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Characteristics of opioid-maintained clients smoking fentanyl patches: The importance of confirmatory drug analysis illustrated by a case series and mini-review

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Abstract

The increase in opioid prescribing in many European countries over the last decade has raised concerns about associated diversion, overdose and mortality. Fentanyl is one of these synthetic opioids that is typically prescribed as a transdermal patch for pain that requires continuous pain relief and has been the focus of investigations due to reports of overdose and death.

We report a case series of 14 drug addiction treatment entrants who entered treatment in one service located in the region of Southern Denmark from August 2015 to December 2015 for smoking fentanyl patches. Clients presented with difficulties breathing and pains in the lungs. The clients had a history of past opioid use, including heroin. Relapses resulted in treatment disengagement.

Immunoassays for fentanyl were used in the service. In some cases, false negative results occurred. Clients' urine samples were subsequently analysed in a collaborating laboratory. Seven clients tested positive for fentanyl. One client was positive for both fentanyl and heroin. Analyses were also positive for other opioids and metabolites in six clients, predominantly codeine and oxycodone. Results from confirmatory analysis contributed to clearer insights into clients' drug histories, which facilitated personalised care plans consisting of opioid agonist therapy informed by confirmed drug use.

In Denmark, prescription levels of fentanyl are high, which has been accompanied by observations of diversion and smoking in a smaller population. In addition to revision of inappropriate prescribing to reduce diversion, we recommend increased reliance upon confirmatory drug analysis in the addiction treatment sector in Denmark.

Keywords: fentanyl, transdermal patches, tampering, smoking fentanyl patches, addiction treatment, confirmatory drug analysis.

Short title: Characteristics of opioid-maintained clients smoking fentanyl patches.

1 Introduction

In the wake of the dire public health situation faced in North America concerning opioid use, where the synthetic opioid, fentanyl, has played a major role in overdose deaths,^{1,2} there has been an recent increase in focus on availability and misuse of fentanyl in Europe.³ Multiple sources of fentanyl contribute to the overall supply, including pharmaceutical fentanyl diverted to the illicit market, and illicitly manufactured fentanyl and fentanyl analogs, also known as fentanils.⁴ Over the last ten years, a number of fentanyl analogs, such as acrylfentanyl, furanylfentanyl, acetylfentanyl, *ortho*-fluorofentanyl and carfentanyl, have been detected in the EU.⁵⁻¹¹ These substances have been linked to over 100 deaths across the EU and a number of acute intoxications.⁸⁻¹¹

Pharmaceutical fentanyl is often prescribed in the form of transdermal patches that deliver a fixed hourly rate of fentanyl through the skin.¹² Fentanyl patches serve to relieve pain in cases of severe and debilitating disease that requires continuous pain management. The World Health Organisation's list of Essential Medicines (2017) includes several new drugs, including transdermal fentanyl for pain in cancer patients with the aim to increase access to medicines for end-of-life care.¹³

Misuse of fentanyl patches in the form of unsupervised dose escalation and altered routes of administration have been associated with adverse events, including respiratory depression.¹⁴ The risk of respiratory depression from fentanyl overdose is high.¹⁵ Common practices of inappropriate usage to induce psychoactive effects include oral administration of patches, smoking patches and injecting fentanyl extracted from patches to circumvent the fixed rate of fentanyl release.¹⁶ Reports have disclosed misuse of fentanyl patches in regional reports of drug-related harm from across Europe.^{14,17-19}

This paper describes a case series of clients seeking drug addiction treatment for fentanyl patch smoking in Denmark. It serves to highlight the challenges to addiction treatment posed by this opioid use and illustrates the benefits of collaboration between addiction services and analytical laboratories to obtain better insights into clients' drug use to initiate personalised care plans and adequate administration of opioid agonist therapy. First, we review clients' case notes and urine drug testing reports. Second, we present a mini-review of fentanyl use and misuse which accounts for different aspects of the fentanyl problem in

Denmark. From here, we discuss the contributions of confirmatory drug analysis in opioid agonist therapy treatment settings.

2 Methods

2.1 Case review

A retrospective review of case notes was conducted for every client entering one addiction service in the Region of Southern Denmark from August 2015 to December 2015 for fentanyl patch smoking. Informed consent was obtained at treatment initiation.

