

# Internet pseudoscience: Testing opioid containing formulations with tampering potential

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## A B S T R A C T

Drug tampering practices, with the aim to increase availability of drug delivery and/or enhance drug effects, are accessible on Internet and are practiced by some portion of recreational drug users. Not rarely, recreational misuse may result in toxic and even fatal results. The aim of the present study was to assess the tampering risk of medicaments containing different formulations of an opioid in combination with paracetamol or dextketoprofen, following the procedures reported in dedicated forums on the web. Tablets and suppositories containing codeine, tramadol and oxycodone were extracted following the reported “Cold water extraction”; dextromethorphan was extracted from cough syrup following the procedure reported as “Acid/base extraction” and fentanyl was extracted from transdermal patches according to the procedure reported in Internet. The tampered products and opportunely prepared calibrators in water were analysed by liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS). The separation of the analytes was carried on Agilent ZORBAX Eclipse Plus C18 (RRHT 2.1 mm × 50 mm, 1.8 μm) by the gradient elution of 0.01% formic acid in water and 0.01% formic acid in methanol. Acquisition was by MRM mode considering at least two transitions for compound. Declared recoveries for these home-made extractions claimed to exceed 99% for the opioid and to completely remove paracetamol, often associated to liver toxicity and thus to obtain a “safer” preparation. In this study, the authors demonstrated that rarely the recoveries for the opioid reached 90% and that up to 60% of the paracetamol amount remained in solution. Thus, high risks for health remained both for the potential lethality of the opioid content, but also for the sub-lethal chronic use of these mixtures, which contained still uncontrolled, ignored, but often important amounts of paracetamol.

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## 1. Introduction

Prescription opioids, such as oxycodone, fentanyl, codeine, tramadol and dextromethorphan, are used in the management of pain, both acute and chronic. These drugs are available in various forms, such as immediate-release (IR), extended-release (ER) and controlled-release (CR) oral preparations, or skin patches, or suppositories. Prescription opioids offer a therapeutic option for

the management of pain, but they can also lead to physical and psychological dependence and therefore be misused and abused, resulting in harms such as addiction, overdose and even death. In fact, in recent years, an increase in the rates of deaths involving controlled prescription opioids, including fentanyl, has been recorded in the European countries [1,2] as well as in United States [3–6]. Abuse and misuse of psychotropic pharmaceuticals have been defined according to “The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)” as “use of pharmaceutical drugs . . . that deviate from accepted medical practice and/or scientific knowledge” and ‘the intentional or unintentional use . . . contrary to directions, regardless of whether a harmful outcome occurs’ [7], respectively. Such misuse and abuse include borrowing

