulation was a generic medicine and the cheapest available at a price of less than £1.50 for 32 tablets.

Codeine Extraction

A study protocol was made which followed the Internet procedures closely (Table 2). Extraction of codeine from Product 1 (codeine/acetylsalicylic acid) and Product 2 (codeine/ibuprofen) was repeated in triplicate. Extraction of codeine from Product 3 (codeine/paracetamol) was repeated eight times to assess variation in the amounts of codeine and paracetamol. For each attempt at extraction, tablets containing a total amount of approximately 150 mg of codeine phosphate hemihydrate were used. This dose was generally considered a 'beginner's dose' on many websites where dosage regimens were determined by self-experimentation, but sometimes adjusted according to age, body weight, and opioid tolerance. 'Cold water extraction' is made possible by the variation in solubility between codeine (highly soluble in water) and paracetamol, ibuprofen, and acetylsalicylic acid (poorly soluble in water). However, the concrete stages involved in codeine extraction are briefly described below.

Extraction of Codeine from Product 1 (Codeine/Acetylsalicylic Acid)

With the use of a mortar, tablets were crushed into a fine powder and mixed with water and ordinary household citric acid (95–100%, Matas, Denmark). In accordance with the Internet procedure [46], 12 g citric acid were added, which was supposed to enhance precipitation of acetylsalicylic acid so that it can be removed by filtration. However, adding citric acid in order to improve separation did not have the desired effect as the tampering products contained high amounts of acetylsalicylic acid. The solution was filtrated with the use of a coffee filter (Non-bleached, size 1 × 4; Abena, Denmark).

Extraction of Codeine from Product 2 (Codeine/Ibuprofen)

Tablets were submerged in water, mixed thoroughly, and left in the refrigerator. After an hour, a thick, white layer containing tablet fillers and ibuprofen was left at the bottom of the container, whereas a clear, aqueous layer of codeine was harvested with a pipette from the top of the container. In keeping with the Internet procedure, water was added to the substance consisting of tablet fillers and ibuprofen for another round of extraction of any remaining codeine.

Extraction of Codeine from Product 3 (Codeine/Paracetamol)

Tablets were placed in water and heated in a water bath. Next, the solution was filtered using a coffee filter and left in the freezer until the temperature was below 2 °C. After this, the solution was filtered a second time. Similar to the procedure used for Product 1, the highly soluble codeine is supposed to flow through the filter in aqueous form, the poorly soluble paracetamol in solid form is not. For samples 6–8, the procedure was amended, leaving out the use of a heated water bath. Here, tablets were placed in water, after which the mixture was stirred for 15 min and put in the freezer until the temperature reached 1 °C. This time, the mixture was filtered only a single time.

Analysis of Tampering Solutions

Extraction and analysis of the tampering products were conducted at the Department of Clinical Biochemistry, North Denmark Regional

Table 2 'Cold water extraction' tampering procedures from the Internet

Examples of text from site	Study protocol
Extraction of codeine from Product 1 (codeine/acetylsalicylic acid/magnesium oxide)	
"The first thing to do is crush the tablets in a mortar"	16 tablets are crushed in a mortar
"Add approximately 3 mL water for each tablet you use, along with 0.55 g of citric acid per tablet"	48 mL water (20°C) is poured into a container, along with 12 g citric acid
"IMPORTANT! If you use the tablets containing 150 mg magnesium oxide despite the risk of diarrhoea, you will need to use 0.75 g of citric acid per tablet"	The crushed tablets are added to the container containing water and citric acid
"Pour the solution with citric acid into the mortar containing the crushed tablets, or pour the tablets into the container with the citric acid. Stir thoroughly for about 5–10 min"	The mixture is stirred for 10 min using a glass spatula
"Measure the pH of the solution. If it isn't below 3.5, more citric acid should be added"	The pH is measured
"Next, the mixture is filtered. The solution now contains nearly all the codeine from the tablets, but almost none of the acetylsalicylic acid"	The solution is filtrated, using a coffee filter
"Citric acid is used because it prevents acetylsalicylic acid from transforming into its salt, whereby precipitation is ensured"	
Extraction of codeine from Product 2 (codeine/ibuprofen)	
"The tablets are removed from the package and dropped into a small amount of warm water. Once the tablets have absorbed the water, they will swell up and can now be easily mixed with a fork. At this point, the product is ready for extraction"	12 tablets are submerged into 50 mL water (20°C)
	Tablets are mixed with a glass spatula
	100 mL water is added (10°C)
	The solution is left in the refrigerator for an hour
"The container is topped up with cold water and the mixture is agitated to help dissolve the codeine"	The supernatant codeine solution is recovered with a pipette
"After around 30 min the mixture will have settled, leaving the insoluble ibuprofen and binders at the bottom, and the aqueous codeine solution at the top of the container"	50 mL water (10°C) is added to the remaining mixture containing ibuprofen and tablet fillers
	The container is left in the refrigerator for an hour and a half
"Using a syringe or dropper, the aqueous layer is harvested into another container. A second pull using half the original volume of water is then carried out in order to retrieve any remaining codeine"	The supernatant codeine solution is recovered with a pipette, and added to the codeine containing solution previously extracted