In addition to demographic information, including date of birth and gender, case notes contained information about clients' drug histories recorded during the initial clinical assessments and descriptions of fentanyl use patterns. The case notes varied substantially in detail, reflecting a range in difficulty regarding client engagement.

2.1.1 Background on the treatment service

The treatment service is located in Fredericia municipality (Region of Southern Denmark) with a population of around 50000 people. Clients entering treatment for opioids receive opioid agonist therapy with administration of either methadone, buprenorphine or buprenorphine/naloxone (Suboxone®).²⁰ These are dispensed daily by a nurse practitioner. The service offers distribution of sterile needle and syringes to reduce the sharing of injecting paraphernalia during continued opioid use. Individual treatment, built around counselling and cognitive behavioural therapy, is provided by a nurse practitioner and a consulting physician. The service has a treatment capacity of approximately 100 plus additional capacity for young adults (aged 15 to 30 years).²¹

2.2 Urine analysis

Urine analyses were performed in the treatment service using presumptive tests. In a subsequent attempt to gain more detailed information about clients' drug use, urine samples were submitted for confirmed laboratory analysis.

2.2.1 Presumptive tests for fentanyl

On-site immunoassay urine multi-dip tests for fentanyl were used, which did lead to false negative results in a number of cases. Immunoassay tests were used ad hoc throughout

each client's treatment period, such as after suspicion of continued fentanyl smoking. All clients included in the review were tested, but the frequency of testing and results/false negative results were not recorded systematically in the case notes.

2.2.2 Laboratory confirmed urine toxicology

Urine samples were analysed at a collaborating laboratory in the Department of Clinical Biochemistry, North Denmark Regional Hospital. Briefly, automated immunoassay screening for amphetamines, opioids, benzoylecgonine, benzodiazepines and cannabis and determination of creatinine was performed on a Cobas 6000 analyser (Roche Diagnostics).

Positive results from immunoassays were confirmed using either full scanning gas chromatography/mass spectrometry (GC-MS) with mass spectra library search for benzodiazepines (after solid-phase extraction) or high-performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) after diluting the sample with deuterium-labelled internal standards. Prior to determination of the major metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) as a biomarker for cannabis use, solid-phase extraction was performed.²² All results were reported qualitatively (positive/negative) according to cut-off levels, except for THC-COOH that was reported quantitatively and normalised to urine creatinine. Fentanyl and norfentanyl concentrations were measured by LC-MS/MS using 5 ng/mL as cut-off.

Upon completion of laboratory confirmatory testing, results obtained for each client were immediately delivered to the clinical staff to inform of drugs consumed and adherence to medicines dispensed as opioid agonist therapy.

3 Results

3.1 Case series of addiction treatment entrants

From August 2015 to December 2015, 14 clients began treatment for fentanyl smoking (Table 1). The mean age of the clients was 27.9 years ($SD = 4.7$; range: 23 to 37 years). Of the clients, 13 were males and one was female. During the initial clinical assessments, a nurse practitioner encouraged disclosure of current and past drug use. However, often these assessments failed to identify fentanyl smoking as the preferred route of

administration. False negative results from presumptive tests for fentanyl further complicated attempts to obtain a complete drug history.

Of the clients, eight (57.1%) reported daily smoking of fentanyl patches prior to entering treatment and complained of shortness of breath, pain in the lungs and difficulties breathing. Daily fentanyl smokers tended to be older, more experienced in the practices of fentanyl smoking and would often pass on this information to inexperienced and younger clients (Table 1).

All clients received buprenorphine and/or methadone as opioid agonist therapy. It was notable in the case notes that standard doses of buprenorphine/naxolone (Suboxone®) were often inadequate to prevent withdrawal. Several clients were treated with methadone instead, such as detected in urine of clients #4, 5, 6, 8 and 9 or received higher doses of buprenorphine (Table 1). Buprenorphine was detected in urine from clients #2 and 9.

Four clients were new service entrants, whilst ten (71.4%) had previously received treatment for heroin and misused oxycodone. All 14 clients reported past use of heroin and misused oxycodone. Clients' treatment journeys were characterised by disengagement from the service and continued drug use leading to negative impacts on treatment outcomes.

