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Mini Review

Fentanyl transdermal patch: The silent new killer?

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ABSTRACT

Background: Transdermal fentanyl patches represent an excellent alternative for the treatment of chronic and cancer-related pain, but can lead to death due to their incorrect use or increasing abuse.
Purpose: Present an overview of literature regarding fentanyl patch related fatalities.
Methods: Literature research into PubMed database for all types of publications. Search terms were "fentanyl", "patch" and "death". Additional publications by manual examination of references of the PubMed results were included.
Results and conclusions: To date 29 publications about transdermal fentanyl patch related deaths are available on PubMed and their time span is of 26 years. A total of 674 deaths related to fentanyl were found, 658 associated with transdermal fentanyl patch. Use of patches was more frequently in males (68 %) than in females (32 %) and in the 31–40 and 41–50 decades. The most frequent route of administration was the transdermal route, followed by oral and intravenous route. Cause of death was in 63.5 % of cases drug abuse, followed by accidental death (16.2 %), death unrelated to fentanyl (13.3 %) and suicide (2.8 %). The use of concomitant drugs was reported in 19 of the 29 publications and antidepressant followed by benzodiazepines and ethanol were the most frequent discovered drugs. In conclusion, fentanyl transdermal patch misuse and abuse is a major problem and still need to be completely addressed.

Introduction

Novel synthetic opioids continue to surface in the drug market and drug-related deaths increase despite all the efforts against trafficking. Fentanyl, furanyl fentanyl, acetyl fentanyl, and U-47700.3 are the most commonly seized synthetic opioids and new fentanyl analogues are available on the market [1]. Fentanyl abuse is widely reported in literature. In 2016 more than 63.600 drug overdose related deaths were reported in the United States and the so called "synthetic opioid crisis" was certified in the last years also in Europe. In fact, in 2017, Europe had the second highest prevalence of opiate use in the world and an increase in fentanyl abuse in the last 10 years was reported [2,3]. In 2018, 81.7 % of fentanyl consumption was concentrated in 10 countries: USA, Germany, UK, Spain, Italy, France, Netherlands, Canada, Australia and Belgium [4]. Estimating the real incidence of deaths associated with fentanyl and its analogues represents a big concern and the risk of underreporting is realistic [5].

Fentanyl, N-phenyl-N-(1-2-phenylethyl-4-piperidyl) propanamide, is a synthetic phenylpiperidine introduced in the 1960s for pain therapy, as its potency compared to other opioids, was 75–100 times greater. Fentanyl is a μ-opioid receptor agonist and acts on the central nervous system inducing analgesia, sedation and euphoria, in a less pronounced way compared to morphine or heroin. It is used in general and regional anesthesia, in neuroleptoanalgesia (together with droperidol, a neuroleptic). Nowadays, fentanyl is prescribed for chronic or cancer-related pain therapy too [6–9]. Nausea, dizziness, vomiting, fatigue, headache, constipation, anaemia and peripheral oedema are the most common side events, but the most severe toxicity includes respiratory depression, muscle rigidity, seizures and coma. Adverse drug reactions (ADR) are common in overdose or at the beginning of the therapy in patients without enough fentanyl tolerance. Routes of administration are various: intravenous, transdermal, oral, epidural, intrathecal, inhalation and transmucosal [6,10,11]. Since the skin is the largest organ of the body, a major interest in transdermal drug delivery system (TDDS) started early and the risk of fentanyl patches misuse in Western was reported [12].

In this paper, the phenomenon of fentanyl patch overdose is analyzed and all fatal cases reported in literature are reviewed systematically. Unconventional ways of administration, manner and cause of death, association of other drugs were analyzed as well as absorption, metabolism of fentanyl and clinical features of acute intoxication.

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Table 1
Summary of previously published cases related to transdermal fentanyl patch deaths.