Table 2 continued

Examples of text from site	Study protocol
Extraction of codeine from Product 3 (codeine/paracetamol)	
"Added 96 10 mg codeine 500 mg + rubbish tablets to 200 mL cold tap water and left for 10 min or so to dissolve CP"	Procedure for samples 1–5 19 tablets are submerged in 40 mL tap water (10°C)
"So I heated the solution in a hot water bath to about 45 or 50°C"	After 10 min, the mixture is heated in a water bath until the temperature reaches 45°C
"I then filtered the solution and it filtered in a fraction of the time it usually does with cold water"	The solution is filtered using a coffee filter
"This is then placed in the freezer until it almost freezes, by which time almost all of the paracetamol dissolved, crystalizes out in lovely large needle shaped crystals"	The filtrate is placed in the freezer until the temperature is below 2°C
"This near frozen solution is then filtered, which is also fast as paracetamol crystals are now large. This solution is now safe to drink"	The solution is filtered a second time, using a coffee filter Procedure for samples 6–8 19 tablets are submerged in 100 mL tap water (24.5°C) The mixture is stirred for 15 min, until all tablets are dissolved The mixture is placed in the freezer, until the temperature reaches 1°C The mixture is filtered, with the use of a coffee filter

Hospital, Denmark. High-performance liquid chromatography with tandem mass spectrometry (LC–MS/MS) was used to determine the concentrations of codeine, acetylsalicylic acid, ibuprofen, and paracetamol after dilution of the tampering solutions. Quantification was based upon isotope dilution with deuterated internal standards of the target compounds. Calibration curves were constructed by analysis of pure reference standards. Intra-assay imprecision and bias was below 10%. The concentration of magnesium (Mg^{2+}) in tampering solutions derived from Product 1 was determined with inductively coupled plasma atomic emission spectroscopy (ICP-AES) at an ISO 15189 accredited external laboratory, using the European standard method EN ISO 11885 for determination of selected elements in water.

Compliance with Ethics Guidelines

The study presented in this paper examined the content of tampering solutions extracted from codeine formulations using LC–MS/MS. The aim was to assess the tampering potential. This article does not contain any new studies with human or animal subjects performed by any of the authors. No drugs were administered in the study and medicines and resulting waste were disposed of in safe and secure manner.

However, ethical issues were identified. It is recognised that no licensed medicines containing opioid analgesics can completely withstand tampering attempts by experienced users. Examining drug discussion forums on the Internet, it is also clear that users adopt, and disseminate, a range of tampering techniques they believe can be applied with varying degrees of success. Tampering of codeine is no