3.1.1 Fentanyl smoking

According to the clients, smoking fentanyl patches involved placing the whole patch or a smaller piece on aluminium foil. The foil was heated, and the smoke inhaled through a tube. Smoked patches were chewed or applied to the skin. The effects of fentanyl smoking were described as 'strong' and similar to injecting heroin. Frequent smoking of fentanyl patches or subsequent use of heroin and oxycodone were necessary to avoid withdrawal.

3.1.2 Sources of obtaining fentanyl

According to the Danish Misuse of Drugs Act, possession of scheduled drugs is a criminal offence and could lead to a fine and two years in prison.²³ Fentanyl is classified under the Act as a Schedule B substance, which must only be used for medical and scientific purposes. Consequently, clients were generally cautious in disclosing their sourcing of fentanyl patches due to the illicit activities involved in supply and possession without a prescription.

However, the 14 clients all admitted to obtaining fentanyl patches from the illicit market, though the exact route of diversion from legal sources to the illicit marketplace was often

unclear. Four clients (28.6%) reported the involvement of a local pain clinic, either issuing a prescription to the clients themselves (for back pain) or to other patients at the clinic who would sell them on the illicit market. As a result of this disclosure, a warning was issued from service staff to local GP surgeries and pain clinics in order to raise awareness of the potential misuse of fentanyl patches.

Clients preferred patches manufactured by Orion Pharma, which have a higher concentration of fentanyl per surface area. Patches manufactured by Actavis were least sought after based on reports from the clients who identified the emission of unpleasant fumes when heated which caused discomfort and headaches. Table 2 presents a list of fentanyl patches licensed for use in Denmark.

Fentanyl patches were relatively expensive and yet highly sought after. Patches with a release rate of 25 µg/h were sold for around 250 to 300 Danish Kroner (€30 to €40), patches with a release rate of 50 µg/h for 500 to 600 Danish Kroner (€70 to €80) and patches with a release rate of 100 µg/h for 1000 to 1200 Danish Kroner (€130 to €160).

3.2 Interpretation of the analytical results

Presumptive tests conducted by the clinical staff indicated that false negative test results could occur. Although these tests generally identified fentanyl in users with daily fentanyl smoking (57.1% of clients), false negative findings were encountered amongst clients reporting fentanyl smoking less frequently.

Confirmatory drug analysis provided measures of fentanyl and norfentanyl concentrations as well as confirmation of other drug use. Of the 14 clients, nine were tested. Clients #5,6 and 8 were tested on multiple occasions (Table 1). Of the nine clients tested, seven were positive for both fentanyl and norfentanyl (77.8%). For one client (#2) only norfentanyl was detected above the threshold.

3.2.1 Urine fentanyl / norfentanyl concentrations

The mean concentrations of fentanyl and norfentanyl were 466 ng/mL (range: 8.2 to 5000 ng/mL) and 1472 ng/mL (range: 10.4 to 11030 ng/mL), respectively (Table 1). After normalisation by urinary creatinine concentration, this corresponded to a mean value of 23 mg fentanyl/mol creatinine (range: 0.70 to 230 mg/mol) and 82 mg norfentanyl/mol creatinine (range: 0.83 to 507 mg/mol).

3.2.2 Detection of other drugs in urine

The most common illicit drugs were cannabis (88.9% of tested clients), cocaine (44.4%) and amphetamine (33.3%) (Table 1). In total, four of the tested clients (44.4%) were positive for a biomarker metabolite for smoking crack cocaine (ecgonidine) (> 50 ng/mL). The heroin metabolite 6-monoacetylmorphine was detected in the urine of two clients (> 10 ng/mL), of which one (client #4) was also positive for fentanyl (Table 1). Analyses were also positive for other opioids and metabolites in six clients (66.7%), including codeine, morphine, oxycodone and oxymorphone. Client #7 tested positive for both fentanyl and oxycodone (Table 1).

3.2.3 Inhalation as exposure route

Results from the confirmatory analysis suggested that urine concentrations of fentanyl/norfentanyl achieved from inhalation of thermally generated aerosols of fentanyl can exceed those measured after patch application following medical guidelines for usage.^{24,25} Previous findings support that exposure to volatized fentanyl can cause respiratory depression in a dose-dependent manner in mice²⁶ and rapidly elevate the blood fentanyl concentration, which increases the risk of overdose.^{27,28} However, pyrolytic products from the materials used in patches may potentially reduce the absorption of fentanyl inhaled from patch smoking. Patch type and size may also influence the amount of fentanyl absorbed through this route of administration.