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or stealing medications from friends or relatives, deliberately using higher-than-recommended doses, hoarding medications, tampering with the medication or altering the route of delivery and using opioids together with alcohol or other medications that have a sedating effect. Although no statistics appear to be available on the number of individuals who attempt to alter opioid formulations, there is growing evidence that “drug/formulation tampering” is widely prevalent. Pharmaceutical drugs are formulated in many different compositions targeted for specific routes of administration or bioavailability scope and though opioid formulations with tamper-resistance or abuse-deterrent features are developing, physical or chemical modifications of original formulation to enhance drug availability and/or eliminate undesirable excipients are still attempted by drug users. On this regard, Internet offers several home-made tampering procedures that can be exploited by old opioids consumers, which need to artificially increase the amount of ingested drug as well as by new opioids consumers, who can easily provide medications by family members or friends. The risk of using more than one medication simultaneously or to involuntarily exceed the “dose” is associated to drug abuse and fatal poisoning cases [8]. On this regard, a case of fatal codeine intoxication originating from a homemade extraction attempt has been recently experienced and described by the authors [9]. It is not strange that for this reason, starting from the last decade the interest of the scientific society about this topic has been gradually increasing, although limited to codeine formulations, with the publication of papers in which the investigation of Internet procedures for codeine extraction has been carried out [10,11]. The aim of the present study was to assess the tampering potential of medicaments containing an opioid (tramadol, codeine, oxycodone, dextromethorphan) in combination with an analgesic (paracetamol or dexketoprofen) in different formulations, following the procedures reported in dedicated forums [12–14]. Medicaments containing dexketoprofen, although not described in forums, were also included in the study for the availability in drug stores and for the suspected renal and liver toxicity on rats [15]. Experiments on fentanyl transdermal patches have also been performed, based on the possibility of fentanyl misuse both exploiting new and used patches. In many cases, the online statements on recoveries for these home-made extractions claim to exceed 99% for the opioid and, where present, to completely remove the analgesic, associated to liver toxicity, to obtain a “safer” preparation. In this study, the authors will demonstrate that rarely the recovery for the opioid reaches 90% and that up to 60% of the paracetamol original amount remains into solution that is then used for abuse. Thus, high risks for health remain both for the possibility to increase the number of starting tablets/suppositories/liquid/patches containing the opioid, reaching fatal doses, but also in the sub-lethal chronic use of these mixtures, which contain still uncontrolled, ignored, but often important amounts of paracetamol. Paracetamol is usually linked to serious hepatotoxicity after exposure to high-doses, but evidences of toxicity are available also for chronic pain patients at regular doses [16]. Moreover, in this work, the abuse potential of dextromethorphan containing syrup and fentanyl patches will be also evaluated in the frame of tampering potential. The results of this study offer experimental evidence of a widely widespread phenomenon of over-the-counter drugs misuse possibly affecting both the clinical and the forensic toxicologists, who could be involved in the evaluation of intoxication and even death events. Furthermore, investigations on medicine misuse and tampering potential for medicines on the market should have an important role in the pharmacovigilance system thus to help to identify strategies for risk reduction to be exploited by medicine regulators and pharmaceutical industry.

## 2. Methods

### 2.1. Materials

Water, methanol and formic acid were LC-MS grade from Honeywell (Morris Plains, NJ, USA). Tablets and suppositories containing an opioid and paracetamol or dexketoprofen (codeine/paracetamol, codeine/dexketoprofen, tramadol/paracetamol, oxycodone/paracetamol), cough syrup (dextromethorphan/paracetamol) and fentanyl patches were purchased in drug stores or pharmacies. Unbleached coffee filters (Finum, Riensch & Held GmbH & Co.KG, Germany) and whisky at 35% v/v alcohol were purchased at the supermarket. Paper filters were from Merck KGaA, (Darmstadt, Germany). For the extractions, hexane and isopropanol were both from Sigma-Aldrich (Merck KGaA, Darmstadt, Germany) and solutions of 0.1 M of NaOH and 0.1 M HCl were freshly prepared, all from Honeywell. For quantitative analysis a solution of certified reference nalorphine (Cerilliant, Round Rock, Texas, USA) at the concentration of 2 µg/mL in methanol was prepared.

### 2.2. Analytical method

#### 2.2.1. Chromatographic conditions

The separation of the analytes was carried on an Agilent 1290 LC system (Santa Clara, CA, US) equipped with a binary pump and a thermostatic auto-sampler. An Agilent ZORBAX Eclipse Plus C18 (RRHT 2.1 mm × 50 mm, 1.8 µm) was used by the gradient elution of 0.01% formic acid in water as mobile phase A and 0.01% formic acid in methanol as phase B: 0–0.5 min, 5% B; 0.5–7 min, 5–30% B; 7–12 min, 30–90% B; 12–15 min, 90% B; 15.1–17 min, 5%B. The mobile phase was delivered at a flow rate of 0.4 mL/min and the injection volume was 3 µL. The autosampler tray temperature was set at 8 °C, while the column temperature was 30 °C.