exception [46–48]. Still published research findings of assessments of harm, medicine misuse, and tampering will in some cases provide an additional outlet for tampering, offering insights into types of opioids tampered with, specific methods and tools used for tampering, how well formulations can be tampered with, and uptake of tampering solutions by the body [41, 42, 44, 49, 50]. It will come as no surprise to researchers frequenting drug discussion forums that published data are cited amongst users as evidence of which drugs (or way of using drugs) gives the desired effects. However, we would suggest that this is no reason for inaction when it comes to the difficult issues of medicine misuse. Arguably, it is because of a failure to act in the first place that tampering is now established as a serious problem to public health [51]. Investigations of misuse liability and tampering potential for medicines on the market have an important role to play in the pharmacovigilance system—regardless of how the results of such research are used by the public. Not only do they serve to confirm the efficacy of tampering techniques being used by the public but they also can reveal related risks and help identify potential risk reduction strategies for medicine regulators and the pharmaceutical industry.

While the present study did not require ethics approval, consultation was sought with the Research Ethics Office, Psychiatry, Nursing and Midwifery Research Ethics Subcommittees (PNM RESC), King's College London. The Danish Health and Medicines Agency was also informed of the study.

RESULTS

LC–MS/MS showed a recovery of the total amounts of codeine in the final tampering products in the range of 81–84% from Product 1 (codeine/acetylsalicylic acid), 61–67% from Product 2 (codeine/ibuprofen), and 42–71% from Product 3 (codeine/paracetamol) (Table 3). The total amounts of codeine in the tampering solutions ranged from 47 to 95 mg free-base codeine (Table 3), with the largest quantity of codeine found in a tampering product procured from Product 1 (codeine/acetylsalicylic acid) and the lowest in a tampering product from Product 3 (codeine/paracetamol).

Analyses showed that between 57% and 73% of the total amounts of acetylsalicylic acid were still present in the tampering products derived from Product 1. The quantities ranged between 4570 and 5851 mg acetylsalicylic acid, which was the highest amount of any of the accompanying analgesics, measured in any of the tampering solutions. In addition, magnesium ions (Mg^{2+}) were present in the tampering solutions derived from Product 1 in amounts equivalent to a recovery of 82–83%. However, the tampering products procured from the remaining codeine formulations contained low amounts of both ibuprofen and paracetamol. Here recoveries were in the range of 5.5–8.5% ibuprofen (Product 2) and 5.0–9.2% paracetamol (Product 3) (Table 3).

DISCUSSION

The results from the study show that it was possible to separate relatively large amounts of codeine from the accompanying non-opioid analgesics in two out of the three codeine containing medicines, albeit the percentages of extracted codeine and non-opioid analgesics in the tampering solutions varied. Based on the drug recovery percentages achieved in the study, as much as 1300 mg free-base codeine can be consumed from tampering solutions

Table 3 Contents of tampering solutions measured by LC–MS/MS

	Product 1 ($n = 3$)			Product 2 ($n = 3$)			Product 3 ($n = 8$)							
	S1	S2	S3	S1	S2	S3	S1	S2	S3	S4	S5	S6	S7	S8
Final volume (mL)	42	42	41	157	160	163	24	24	21	20	21	70	60	60
Substances in solutions (mg)														
Codeine	92	92	95	70	75	73	74	73	62	47	65	79	75	68
Paracetamol							574	682	555	474	509	873	836	730
Acetylsalicylic acid	5851	4570	5141											
Ibuprofen				205	167	132								
Magnesium (Mg^{2+})	1180	1189	1173											
Extraction recovery (%)[a]														
Codeine	81	81	84	61	67	64	66	65	55	42	58	71	67	60
Paracetamol							6.0	7.2	5.8	5.0	5.4	9.2	8.8	7.7
Acetylsalicylic acid	73	57	64											
Ibuprofen				8.5	6.9	5.5								
Magnesium (Mg^{2+})	82	82	83											