3.3 Comments on adverse health effects

Fentanyl patches contain various types of polymers, such as polyethylene terephthalate (PET), which is used in backing film, membranes and adhesives. Analyses of pyrolytic products of PET have identified a range of volatile compounds, including carbon dioxide, aldehydes, aliphatic hydrocarbons, aromatic hydrocarbons, esters, methyl alcohol and 2-methyl-1,3-dioxolane.^{29,30} Pyrolytic products from fentanyl and materials used in the patches are potentially toxic when inhaled.³¹ However, whether clients' complaints of chest pain and difficulties breathing, as reported by 57.1% of clients, were a result of smoking fentanyl patches or other factors like tobacco smoking, smoking crack cocaine, and sleeping rough is not clear. Of note is that 1 case report has described a patient diagnosed with

pulmonary alveolar proteinosis (PAP) who reported smoking fentanyl patches and presented with similar symptoms, including shortness of breath, coughing and chest pain.³²

3.4 Impact on addiction treatment from laboratory analysis

The results from the laboratory analysis supported the development of personalised and effective treatment plans as well as a better understanding of drug use in the region. Under-reporting of drugs by clients, combined with the uncertainties arising from false negative results conflicting with self-reported fentanyl consumption, resulted in confusion and poor understanding of clients' histories. Results from confirmatory analysis were used to re-assess clients' drug histories during clinical assessment to determine which types of substance use to focus on during individual counselling. Insights into fentanyl smoking, initiated by further client evaluation informed by the concentrations of fentanyl measured, eventually helped explain smoking practices and the reported adverse symptoms, including difficulties breathing, which had not previously been encountered in the service.

Use of heroin and oxycodone to prevent withdrawal from fentanyl smoking had not previously been reported amongst service clients. Positive results for multiple opioid usage led clinical staff to make adjustments in opioid agonist therapy to reduce experiences of withdrawal amongst these clients and discourage ongoing fentanyl smoking and heroin use. This was achieved by increasing dispensed doses or using other medication, such as switching clients from buprenorphine to methadone.

Confirmatory urinary analyses, in conjunction with, and in addition to, clinician-initiated assessments, may be helpful in addiction treatment settings across the Danish regions to gain more detailed insights into clients' drug histories.

4 Discussion

In our case series of fentanyl smoking, clients presented with opioid dependence, withdrawal, chest pains and difficulties breathing as potential harms relating to fentanyl smoking. Polysubstance use, including opioids, benzodiazepines and cannabis, were also recorded in most clients. The addition of confirmatory drug analysis to clients' case notes contributed to more personalised treatment plans and medication monitoring from increased specificity of drug usage, making it a useful assessment tool in addiction

treatment centred around personalised counselling and opioid agonist therapy. Next, we review fentanyl use, misuse and associated harm in Denmark to provide a background to the case series which will lead to a discussion of the need for further implementation of confirmatory drug analysis in addiction treatment in Denmark.

4.1 Fentanyl in Denmark: a mini-review

4.1.1 Fentanyl use in Denmark

The first fentanyl patch entered the Danish market in 1996. The continuous release of fentanyl provided by the transdermal delivery system was preferred over oral sustained formulations in cancer patients.³³ In less than a year, fentanyl had become one of the most commonly used opioids for treatment of cancer patients in Denmark.³⁴ Fentanyl patches were eventually approved for non-malignant types of pain and 1996 to 2003 saw substantial growth in use from 0.14 to 2.27 defined daily doses (DDD) per 1000 inhabitants per day, a 16-fold increase.³⁴ From 2003 to 2004, the number of patients prescribed opioids increased by approximately 5000, mainly due to increased use of oxycodone, buprenorphine and fentanyl.³⁵ By 2008, fentanyl patches and oxycodone accounted for more than half of the annual opioid prescription costs.³⁶ From 2010 through 2014, fentanyl use in Denmark remained stable, but higher compared to in the other Nordic countries measured in DDD per 1000 inhabitants per day.³⁷

4.1.2 Fentanyl misuse and harm

Simonsen et al. performed a review of post-mortem casework in Denmark and found in 2012 that 0.5% of cases of drug-related deaths (ten individuals) involved fentanyl.³⁸ The 2016 Annual Drug Report for Denmark highlights a national decrease in the number of heroin users in drug treatment between 2010 to 2014, whereas the number of other opioid users has increased.³⁹ However, the number of treatment entrants for fentanyl in Denmark is not recorded in these data.