#### 2.2.2. Mass spectrometric conditions

Analyses were performed on a 6460 Triple quadrupole spectrometer (Agilent technologies, Santa Clara, CA, US). The applied ESI ion source conditions were set as follows: drying gas 230 °C, drying gas flow 10 L/min, capillary voltage 2000 V, nozzle voltage 1500 V, nebulizer flow 35 psi, sheath gas temperature and flow were 375 °C and 12 L/min, respectively. Acquisition was in multiple reaction monitoring (MRM) and transitions for each compound are reported in Table 1. Data acquisition and processing were carried out using MassHunter software (Agilent Technologies, Santa Clara, CA, US) with Qual and Quan browsers.

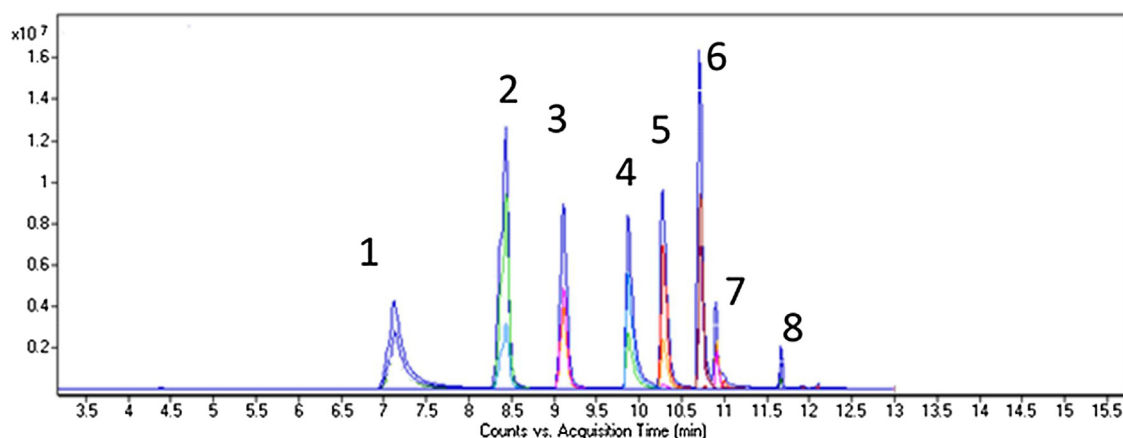
### 2.3. Methodologies

The tampered products and opportunely prepared calibrators in water were analysed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). At this scope, a method for the simultaneous determination of codeine, tramadol, oxycodone, fentanyl, dextromethorphan, paracetamol, dexketoprofen was developed and preliminarily validated in terms of precision and linearity (Fig. 1). Intra and inter-day precision were always below 10% for all compounds while non-including origin, weighted (1/x) linearity, assessed between the 10% and 100% of the declared compound amount, showed residuals to be randomly scattered without displaying any systematic patterns. Prior to analysis, samples and calibrators were diluted to fall into the instrumental linearity range (i.e. 1: 100000) and added of I.S. at the concentration of 60 ng/mL.

All material was prepared according the procedures found in Internet in dedicated forum following the research with keywords “opioids and extraction” or “opioids and tampering” or “fentanyl and patches”. Tablets and suppositories containing codeine; tra-

**Table 1**  
MRM transitions and collision energies of the LC-MS/MS method.

Compound	Quantifier ( <i>m/z</i> )	Qualifiers ( <i>m/z</i> )	Collision energies (V)
Codeine	300.2	165.1; 128; 58.1	45; 60; 29
Dextromethorphan	272.2	215.1; 231; 171	22; 26; 42
Dexketoprofen	253.1	209.2; 105	2; 40
Fentanyl	337.2	188.1; 132.1; 105.1	21; 33; 41
Nalophine (I.S.)	312.2	201.1; 165.1	29; 49
Oxycodone	316.2	298.1; 256.1; 241.1	17; 25; 29
Paracetamol	152.1	110; 65.1; 43.1	13; 29; 29
Tramadol	264.2	246.1; 59.2; 58.2	6; 14; 14



**Fig. 1.** MRM chromatogram of standard solution. 1: nalorphine; 2: paracetamol; 3: codeine; 4: oxycodone; 5: tramadol; 6: dextromethorphan; 7: fentanyl; 8: dexketoprofen.