First author (year of publication)	Country	Study type (number of participants)	sex	age	Fentanyl concentration (ng/mL)	other drugs (Y/N)	Route of administration	Manner of death	Cause of death
Marquardt (1994)	USA	case report (N = 1)	M	36	Femoral blood 2.66, heart blood 6.05	N	inhalation	accidental	fentanyl overdose
Edinboro (1997)	USA	case report (N = 1)	F	83	Blood 25	N	transdermal	undetermined	fentanyl overdose
Yerasi (1997)	USA	case report (N = 1)	M	31	Serum 31	N	transdermal	accidental	fentanyl overdose
Kramer (1998)	USA	case report (N = 1)	M	31	Blood 17.2	Y	transdermal and oral	accidental	fentanyl overdose
Anderson (2000)	USA	Retrospective study (N = 25)	7F and 18M	from 19 to 86	Heart blood from 1.8 to 139	Y	24 transdermal; 1 transdermal + IV	5 natural, 3 suicide, 15 accidental and 2 undeterminated	4 fentanyl overdose, 9 mixed drug toxicity, 12 other cause
Reeves (2002)	Australia (Tasmania)	case report (N = 1)	F	35	Serum 2	Y	IV	accidental	fentanyl overdose
Kuhlman (2003)	USA	Retrospective study (N = 23)	7F and 16M	from 16 to 53	Blood: range 2–49; mean 19.96	11Y 12N	3 oral; 5 transdermal; 2 transdermal + IV; 4 IV; 9 NR	2 natural, 1 suicide, 20 accidental	8 fentanyl overdose, 13 mixed drug toxicity, 2 other cause
Lilleng (2004)	Norway	case series (N = 2)	M	NR	Blood 2.7 and 13.8	Y	IV	accidental	fentanyl overdose
Tharp (2004)	USA	case series (N = 4)	M	from 35 to 42	Aortic blood 5, 27, 22 and 17	3Y 1N	IV	3 accidental and 1 suicide	fentanyl overdose
Martin (2006)	Canada	Retrospective study (N = 112)	49 F and 63 M	from 4 to 93	Blood range 2.7–119	40Y 72N	62 transdermal; 12 IV; 6 oral; 1 inhalation; 2 transdermal + IV; 1 oral + transdermal; 28 NR	11 natural, 6 suicide, 57 accidental and 38 undetermined	54 fentayl overdose, 40 mixed drug toxicity, 11 natural, 7 NR
Coopman (2007)	Belgium	case report (N = 1)	F	78	Sampling (ng/mL) from subclavian blood side right = 28.6 ; left = 28.2. Sampling from femoral blood side right = 21.3 ; left = 20.9. Sampling from ventricular blood side right = 37.6 ; left = 33.9	N	transdermal	suicide	fentanyl overdose
Teske (2007)	Germany	case report (N = 1)	F	1	Femoral blood 5.6, heart blood 19.0	N	oral	accidental	fentanyl overdose
Thompson (2007)	USA	Retrospective study (N = 23)	NR	NR	Blood range 2–120; mean 37.57	NR	7 transdermal; 16NR	1 natural and 6 accidental	3 Fentanyl overdose, 3 mixed drug toxicity, 1 other cause
Thomas (2008)	USA	case report (N = 1)	M	42	Femoral blood 11	Y	transdermal and oral	accidental	fentanyl overdose
Wiesbrock (2008)	Germany	case report (N = 1)	M	63	femoral vein blood 94.9 ng/g, left heart blood 45.9 ng/g, right heart blood 74.8 ng/g	N	transdermal	suicide	fentanyl overdose
Woodall (2008)	Canada	case series (N = 7)	3F and 4M	from 20 to 51	heart blood = 22 heart blood = 7 heart blood = 8 femoral blood = 13 femoral blood = 97 femoral blood = 19 femoral and heart blood = 28 and 32 ng /mL	Y	6 oral; 1 transdermal	accidental	fentanyl overdose
Biedrzycki (2009)	UK	case report (N = 1)	M	32	Femoral vein blood 40	Y	transdermal	accidental	fentanyl overdose
Carson (2010)	USA	case report (N = 1)	M	28	Femoral blood 8.6	Y	oral	accidental	mixed drug toxicity
Jumbelic (2010)	USA	case series (N = 8)	3F and 5M	from 16 to 49	Femoral blood ranged from 10 to 28	Y	transdermal	accidental	fentanyl overdose
Gill (2013)	USA	Retrospective study (N = 92)	40 F and 52M	from 13 to 86	Blood range 1–462	Y	transdermal	36 natural, 8 suicides, 5 therapeutic complications, 40 accidental and 3 undetermined	6 fentanyl overdose, 41 mixed drug toxicity, 43 other cause, 2 uncertain