Analytical results are reported in free-base codeine

Sx sample number

[a] Calculated from the total amount of active substances in the tablets used for extraction

procured from Product 2 without exceeding the maximum dose of 2400 mg ibuprofen daily [recommendations by the British National Formulary (BNF) [52]]. This is five times the daily recommended dose of codeine, according to BNF guidelines [53]. From tampering products procured from Product 3, up to about 500 mg of free-base codeine can be consumed without exceeding the BNF stated 24 h limit of 4000 mg paracetamol [54]. However, the remaining quantities of acetylsalicylic acid in the tampering solutions procured from Product 1 (4570–5851 mg acetylsalicylic acid) exceeded the recommended dose of maximum 4000 mg acetylsalicylic acid in a day (BNF recommendations) [55]. These findings are important to the post-marketing surveillance of opioids with misuse liability [56], in this case, highlighting the lack of barriers toward tampering in low-strength codeine formulations. The 'discovery' of the tampering possibilities of codeine containing analgesics amongst users demonstrates how new patterns of misuse can emerge, even in medicines which have been on the market for a long period of time.

Interpretation of Findings

A previous study reported recoveries of 83–100% codeine and 7.6–8.1% paracetamol in solutions extracted from 20 tablets with the use of methods from the Internet [44]. In eight attempts of codeine extraction from 19 tablets of codeine/paracetamol, the recovery of codeine peaked at 71% with 9.2% of the original amount of paracetamol left in the mixture in the present study. However, a potential

overestimation of the amounts of codeine in the tampering solutions procured by Fleming et al. [44] due to poor peak resolution caused by interference from tablet excipients may account for the differences in findings between these two studies.

The highest recovery of codeine from Product 3 (codeine/paracetamol) was reached in sample 6 where tablets were dissolved in 100 mL water instead of 40 mL used in samples 1 through 5 (Table 2). However, unlike in previous studies [44, 45], a proportional relationship between the volume of water and the amounts of codeine present in the tampering solutions was not supported by the findings of this study. The lowest percentages recovered of both codeine (42%) and paracetamol (5.0%) were found in sample 4, where the solution reached the lowest temperature recorded in any of the tampering products before they were taken out of the freezer. Large crystals were observed in sample 4, but may not necessarily account for why separation was less effective than in the other attempts.

Following a procedure for codeine extraction reported by users, Paterson et al. [31] removed approximately 30% acetylsalicylic acid from ten tablets, whereas Fleming et al. [44] removed between 63% and 92% acetylsalicylic acid from one tablet. Following an Internet procedure for codeine extraction from codeine/acetylsalicylic acid formulations, removal of acetylsalicylic acid ranged from 27 to 43% in this study. The findings of this and previous studies suggest that the consumption of tampering solutions derived from codeine/acetylsalicylic acid preparations poses a risk of acetylsalicylic acid poisoning, associated with interference with thrombocyte function [57] and, in large doses, electrolyte disturbances, dehydration, and non-cardiogenic pulmonary edema [58–61].

Risks to Users

The study shows that multiple factors may influence the composition of extracted solutions, making it difficult for users to know the quantities of drugs consumed. For this reason, the results from this study should not be generalised to users' own attempts at codeine extraction; it should not be assumed that tampering solutions contain the same amounts of active substances, even when following the same procedures and using the same codeine formulations. Imprecise descriptions of extraction procedures in regards to temperature, time, and volume are part of the problem. Clotting of the coffee filters was observed during extraction—a consequence of using non-laboratory equipment. The use of different materials for filtration, too, can affect how much of each substance is left in tampering products (the use of coffee filters, paper tissues, t-shirt fabrics, and socks were reported on the Internet). Finally, the recovery percentages of both codeine and non-opioid analgesics might also depend on the number of tablets used for extraction. The unknown amounts of drugs contained in tampering solutions can result in accidental drug overdoses from codeine and/or non-opioid analgesics.

Tampering carries added risks when part of a regimen of large quantities of codeine and can lead to opioid dependence which is associated with excessive dose consumption, tolerance, and cravings [4, 19, 29, 62]. Additional hazards linked to tampering of codeine include those arising if tampering solutions are injected intravenously as tablets contain fillers that are safe to ingest, but dangerous when introduced into the blood circulation [63]. For users who drink the solutions obtained from Product 1 (codeine/acetylsalicylic acid/magnesium oxide),

the high quantities of magnesium (Mg^{2+}) present an increased risk of diarrhoea. Further, the consumption of high codeine doses could set off the use of stronger opioids in order to mediate aspects of tolerance and withdrawal. Transitions from the use of prescription opioids into heroin use have also been recorded in both the US [64–66] and the UK [67]—although these reports rarely involve codeine.