**Table 2**  
Opioid containing analgesics used toward tampering procedures (\* for 100 mL of syrup).

Product number	Pharmaceutical form	Type of opioid/accompanying analgesic	Amounts/tablet (mg)	Number of tablets used for extraction	Final volume (mL)
1	tablets	Oxycodone/paracetamol	5/325	12	100
2	tablets	Tramadol/dexketoprofene	75/25	12	100
3	tablets	Tramadol/paracetamol	37.5/325	20	50
4	suppositories	Codeine/paracetamol	20/400	4	100
5	syrup	Dextromethorphan/paracetamol	50/2000*	30 (mL)	30
6	patches	Fentanyl	1.8/patch	1	50

madol and oxycodone were extracted following the reported “Cold water extraction”; dextromethorphan was extracted from cough syrup following the procedure reported as “Acid/base extraction” and fentanyl was extracted from transdermal patches according the procedure reported in Internet after the research “fentanyl extraction from patch”. Type and amount of analysed analgesic is described in Table 2. Each extraction was repeated three times to assess variation in the amounts of opioid and analgesic.

### 2.3.1. Cold water extraction

This procedure [12] has been applied to all tablets or suppositories containing tramadol, codeine and oxycodone in association with paracetamol or dexketoprofen. The original procedure has been adapted and standardised to laboratory protocol in terms of volumes, temperatures and times. Briefly, tablets were grinded in a mortar and powder was placed in water at 18 °C (room temperature) and stirred for 15 min. Suppositories were placed in water at 50 °C (hot water) and stirred until dissolution. The solutions were put in freezer until the temperature reached 1 °C and then filtered using a paper filter. The filtered solution was finally analysed by LC-MS/MS.

### 2.3.2. Acid/base extraction

This extraction has been applied to a cough syrup containing dextromethorphan and paracetamol following the instructions

found in Internet [13]. Thirty mL of syrup were diluted in a separatory funnel with an equal volume of double-distilled water and added of 10 mL of NaOH 0.1 M (pH about 9). The mixture was manually mixed before adding 50 mL of toluene as organic phase and then mixed for 5 min again. The layers were left for spontaneous separation and the bottom layer was drained off and used for a second step of extraction with toluene, while the organic phase was collected in a clean tube. A total of 100 mL of organic phase collected from the 2 extractions was submitted to a “wash step” with double distilled water. After this step, the dextromethorphan was supposed to be in the toluene solvent as free base form, but the procedure recommended it to be converted into the HCl salts form in order to easily manage the storage of the dextromethorphan crystals. To do that, 30 mL of acidified (pH 4) double distilled water were added to the toluene solution into the separatory funnel and mixed for 5 min. The aqueous bottom layer was collected and left for evaporation an oven overnight in an oven. An aliquot of the aqueous solution was injected into the LC-MS/MS system after dilution.

### 2.3.3. Fentanyl extraction from patch

Two patches of transdermal fentanyl (25 µg/hr, 72 h) were submitted to the extractions described on the forum [14]. Forum users suggested to use either isopropanol or to exploit the alcohol content of vodka/whisky for the extraction of fentanyl from gel or

non-gel patches to obtain an injectable form of fentanyl. Following the instructions, the disposable protective plastic liner over the front of patches was peeled off and one patch was placed under stirring in 50 mL of isopropanol and one patch was extracted in 50 mL whisky (35%, v/v) under stirring. After 2 h the isopropanol was collected for analysis and the patch was left to dry. A further extraction was repeated with other 50 mL of isopropanol for 1 h. The patch in whisky was left 4 h under stirring for extraction and then the supernatant was collected for analysis.