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Table 1 (*continued*)

First author (year of publication)	Country	Study type (number of participants)	sex	age	Fentanyl concentration (ng/mL)	other drugs (Y/N)	Route of administration	Manner of death	Cause of death
Juebner (2014)	Germany	case report (N = 1)	F	46	Femoral blood 60.6, heart blood 94.1	Y	transdermal	accidental or suicidal	fentanyl overdose
Bakovic (2015)	Croatia	case report (N = 1)	F	2	Femoral blood: just above the level of detection (approximately 2 ng/mL)	N	transdermal	accidental	fentanyl overdose
Moore (2015)	USA	case report (N = 1)	M	42	Femoral blood: sample 30 min postmortem = 1.6, 2 h postmortem = 14	Y	transdermal and oral	accidental	fentanyl overdose
Oppliger (2016)	Switzerland	case report (N = 1)	F	54	Heart blood 25	N	oral	suicide	fentanyl overdose
Sinicina (2017)	Germany	Retrospective study (N = 242)	44 F and 198M	from 18 to 62	Femoral blood in 227 cases: mean 16.9 ± 23	Y	1 inhalation; 10 oral + IV; 2 oral; 12transdermal + IV; 4 transdermal; 72 IV; 141 NR	accidental	20 fentanyl overdose, 222 mixed drug toxicity
Geile (2019)	Germany	Retrospective study (N = 35)	20 F and 15M	from 17 to 95	NR	Y	transdermal	21 natural, 9 accidental 5 undeterminated	7 mixed drug tox, 23 other cause, 5 uncertain
Nara (2019)	Japan	case report (N = 1)	F	40	Femoral blood 51, heart blood 33	Y	transdermal	accidental	fentanyl overdose
Thornton (2020)	USA	Retrospective study (N = 8663) Only 85 deaths were related to fentanyl patch	NR	from 1 to 90	NR	NR	oral	NR	NR

Materials and methods

A literature research using the database of the National Center for Biotechnology Information (PubMed) was performed, followed by a critical appraisal of the collected studies. Search terms were “Fentanyl”, “Patch” and “Death” in title, abstract and keywords. Abstracts of 63 articles were examined and only those related with fatalities involving fentanyl transdermal patches were chosen for further studies. Of these, only 23 matched our target. References of the chosen articles were manually examined and 6 additional publications that matched our interests were found. All types of papers were included in our study.

At the end, 29 articles were included in this overview: 20 case reports or case series, 8 retrospective studies and 1 review (each case described in this review had already been considered in the other articles). This review includes publications from all over the world and from a span of time of 26 years (from 1994 to 2020) (Table 1).

Results

Absorption

Fentanyl lipophilic properties allow the absorption of 46–66 % of the given dose into the dermal tissue, but a slower absorption into water-rich tissues. The result is the formation of a depot into the keratinaceous layer of the epidermidis, which is associated with a slow onset and prolonged effects after administration. However, the transdermal fentanyl absorption may depends on many factors such as the thickness, temperature, damages or irritation, depilation, cosmetic treatments and degree of keratinization of the skin. The rate of absorption of the medication can also be influenced by the degree of blood flow through the skin where the patch is applied. For example, any increase in the skin temperature due to fever, external heat application, muscular activities or local inflammatory state, may allow a gradual increase in cutaneous blood flow. The increased perfusion results in increased systemic absorption and serum concentrations of fentanyl. It has been supposed that blood fentanyl concentrations may increase by one third in patients with a body temperature of 40 °C because of increased skin permeability and accelerated drug release [13,14]. The narrow therapeutic index of fentanyl and the effect of heat on transdermal fentanyl absorption may represent a fatal combination in some cases [15–18].