Policy Measures

Restrictive measures have been imposed on the 'over-the-counter' sale of codeine in order to minimise misuse and dependence, including limitations on pack size and sale (one customer, one package), strengthened labelling and patient information leaflet warnings, banning of advertising, and brief pharmacy-based interventions [24].

In addition to these regulatory steps, however, policy measures should also involve proactive steps in form of better surveillance of misuse and tampering of high risk opioids. As new trends in tampering emerge and scatter into larger groups of users, it is of concern that existing monitoring and early warning systems in Europe are poorly configured to capture these developments [5, 51]. In addition to data commonly used to conduct risk assessments of licensed medicines, such as adverse drug reactions (ADRs) collected by national medicines agencies, data on tampering and associated harms should play a bigger role in pharmacovigilance and regulation.

Tampering-resistant formulations have been introduced to transition the market in order to reduce the rates of tampering and misuse. Tamper resistant features include (1) crush resistance, where tablets cannot easily be broken into a powder (2) combining an opioid with an opioid antagonist, counteracting opioid activity if manipulated with, and (3) tablets forming a viscous substance when dissolved [68, 69]. The latter strategy may be the most suitable option in terms of preventing codeine extraction. However, it is worth highlighting that many tamper-resistant formulations were introduced as substitution for potent controlled prescription opioids, not opioids sold 'over-the-counter'. Furthermore, concerns have been raised that individuals thwarted by tamper-resistant formulations turn to other opioids instead, such as heroin, fentanyl, and new psychoactive substances, including acetylfentanyl and U-47700 [69, 70].

Prescribers of controlled prescription medicines should keep in mind the potential for tampering of certain opioids. Health professionals should ask patients about the use of codeine and report both tampering and harm to public health bodies. In the UK via the Yellow Card Scheme [71] and in Denmark with the E-Form [72]. The lessons from the assessment of 'cold water extraction' procedures in this study are that evidenced-based medicine regulation, along with strategies to reduce harm in users and access to appropriate treatment services, are central components of a well-balanced public health approach.

Limitations

The study has some limitations. Codeine was extracted from preparations that contained either paracetamol, ibuprofen, or acetylsalicylic acid. However, other codeine formulations are sold without a medical prescription, including preparations consisting of codeine, a non-opioid analgesic, and caffeine, for which the results of this study do not necessarily apply. Codeine combination

analgesics are also supplied and sold as prescription only medicines. In the UK, high-strength formulations contain 30, 45, or 60 mg codeine in combination with 500 mg paracetamol. Given the more favourable ratio of codeine/paracetamol, compared to in low-strength formulations, there is potentially a higher level of attractiveness for tampering. Tampering with these products may yield different results and extents beyond the scope of the study. Our findings cannot be applied to other types of combination analgesics, including combinations of hydrocodone/non-opioid analgesic and oxycodone/non-opioid analgesic [20].

It was noted that on some drug discussion forums, codeine users reported extracting codeine from as many as 60 tablets at a time—three times as many as were used in this study. Notable, increasing the number of tablets is likely to impact the recovery percentages of drugs in the tampering products. Lastly, the focus of this study was on tampering methods used by codeine taking individuals, as opposed to specialised laboratory procedures which could enhance the separation of codeine from non-opioid analgesics [45]. As tampering procedures develop over time, and considering that specialised laboratory equipment is already available from many shops on the Internet, further assessment of codeine tampering is possibly needed.

CONCLUSION

Tampering of codeine combination analgesics allows for consumption of high doses of codeine without consuming toxic doses of accompanying non-opioid analgesics. The availability of low-strength opioids without the requirement of a medical prescription in many European countries and elsewhere represents incremental access to pain medication. However, their association with simple, yet effective tampering procedures that are easily accessible on the Internet presents a difficult challenge to regulators and the pharmaceutical industry to minimise misuse.

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