### 3. Results and discussion

The “Cold Water Extraction” (CWE) procedure has been applied to commonly classified as over-the-counter painkillers, three tablets and one suppositories formulations, containing variable amounts of opioid, namely oxycodone, tramadol and codeine and a non-opioid analgesic (samples 1–4, Table 2). Type and amounts of each opioid and relative non-opioid analgesic are reported in Table 2. As can be seen, the amount of analgesic, most frequently paracetamol, variably exceeded the amount of opioid from a factor of 9 up to 65. A formulation including dexketoprofen, as analgesic component, was also studied to test the tampering potential, even if no specific reference was found in the investigated forums. Following the instructions of the CWE, a variable number, but higher than the supposed dose, of tablets/suppositories was analysed according the main steps of the procedure. The entire procedure, basically referring to codeine tablets, but allegedly applicable to other opioid-containing formulations, claimed to exploit the different solubility values in cold water of the opioid (codeine hydrochloride > 100 mg/mL) vs paracetamol (15 mg/mL) [17]. Difficulties for the authors were mainly based on the standardization of the described procedure in terms of times, temperatures and volumes, but also in the selection of the materials used for filtration. Both coffee filters, as suggested, and laboratory paper for filtration were used, while “cold water” was arbitrary defined at a temperature of 1 °C and “hot water” at 50 °C, as suggested by other authors [11] in similar experiments. No difficulties were instead encountered with fatty material from suppositories, because of easy separation at freezing conditions prior filtration. Obtained solutions were analysed by the developed LC-MS/MS method on the same day of the extraction. As a result, the mean recovery for opioid ranged between 41 and 94%, while paracetamol was present in the range 39–57% and dexketoprofen remained in the solution in the amount of 69% (on average) (Table 3). These highly variable results were not in agreement with the often-assured recoveries found on the forums, or in other authors' similar experiments and the reasons could lay in difficulties encountered during the extraction (i.e. clotting of the filters during extraction, observed both for coffee filters and laboratory paper, forcing to substitute the filter during extraction; on this point, the use of paper tissues, t-shirt fabrics and socks were also reported in Internet) or the number of tablets used for the extraction, but more probably lay in the empirical design of the experiment, leading to unpredictable results depending on the conditions of the moment (opioid amount availability, materials, times, volumes. . .). Beside the toxicity of the opioid component, in reason of the potential great number of starting tablets/pills/suppositories consumed, severe risks are also posed by the analgesics. Although paracetamol is advertised as safe in pharmaceutical doses, with toxic ingestions causing hepatic failure usually exceeding 150 mg/kg, an increasing recent number of reports has arisen to suggest that lower doses of paracetamol, usually considered as “safe”, may confer acute liver injury and liver failure [18–21]. In fact, some of these patients may display some subjective risk factors, such as nuances in metabolism at the mitochondrial and molecular level [22].



Fig. 2. Fentanyl crystals after extraction and drying.

Acid/base extraction has been applied to extract dextromethorphan from cough syrup containing dextromethorphan and paracetamol (sample 5, Table 2). The procedure described in the forum detailed very carefully each step of the dextromethorphan extraction from the syrup exploiting pKa differences (acid/base), including washing steps to remove sugars and colorants, mainly water-soluble. The online procedure also recommended to repeat the extracting steps with the solvent more than once, combining the toluene layers each time, to improve the recovery of the dextromethorphan from the syrup. However, the recovery of the opioid after only two repetitive extractions, as performed by the authors, already reached the 98% of the original amount, showing a high yield of the procedure. Since dextromethorphan recreational induced effects, such as mild hallucinations, slurred speech and short-term memory loss are supposed to begin at a dose of 2.5 mg/kg, for a 70 kg individual, four bottles (i.e. 90 mL) of over-the-counter cough syrup could be enough to induce psychotropic effects. Contrary to the CWE, this procedure was surprisingly detailed in terms of volumes, pHs and washing steps and no difficulties were encountered in obtaining a clear extract even in the presence of high amounts of sugars and colorants. The remaining amount of paracetamol in solution was still 17% of the original and although lower than in CWE, the considerations on the arbitrary volumes and the toxicity of paracetamol persist. As a last point, the extraction of fentanyl from transdermal patches in two different extracting media have been tested, isopropanol and whisky as suggested by forum users. The choice of the extracting media probably lays in the addiction habits of the consumer as well as from the initial availability of a consistent number of patches. After extraction with isopropanol, solution should be dried to get crystals (Fig. 2) and other routes of administration can then be sought, while the mixture with whisky can be directly ingested. Not sur-