Transdermal therapeutic fentanyl was introduced in the 1990s [6,7,19,20]. Two different types of transdermal systems are available: the reservoir (membrane-controlled) and the matrix system (drug-in-adhesive). The first design has the drug dissolved into a gelled mixture and is contained into a pouch (reservoir) and thus it is easier to be aspired with a needle. The drug has to move from the pouch through a rate-limiting membrane and then into the skin. The second design is easier: it has the drug suspended into a solid silicone matrix and fentanyl is easy to extract by boiling the patch. Both come with 5 different dosages: 12.5, 25, 50, 75 and 100 μg/h with respectively 1.2, 2.5, 5.0, 7.5 and 10 mg of fentanyl (10–20 times the initial therapeutic dose of IV fentanyl). In both cases, the release of the drug occurs at a constant rate for 72 h [20–23]. After the patch application, serum levels of fentanyl increase gradually and become stable in 12−24 h so fentanyl interactions with sedatives, hypnotics and other opioids are still possible hours after the patch has been removed [7]. After removal of the patch, the absorption continues for approximately 12 h thanks to the stratum corneum depot thus removal of the patch does not quickly eliminate the risk of fentanyl interactions with other drugs [6,20]. Fentanyl tolerance is related to cellular adaptation due to prolonged administration.

Metabolism and elimination

Once absorbed, fentanyl bounds to plasma proteins at a physiological pH. However, when the pH decreases the protein binding also decreases

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and blood concentration rises.

Fentanyl is mainly metabolized in the liver by CYP3A4 and 3A5 isoenzymes and transformed by a N-dealkylation at the piperidine ring in norfentanyl, which has a negligible pharmacological activity [24]. The inactive metabolites and less than 10 % of the intact molecule, are mainly excreted in urine and faeces. Less than 1% is metabolized by alkyl hydroxylation, N-dealkylation or amide hydrolysis to the inactive compounds hydroxyfentanyl, hydroxynorfentanyl and despropionylfentanyl [6,7,21,25,26]. Minor metabolites such as hydroxypropionylfentanyl and hydroxypropionyl-norfentanyl are created through different pathways without relevant pharmacological activity.

Clinical features

The use of transdermal fentanyl patch is associated with a significant decrease of the severity of pain. Its repeated use leads to the development of tolerance and dependence. Nausea, vomit, constipation and sleepiness represent major side effects. Elevated levels of fentanyl increase the potential for respiratory depression, even in patients with increased opioid tolerance. Maximal respiratory depressant effects are reached very quickly after IV use, perhaps within 2 min, further highlighting the potentially dangerous nature of non-medical use of the drug. When compared to heroin, fentanyl has an explosive onset of strong opioid effect ("rush sensation"), a shorter duration of effect, typically 1–2 h, and a greater potency that allows some users to overcome the tolerance they had developed to heroin or effects of opioid antagonists [27]. The most common overdose symptoms are coma, lethargy, respiratory depression and arrest. A recent review of fentanyl and non-pharmaceutical fentanyl highlighted the rapid nature of many deaths following fentanyl use, which contrasts with most of opiate deaths [28].

Epidemiology

Fentanyl patch overdose and abuse is a worldwide issue. 674 fatal cases of fentanyl patch overdose were reviewed. Sex distribution was available in 26 of the 29 papers with a prevalence in male (68 %) than in female (32 %) [6,7,10–12,22,29–48]. Age distribution was available in 25 of the 29 studies with a range from 1 to 95 years and a prevalence of deaths for the 31–40 and 41–50 decades [6,7,10–12,22,29–47]. Prescription of the fentanyl patch was available in 19 of the 29 papers; 134 cases had a medical prescription for the fentanyl patch while in 27 cases it was not prescribed from healthcare providers. In 1 case the patch was illegally purchased from the street. In 427 cases, this data was unavailable [6,7,11,12,29–31,34,35,37–42,44,45,47,48].

Way of administration

The way of the administration of patch-stored fentanyl was reported in 27 of the 29 articles. In 154 cases (22.9 %) the normal transdermal way of administration of the fentanyl patch was recorded [6,7,10,12,13,29–32,34,35,40,41,44,45,47,49]. Transdermal administration of fentanyl can be combined with intravenous (2.5 %) [6,12,29,34] or oral (0.6 %) administration [29,37,43,40]. Single oral administration was reported in 105 cases (15.6 %) [12,13,29,33,34,39,41,44] while in 10 cases (1.5 %) both oral and IV administration were used [12]. Intravenous administration of patch-stored fentanyl was described in 95 cases (14.1 %) [12,29,38,43,48] and in 3 cases (0.4 %) inhalation of the smoke from a heated patch was reported [12,29,36]. In the other 286 cases (42.4 %) the way of administration was not specified [11,12,29,34,49] (Table 2).