The Danish Medicines Agency (DMA) collects information about suspected side effects to medicines known as adverse drug reactions (ADRs). ADRs are likely to go undetected and under-reported for a number of reasons, such as failure to draw links between adverse events and drugs consumed.⁴⁰ Since 1996, the DMA has received 109 ADRs reports related to fentanyl.⁴¹ The number of reports was relatively stable from 1996 through 2007.

However, a 10-year analysis shows a 250% increase in the mean number of reports from 2.4 between 1997 to 2006 to 8.4 between 2007 and 2016.⁴¹ There were three reports in 2009, of which one was serious, and 12 reports in 2014 (five serious and one fatal) as compared with 18150 fentanyl prescriptions in 2009 and 19504 in 2014. The proportion of serious reports between 2007 to 2016 is 105% higher than between 1997 to 2006 and includes two reports with fatal outcome (one in 2013 and one in 2014).⁴¹

Oral consumption of fentanyl contained in patches has been reported in a case report from 2014. A patient (34 year-old male) steeped two fentanyl patches in a cup of tea and drank it.¹⁴ He was found unconscious at home with convulsions and respiratory depression. On arrival at the hospital, intravenous naloxone administered over a 4-hour period resulted in reversal of the fentanyl effects.

In the preceding section, we present recommendations for prescribing and diversion prevention practices and addiction treatment for fentanyl in Denmark.

4.2 Misuse of fentanyl in the context of medicine regulation

The increasing number of ADRs in the past ten years is likely related to increased fentanyl use since the mid-1990s,³⁴ especially amongst an ageing population. However, the recent increase in the proportion of serious ADRs reports, as well as reports of diversion, smoking and mortality warrants a review of potent opioid use in Denmark.

Prescribers' decisions to prescribe fentanyl should reflect evidence on benefits and harms as well as the wider public health concerns about fentanyl, including risks of diversion.⁴²

Medicine regulators in Denmark should stress the risks linked to fentanyl patches by including and emphasising information provided in summaries of product characteristics (SPCs) about potential diversion and smoking. Fentanyl is used for management of very severe pain and as part of end-of-life care.¹³ When fentanyl is only prescribed to patients where fentanyl is the optimal choice, the risk of diversion is most likely reduced. Though there are difficulties in identifying and working with patients who obtain fentanyl patches with the aim of diversion or misuse,⁴³ safe opioid prescribing, taught through campaigns and guided by policy guidelines,⁴⁴ can help prescribers reduce rates of inappropriate prescribing. Improved prescribing practice includes comprehensive initial assessments, regular monitoring and review of patients, including thorough routine drug testing, and nondrug

therapy,⁴⁵ such as physical therapy, especially amongst long-term opioid users in chronic pain where the risks of opioids may outweigh the benefits.⁴⁶ The overall aim should be to reduce inappropriate prescribing and subsequently reduce diversion of fentanyl patches through illicit channels which was the main source of obtaining patches amongst clients in this case series.

Education of patients on proper storage and disposal of medicines and take-back schemes of unwanted medicine, such as 'patch-for-patch' return programmes,⁴⁷ could help ensure that left-over fentanyl is always returned to pharmacies for safe disposal. A study measured the amount of fentanyl in patches worn for 72 h and found 24 to 84.4% of the content remained unreleased from the patches.⁴⁸ Poor adhesion can result in premature replacement after less than 72 h, which can result in substantial amounts of unreleased fentanyl in these patches.^{49,50} In hospitals, used patches must therefore be returned to hospital pharmacies and safely disposed. Though these systems help to stop the diversion of pharmaceutical waste and medicines to the illicit market and unintended individuals,⁵¹ poor adherence to policy guidelines and lack of understanding of the effectiveness is an important area for improvement of fentanyl regulation.^{52,53}

The pharmaceutical formulation of fentanyl patches is also an aspect of consideration, as current transdermal delivery systems do not offer protection against tampering. As reported by the clients in this case series, patches can be easily prepared for smoking with inhalation of vapors resulting in rapid onset of psychoactive effects as desired by the clients.