**Table 3**  
Mean recovery for the opioid and the analgesic, expressed as percentage of the expected amount.

Product number	Opioid	Non-opioid analgesic	Opioid recovery (%)	Non-opioid analgesic recovery (%)
1	oxycodone	paracetamol	61	39
2	tramadol	dexketoprofene	42	69
3	tramadol	paracetamol	89	57
4	codeine	paracetamol	94	54
5	dextromethorphan	paracetamol	98	17

**Table 4**  
Absolute and relative recoveries of fentanyl extraction from patch in isopropanol and whisky.

	Fentanyl/patch ( $\mu\text{g}$ )	2 h in isopropanol ( $\mu\text{g}$ )	Extra 1 h isopropanol ( $\mu\text{g}$ )	4 h in whisky 35% v/v ( $\mu\text{g}$ )
	1800	650	5	3
Recovery	–	36%	0.3%	0.2%

prisingly, extraction carried on with isopropanol after 2 h under stirring yielded higher recoveries than extraction carried out with whisky in 4 h (Table 4). The reason should be likely ascribed to a lower content of alcohol in whisky, which hampered the extraction recovery, but the additive effect of consuming fentanyl and high doses of alcohol could overcome such limitation. Even if the extracted amounts from one patch in whisky are lower than the estimated lethal dose of fentanyl in humans, about 1000-fold lower, the risk for facing a respiratory depression in some subjects still may occur at sub-lethal doses.

A realistic evaluation of the prevalence and impact of prescription opioid abuse and tampering among adults would be of great interest, but statistics are mostly based on self-reported surveys which limit a truthful evaluation of the phenomenon [23,24] and in most cases, fatal intoxication is the only final evidence available to the forensic toxicologist. However, some authors report that opioid abuse increases with younger age, male sex, minority race, psychiatric illness, alcoholism, cigarette smoking, being employed, and higher household income [23]. It should be noted that manufacturers of prescription drugs continue to work on new formulations of opioid medications, known as abuse-deterrent formulations (ADF), which include technologies designed to prevent people from misusing them by snorting or injection. Approaches currently being used or studied for use include:

- physical or chemical barriers that prevent the crushing, grinding, or dissolving of drug products;
- agonist/antagonist combinations that cause an antagonist (which will counteract the drug effect) to be released if the product is manipulated;
- aversive substances that are added to create unpleasant sensations if the drug is taken in a way other than directed;
- delivery systems such as long-acting injections or implants that slowly release the drug over time;
- new molecular entities or prodrugs that attach a chemical extension to a drug that renders it inactive unless it is taken orally.

Numerous concerns with the integration of these formulations into clinical practice remain, as no product is intended or capable of addressing all types of misuse or abuse, but they can really help in reducing this phenomenon as verified after the release of tamper-resistant controlled-release oxycodone [24]. Furthermore, proper patient assessment to identify risk factors for misuse and abuse would be helpful for considering these formulations in patients who appear to be at high risk of misuse, abuse and/or diversion.

#### 4. Conclusions

Drug tampering practices, with the aim to increase availability of drug delivery and/or enhance drug effects, are accessible on Inter-

net and are practiced by some portion of recreational drug users as already reported by literature. Not rarely, recreational misuse may also result in toxic and fatal results. The development of successful formulations that inhibit or prevent drug tampering should be of primary interest for drug developers and for this scope the knowledge of the procedures freely available on the web should be included in the study.

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