Table 2
Route of administration of patch stored fentanyl in fatal cases.

Route of administration	%
Transdermal	22.9
Transdermal and i.v.	2.5
Transdermal and oral	0.6
Oral	15.6
Oral and i.v.	1.5
Intravenous	14.1
Inhalation	0.4
Unknown	42.4

Manner and cause of death

Manner and cause of death were analysed and were available in 27 of the 29 publications. In 63.5 % cases the manner of death was classified as drug abuse. In 93 cases (16.2 %) administration of fentanyl was accidental due to the misuse of transdermal patch. The misuse is not restricted to the transdermal application: intravenous injection, ingestion, inhalation and transmucosal administration of patch-stored fentanyl are widely reported [29]. Accidental domestic cases of misuse of fentanyl transdermal patch have been also described in children fatal poisoning [30]. A concerning problem is represented from misuse of used prescribed fentanyl patches that can contain residual fentanyl (28–84 % of the initial concentration) [19,20]. In 76 cases administration of fentanyl was not relevant on the mechanism of death and manner of death was classified as natural, while only in 16 cases (2.8 %) a suicidal intent was ascertained. Finally, in 0.9 % cases (n = 5) the death was related to therapeutic complications of fentanyl administration. In 19 cases manner of death remain undetermined. In most cases (58.6 %), death was related to the association of fentanyl with other drugs (mixed-drug intoxication). Fentanyl overdose was indicated as the cause of death in 131 cases (22.9 %) followed by 2.4 % of cases in which the cause of death remained uncertain after postmortem investigation. "Other causes" accounted for 16.1 % of cases [6,7,10–12,22,29–48].

Associated drugs

Use of other drugs in combination with fentanyl was reported in 18 of the 29 publications. Opioids and antidepressant were mainly mixed with fentanyl, followed by benzodiazepines, ethanol, cocaine and methamphetamine. Cannabinoids, non-opioid analgesics, diphenhydramine (an antihistamine) and medicinal products were rarely recorded [6,7,10–12,22,29,31,33–35,37,38,42–44,46,48].

Fentanyl concentrations

Fentanyl concentrations were available in 26 of the 29 articles, but the type of samples and the quantitation system applied were different. Gas chromatography–mass spectrometry (GC–MS) was used in 11 articles while a liquid chromatography/tandem mass spectrometry (LC–MS) study was performed in 7 articles. In the other cases, the quantitation system was not reported. Moreover, differences exist about the source and size of blood samples used for the fentanyl quantification and quantitation; in particular, blood was sampled from femoral artery, femoral vein, subclavian artery, left and right side of the heart indistinguishably. In few cases sample size was reported (Table 3). Timing of collection of blood samples was different ranging from 30 min to 2 h postmortem [6,7,11,12,22,29–48]. 34 ± 7 ng/ml represented the fentanyl serum concentration at which loss of consciousness occurred, while 1–5 ng/mL was the range of serum concentrations in the cases in which respiratory depression was observed [6,7]. Interpretation of fentanyl postmortem concentrations should take account of the possible postmortem redistribution (PMR). Decrease of blood pH and increase of permeability of biological membranes cause an increase of the distribution volume and as a result, the drug concentration changes from death until autopsy. PMR includes drug movements into the vessels based on a concentration gradient and the release of drug from tissues such as skeletal muscle, vascular endothelium, stomach and adipose

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Table 3
Fentanyl concentrations in blood samples. NR: not reported.