Tampering-resistant formulations have been developed and are being tested, including a fentanyl patch with integrated ceramics (geopolymer granules) to protect against common tampering techniques.¹² However, further research is needed to determine whether such tampering-resistant patches will curb the harm caused by fentanyl.⁵⁴

4.3 Misuse of fentanyl amongst addiction treatment clients

Fentanyl smoking, which has not previously been reported in Denmark, appears to be confined to smaller, isolated populations of opioid users who are vulnerable to dependence, withdrawal and relapse. Findings indicate that fentanyl patches are sought after for purposes of tampering to use fentanyl excessively, resulting in demand for drug treatment

provision. This is consistent with reports from other European countries, Canada and the United States.^{18,55,56}

Urine concentrations of fentanyl measured amongst some clients exceeded those measured after appropriate patch application.^{24,25} Furthermore, fentanyl smoking was associated with use of heroin and oxycodone. Use of multiple opioids may explain the severe level of dependence and withdrawal affecting many of the clients. Previous research have shown that opioid agonist therapy may be perceived as inadequate amongst opioid-dependent individuals with high withdrawal scores,⁵⁷ with resulting continuing episodes of drug use. In this present study, only one client (less than 10%) was abstinent from fentanyl after 12 months treatment. Inadequate doses may explain the difficulties encountered during the treatment of the 14 clients where many disengaged from the service due to relapse, highlighting the impact from laboratory testing to get an full overview of clients' opioid use to adjust opioid agonist therapy accordingly.

5 Perspective

5.1 The importance of confirmatory drug analysis

In this case series, using confirmatory tests in addiction services has been shown to improve clinicians' understanding of clients' use of opioids and help in designing personalised treatment plans based on opioid agonist therapy. Confirmatory testing added significant value to presumptive testing, as these produced false negatives and did not provide a complete overview of drug usage. Next, we discuss the contributions from further collaboration between drug addiction services and analytical laboratories on a national scale.

5.1.1 Pitfalls of on-site screening

Using self-report and clinician-administered questionnaires are common practice to assess history of drug use in addiction treatment, although these are vulnerable to omission by clients and may suffer in accuracy and detail.⁵⁸ As part of the routine clinical care in the service, drug use was also monitored with the use of on-site screening with immunoassays. However, the general limitations of immunoassays in urine drug testing and pain management include their lack of sensitivity and selectivity.⁵⁹⁻⁶¹ Although not detected in

clients investigated here, immunoassays for fentanyl have been reported to cross-react with the drug risperidone causing false positives,⁶² and fentanyl has been reported to cause false positives in immunoassays for lysergic acid diethylamide (LSD).⁶³ A preliminary study done by Health Canada found that presumptive tests gave false positives and false negatives in samples with known content of illicit fentanyl and fentanyl analogs.⁶⁴ With the presence of tampering of prescription opioids (e.g. patch smoking) and polysubstance use in Denmark, immunoassays appear to no longer be sufficient as a tool to accurately determine drug use amongst clients entering drug addiction treatment and would benefit from support from confirmatory analysis.⁶⁵

5.1.2 Poor adherence to drug testing guidelines

According to the Danish guidelines for opioid agonist therapy, urine drug testing is not mandatory.⁶⁶ However, if immunoassays are used, positive results must be confirmed by mass spectrometry. The Danish Society of Clinical Biochemistry has published guidelines for urine drug testing, which recommend the use of confirmatory analysis.⁶⁷ Yet, to the best of our knowledge, these guidelines are poorly implemented in clinical practice. Better use of drug testing amongst primary care patients undergoing pain management with opioid could reduce the risk of dependence and provide better understanding of opioid misuse and non-compliance (e.g. amongst patients selling their medicine on the illicit market). The limitations of on-site urine screening reported at the treatment service, including the lack of proper registration of test use, is evidence of a gap in testing procedures in the drug addiction treatment sector in Denmark, which should be improved by implementation of confirmatory analysis.