First author (year of publication)	Source of blood sample (fentanyl concentration)	Sample size
Marquardt (1994)	Femoral blood (2.66 ng/mL) Heart (6.05 ng/mL)	NR
Edinboro (1997)	NR (25 ng/mL)	NR
Yerasi (1997)	Serum (31 ng/mL)	NR
Kramer (1998)	NR (17.2 ng/mL)	NR
Anderson (2000)	Heart (range 1.8−139 ng/mL)	3 mL
Reeves (2002)	Serum (2 ng/mL)	NR
Kuhlman (2003)	NR (range 2−49 ng/mL)	4 mL
Lilleng (2004)	NR (range 2.7−13.8 ng/mL)	NR
Tharp (2004)	Aorta (range 5−27 ng/mL)	1 to 5 mL
Martin (2006)	NR (range 2.7−119 ng/mL)	2 mL
Coopman (2007)	Right subclavian blood (28.6 ng/mL) Left subclavian blood (28.2 ng/mL) Right femoral blood (21.3 ng/mL) Left femoral blood (20.9 ng/mL) Heart-right side (37.6 ng/mL) Heart-left side (33.9 ng/mL)	1 mL
Teske (2007)	Femoral blood (5.6 ng/mL) Heart (19.0 ng/mL)	200 μL
Thompson (2007)	NR (range 2−120 ng/mL)	NR
Thomas (2008)	Femoral blood (11 ng/mL)	NR
Wiesbrock (2008)	Femoral vein (94.9 ng/g) Heart-left side (45.9 ng/g) Heart-right side (74.8 ng/g)	NR
Woodall (2008)	Heart (range 7−32 ng /mL) Femoral blood (range 13−97 ng /mL)	NR
Biedrzycki (2009)	Femoral vein (40 ng/mL)	NR
Carson (2010)	Femoral blood (8.6 ng/mL)	NR
Jumbelic (2010)	Femoral blood (range 10−28 ng/mL)	NR
Gill (2013)	NR (range 1−462 ng/mL)	NR
Juebner (2014)	Femoral blood (60.6 ng/mL) Heart (94.1 ng/mL)	NR
Bakovic (2015)	Femoral blood (just above the level of detection - approximately 2 ng/mL)	5 mL
Moore (2015)	Femoral blood (1.6 ng/ml – sampled 30 min postmortem) Femoral blood (14 ng/ml – sampled 2 h postmortem),	NR
Oppliger (2016)	Heart (25 ng/mL)	NR
Sinicinaa (2017)	Femoral blood (mean 16.9 ± 23 ng/mL)	NR
Geile (2019)	NR	200 μL
Nara (2019)	Femoral blood (51 ng/mL) Heart (33 ng/mL)	100 μL

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tissue, resulting in differences between ante- and postmortem concentration as well as central and peripheral drug concentrations. The postmortem decrease of pH causes an increase in fentanyl solubility thus an increase in its concentration. Continued postmortem release of fentanyl from the patch is unlikely. Postmortem differences between central and peripheral blood concentrations can be found, but there is no certain data: central blood has often a greater concentration, but multisite sampling is recommended. A prolonged agonal state can lead to lower postmortem concentrations due to drug metabolism. A strict correlation between the patch dose and fentanyl postmortem concentration has not been established. Interpretation of postmortem fentanyl concentrations must consider also the possibility of drug tolerance [11,21].

Norfentanyl blood concentration was available only in 7 of the 29 articles. In 4 cases multisite sampling was performed (femoral blood and heart blood), in 5 cases the blood sample was collected from the femoral vein, in 1 case the sample was collected from the heart and in 1 case the source of sampling was not reported. Values ranged from 1.4–298 ng/mL. Norfentanyl concentrations could be used to determine whether death occurred rapidly after administration, but correlation with antemortem fentanyl concentrations is not supported from reliable evidences. The short half-life of fentanyl, particularly following IV injection, means that unless the drug user died within minutes of injection, i.e. “on the needle”, then norfentanyl is likely to be present together with parent drug. A high ratio of fentanyl/norfentanyl would be expected to be consistent with acute fentanyl intoxication and to be likely with rapid death. A post-mortem blood fentanyl/norfentanyl ratio of >8 is highly suggestive for for acute fentanyl toxicity, whereas a ratio of <2.5 is related with chronic fentanyl usage [50].