5.1.3 Biomarkers for fentanyl smoking

Analytical procedures to discriminate between fentanyl smoking and other routes of administration are currently unavailable. A pyrolysis GC-MS study of potential biomarkers of smoked fentanyl found propioanilide and semi-volatiles (pyridine, styrene, benzaldehyde, aniline, phenylacetaldehyde, 2-chloroethylbenzene) as the major components after aerobic pyrolysis of fentanyl.⁶⁸ Upon inhalation, these products will undergo hepatic metabolism and the resulting metabolites may be difficult to distinguish from food components, traces of environmental pollutants, products from tobacco smoking and endogenous compounds. Increased reliance upon specialised laboratories in addiction treatment settings may

facilitate development of methods to detect new substances reported and biomarkers relevant to specific types of reported tampering, such as fentanyl smoking.⁶⁹ A retrospective toxicological investigation of hair samples collected from 24 victims of drug facilitated crime demonstrate the value of segmental hair analysis to determine fentanyl concentrations and confirm exposure,⁷⁰ and may represent another important area of drug analysis development.

5.2 A national shift in drug testing

Advances in the use of high resolution mass spectrometry or triple quadrupole mass spectrometry in clinical and forensic toxicology have facilitated the development of routine methods where hundreds of compounds can be detected simultaneously.⁷¹⁻⁷³ Greater access to these methods is important to assure a high quality in urine drug testing in addiction treatment,⁶⁵ especially when confronted by new forms of drug use, such as fentanyl smoking. For this purpose, mass spectrometry is superior to immunoassays and we propose a shift in drug testing practice in Denmark where clinical laboratories play a greater role.

6 Conclusion

During a 5-month period in 2015, 14 clients sought treatment for fentanyl smoking in an addiction treatment service in Fredericia, Region of Southern Denmark, as compared to none the year before. This took up approximately 13% of treatment capacity in the service.²¹ The rise of fentanyl smoking in addition to, or replacement of, heroin and oxycodone diverged from regional patterns in substance use, but is consistent with trends recorded across Europe. According to EU-level data, the 'opioid problem' increasingly involves both traditional opioids (heroin), prescription opioids and illicitly manufactured fentanyl analogs.⁷⁴

In Denmark, the national level of fentanyl prescribing is high³⁷ with confirmed, but unknown levels of diversion of fentanyl to the illicit market, reported deaths linked to fentanyl as well as inappropriate route of administrations in populations of opioid users gaining access to addiction treatment. These observations of diversion, misuse and deaths have prompted a need to revise prescribing practices of opioids to minimise diversion of fentanyl patches to the illicit market.

We encourage collaboration between clinical staff in the drug addiction treatment field and analytical laboratories to analyse drug samples, urine and blood, as part of a client's treatment journey. In the case series presented here, confirmatory analyses provided important insights into clients' drug use and results added to self-reported usage data to instigate personalised care plans based on confirmed drug use and adjustments of opioid agonist therapy (dose and medication). Overall, more personalised and specific care plans have the potential to improve addiction treatment in Denmark and reducing drug-related harm.

6.1 Limitations

In the analysis of data from this case series, we make no claims of statistical generalisation. The lack of data for investigating the extent of fentanyl misuse and harm across all regions of Denmark makes it difficult to determine the full extent of the problem. None of the clients reported exposure to fentanyl analogs and the analysis of these substances was not included in the testing procedure. Several fentanyl analogs, including acrylfentanyl, have since been identified in Denmark,⁶ and available evidence now suggests an association between heroin use and exposure to fentanyl analogs in reports from EU countries.⁷⁵ It is recommended that laboratory analysis investigate for fentanyl analogs amongst opioid users currently undergoing drug treatment.⁶⁵ We also recognise that the applied urine testing methods do not distinguish between different routes of fentanyl administration (appropriate application to the skin versus smoking). Furthermore, the retrospective design of the study precludes additional data collection. Areas of interest to an investigation of fentanyl smoking, such as sourcing of fentanyl, treatment outcomes, including number of relapses, and further confirmatory testing (to include specific biomarkers and other opioids) were under-reported or unavailable from the case notes and the toxicological investigation.

6.2 Implications for research

While case reports/case series can represent the first and only source of information of rare or new events, they do not offer the same insights as other research designs used in the field of addiction research. We propose a future investigation of fentanyl smoking and injection of fentanyl extracted from diverted patches in large national research, which includes confirmatory drug testing programmes that explores potential biomarkers of

smoked fentanyl patches, such as propioanilide and semi-volatiles including pyridine, styrene, benzaldehyde, aniline, phenylacetaldehyde and 2-chloroethylbenzene.⁶⁸

Implementing routine laboratory testing within addiction treatment services would come with costs to carry out these tests, which is currently difficult to justify in the absence of an evidence-base for their added value in health care provision, especially in the presence of recent cuts in funding in the sector. Reduced treatment demand and length as well as fewer relapses due to improved personalised care would be associated with a cost reduction for services. Systematic comparisons of treatment outcomes, for instance in services using frequent laboratory confirmed testing compared to services relying predominantly on self-reported drug use and presumptive tests, could provide data to estimate the impact of laboratory analysis. Importantly, a case series design does not allow to make such assessments.

With improved detection of drug use in addiction services, data could feed into to national and internationally early warning systems. Real-time data or data produced with minimal delay from services across Denmark could be used to informed other services and users of potential risks from new drugs and drug trends, such as fentanyl smoking. Improvement of early warning systems presents another area for further research.

Conflicts of interests

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Table 1: Demographics and confirmed analytical findings for clients in addiction treatment for fentanyl patch smoking tested between August 2015 and July 2016

Client ^a	Gender	Age	Creatinine ^b mmol/L	Fentanyl ^c ng/mL	Norfentanyl ^c ng/mL	Fentanyl/Creatinine ^d mg/mol	Norfentanyl/Creatinine ^d mg/mol	Other drugs detected ^{e,f}
1	Male	37				No test results available		Codeine, morphine, 6-monoacetylmorphine, desmethyldiazepam.
2	Male	36	12.2	< 5	18.4	Concentration below cut-off	1.5	Buprenorphine glucuronide, methylphenidate, oxymorphone, THC-COOH.
3	Male	34	12.4	8.7	10.4	0.7	0.8	Amphetamine, benzoylecgonine, THC-COOH, methylphenidate.
4	Male	34	24.1	18.8	762	0.8	32	Codeine, morphine, 6-monoacetylmorphine, benzoylecgonine, ecgonidine, THC-COOH, EDDP, desmethyldiazepam.
5	Male	32	11.8	15.3	182	1.3	15	THC-COOH, EDDP.
			6.7	120	316	18	47	
			17.5	36.9	704	2.1	40	
6	Male	28	32	34.5	211	1.1	6.6	THC-COOH, EDDP, methylphenidate.
			25.5	28.9	221	1.1	8.7	
			13.1	123	843	9.4	64	
			10	8.2	40	0.8	4	
7	Male	28	20.1	615	3808	31	189	Amphetamine, benzoylecgonine, ecgonidine,

								THC-COOH, oxycodon, oxymorphone.
8	Female	24	14.6	< 5	< 5	Concentration below cut-off		Amphetamine, benzoylecgonine, ecgonidine, THC-COOH, diazepam, morphine, EDDP, methylphenidate.
			21.8	5000	11030	230	507	
			10.5	37.6	2122	3.6	202	
9	Male	24	15	15.6	343	1	23	Benzoylecgonine, ecgonidine, buprenorphine glucuronide, THC-COOH, morphine, EDDP, desmethyldiazepam.

^a Some clients were tested on multiple occasions.

^b Urine concentration of creatinine (shown only for positive fentanyl or norfentanyl results).

^c Threshold concentration (cut-off) used for fentanyl and norfentanyl was 5 ng/mL.

^d Normalised ratio to urinary creatinine concentration calculated by dividing fentanyl or norfentanyl concentrations with creatinine concentrations with rejection of samples with creatinine below 0.5 mmol/L.

^e Confirmed by gas- or liquid chromatography with mass spectrometry (GC-MS, LC-MS/MS).

^f EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; THC-COOH: 11-nor-9-carboxy-delta-9-tetrahydrocannabinol.

Table 2: Fentanyl patches licensed for use in Denmark.

Name of product	Company name	Dose ($\mu\text{g}/\text{h}$)
Durogesic [®]	Janssen-Cilag	12, 25, 50, 75, 100
Fentanyl Orion [®]	Orion Pharma	12, 25, 50, 75, 100
Fentanyl Sandoz [®]	Sandoz	12, 25, 50, 75, 100
Matrifen [®]	Takeda Pharma	12, 25, 50, 75, 100
Fentanyl Mylan [®]	Mylan AB	12, 25, 50, 75, 100