Conclusions

An overview about fatalities connected with therapeutic and non-therapeutic use of transdermal patch of fentanyl, mechanisms of toxicity, the clinical symptoms, and the analytical procedures concerning post-mortem examination sampling is here presented. Misuse and abuse of fentanyl transdermal patches can be considered a serious issue in many countries, all around the world. Fentanyl-related death is more frequent in males (68 %) than in females (32 %) with a wide range of age of consumers. Most of the deaths were related to prescribed fentanyl patches, anyway in most of the studies the way the patch was obtained was not reported and thus it is difficult to understand the prevalence of illicit prescription and recreational use. Unconventional routes of administration of fentanyl stored in the patch are mainly related with fatalities: oral (15.6 %), intravenous (14.1 %), inhalation of the smoke of a heated patch (0.4 %) and multiple concomitant ways of administration are reported. When drug-related deaths are suspected, a complete post mortem examination must be performed and toxicological investigations are mandatory. Despite its wide use for therapeutic and recreational use, the risk of under-reporting fentanyl related death is still considered too high [1]. Fentanyl related fatalities represent a great challenge for forensic toxicologists and pathologists due to the several factors (tolerance, postmortem interval, redistribution, metabolism) affecting postmortem concentrations. Because

of its structure, fentanyl should not produce a positive result of the opiate compound search in urine based on an immunoassay. The liquid chromatography-mass spectrometry is the gold standard for fentanyl measurements in blood and serum [20]. Fentanyl is highly lipophilic, 80 % plasma protein-bound with a high data volume of distribution all characteristics that would suggest that fentanyl would display significant postmortem redistribution. Overview of literature increased concerns for under-reporting of fatalities related with fentanyl transdermal delivery systems. In fact, only eight larger studies respected inclusion criteria, while the majority of other studies were limited to case reports. In 22.9 % of the cases, the death was due to fentanyl overdose, but in more than a half of cases, fatality was related to a concomitant administration of other drugs (opioids, antidepressants, benzodiazepines and ethanol consumption). Additionally, concomitant use of inhibiting CYP3A4 drugs and affecting the metabolism of fentanyl resulted with higher concentrations than expected. Source and type of samples, methodologies of quantitation were very variable in the analyzed studies. Several published reports have indicated postmortem fentanyl blood concentrations, whether specimens are obtained from the heart or femoral artery, are unreliable for the determination of the fentanyl blood concentration at the time of death and ascribing fentanyl overdose as a cause of death. In an extensive published review of the postmortem fentanyl literature, deaths involving the rapid administration of fentanyl or the administration of large bolus doses of fentanyl were found to have incomplete fentanyl distribution throughout the body tissues and fluids. Thus, nonequilibrium pharmacokinetics results in higher fentanyl heart blood concentrations than femoral blood values simply due to relative blood flow through the various vessels and organs prior to death. Thus, discriminating between fentanyl overdose or therapeutic concentrations of a fentanyl-tolerant patient becomes difficult and in various studies the range of these values partially overlaps [9].

Post-mortem toxicological considerations relating to fentanyl have recently been reviewed and measurement of both fentanyl and norfentanyl blood concentrations has been recommended [51]. Cummings et al. have recently investigated fentanyl-related deaths and proposed that the ratio of urinary fentanyl to norfentanyl concentrations can be useful as an adjunct to determining acute fentanyl toxicity [52]. Vitreous humor is a stable matrix in which both fentanyl and norfentanyl are readily detectable so it can be a very useful postmortem sample for the forensic toxicologist [53].

Overviewing of literature may help to investigate mechanism of death related with fentanyl and transdermal delivery systems and to address efforts for future investigations. Actually, existent scientific contributes related with fentanyl transdermal patch fatalities are mainly limited to case reports except for three larger studies, methodology is sometimes not completely explicated so that comparing results still remain difficult and epidemiological analysis incomplete. The risk of under-reporting makes these fatalities still “silent” to the most part of the public opinion and healthcare providers but the relevance of the phenomenon should provide to address future forensic efforts towards fentanyl transdermal patch-related deaths and a standardized scientific methodological approach.

Author contribution

All the authors contributed equally to the conception and design of the study, acquisition of data, or analysis and interpretation of data, drafted and revised the article critically for important intellectual content, and approved the final version before its submission.

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Declaration of Competing Interest

None.

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