Science & Justice 64 (2024) 677–687

Contents lists available at ScienceDirect

Science & Justice

journal homepage: www.elsevier.com/locate/scijus

Review

How 3D printing technologies could undermine law enforcement strategies targeting the production and distribution of designer drugs

Victoria Gilpin [a], Robert B. Smith [b], Jason W. Birkett [c], James Davis [a,*]

[a] School of Engineering, Ulster University, Belfast, Northern Ireland BT15 1ED, UK
[b] Institute for Materials and Investigative Sciences, School of Engineering and Computing, University of Central Lancashire, Preston PR1 2HE, UK
[c] Pharmacy and Biomolecular Sciences, Faculty of Science, Liverpool John Moores University, Liverpool, L3 5AH, UK

ARTICLE INFO

Keywords:
Fentanyl
Counterfeit Pills
Pill Press
CNC Milling
3D Printing

ABSTRACT

Countering the supply of counterfeit and designer drug pills laced with fentanyl or its analogues has long been a challenge with the potency of the drug and the ease with which it can be obtained impacting greatly on families and the wider society. The introduction of legislative measures to restrict access to the machinery that allows the production of the pills has yielded considerable gains with numerous seizures of pill presses reported. However, the increasing availability of bench top milling machines and advances in 3D printing could render this a short term victory where the technology may be set to outpace the capabilities of conventional law enforcement. While pill presses were once born from high specification industrial machining, low cost mills and 3D printing systems are already at the stage of producing small format presses within the domestic home. Here, a spotlight is trained on fentanyl (and its analogues) from the perspective of pill manufacture and their supply. An overview of pill press mechanics and the approaches presently taken to counter distribution is provided and the potential influence that both milling systems and 3D printing technologies could have in the future is critically evaluated.

1. Introduction

Opioid use disorder (OUD) presents many challenges to patients, their families and wider society [1–5]. In the US alone, it was estimated that the consequences OUD and fatal opioid overdose in 2017, in terms of increased health care provision, criminality and the inevitable impact on employment/productivity amounted to over $1 tn [6]. It must be noted, however, that this is a conservative figure, with the OUD epidemic casting a long shadow and will inevitably increase [7]. While prescription misuse is a large factor in OUD, the contribution arising from the illicit manufacture of synthetic opioids is of increasing concern to those in public health professions. However, despite many community initiatives and increased regulatory and legislative powers, the illicit material's reach appears to have an unrelenting impact on society. Unintentional overdose mortality rates in the US have been steadily increasing with some 33,000 opioid deaths in 2015 being a mere prelude to the 100,000 deaths recorded in 2022 [8].

Fentanyl, the predominant synthetic opioid (SOp) associated with OUD, has garnered considerable notoriety as an illicit substance. However, it is important to note that it is a licensed medicine which, under proper use, has clear medical efficacy and is particularly effective for anaesthesia and pain management [9–12]. Whilst its prescription was once the preserve of hospitals, it is now widely used in the community where transdermal patches have helped to revolutionise pain control – particularly for palliative purposes [13–16]. Fentanyl targets a series of receptors within the brain and nervous system but its interaction with the μ opioid receptor is particularly critical as this is the principal mediator of analgesia, respiratory depression and euphoria [3,17]. It is also a core mediator of dependency which has become a characteristic of the use of morphine and other opioids [18]. The benefits of fentanyl prescription for therapeutic purposes relate to its increased potency where, it has been estimated to be some 50–100 times that of morphine [3]. This increased potency results from its high lipid solubility – allowing rapid transport across the blood–brain barrier and resulting in high concentrations at its site of action within the brain [19]. Somewhat ironically, Fentanyl, and its analogues, were chiefly developed as a means of acquiring a new class of drug that would be clinically safer. The intention was to allow lower doses that could achieve the desired degree of pain relief whilst reducing the risk of respiratory depression and hence reducing the risk of inadvertent overdose.

There have been many strategies aimed at reducing the impact of illicit fentanyl across nations but it within the US that its effects are most

* Corresponding author.
E-mail address: james.davis@ulster.ac.uk (J. Davis).

https://doi.org/10.1016/j.scijus.2024.10.004
Received 20 August 2024; Received in revised form 16 October 2024; Accepted 21 October 2024
Available online 28 October 2024

acutely felt. As such, US legislative instruments have been directed at both international and domestic regulation of chemical precursors but also the equipment associated with pill production [20–22]. The restriction and prohibition of pill presses has received considerable attention[20] and there have been many seizures of tabletting machinery which could be viewed as validation of the strategy. However, as many other nations ponder the adoption of similar enforcement policies, it is important to cast a critical eye over the fundamentals of the issue and potential impact that the increasing availability of bench top milling machines and 3D printing will have. While traditional pill presses are considered high value industrial machinery whose procurement and operation are far from trivial, 3D printing offers a facile entry point to the technology. The increasing availability and accessibility of computer numerical control (CNC) milling machines and 3D printers could revolutionise illicit pill production and jeopardise the effectiveness of legislative prohibition efforts. The aim of the present report is to provide context to the current issues relating to the production and supply of illicit fentanyl and its analogues in pill form and to critically appraise the potential impact of 3D printed pill presses.

2. Search Methodology

The threat of 3D printers impacting the production of illicit pill presses is very much an emerging topic and, as such, there is scant information within the conventional scientific literature relating directly to the area. As such, this report is not a true review but rather aims to provide a critical assessment / perspective of the potential for the technology to be harnessed for such purposes. A narrative approach has been adopted where background scientific content has been obtained from the Clarivate ISI Web of Science using the key phrases associated with fentanyl (opioid, abuse, misuse) and those relating to 3D printing and CNC milling. The literature was scanned with a view to obtaining relevant contextual information and engineering performance data. The search process was supplemented with statistical information harvested from a variety of international governmental reports (principally from the US, Canada, China, Australia and the UK). The issues surrounding the illegal production and distribution of fentanyl and its analogues are placed in context and a critical examination of the translation of milling and 3D printing technologies to pill manufacture are considered in turn in the following sections.

3. Therapeutic fentanyl diversion

It is possible to defragment OUD into a number of groupings where, at a high level, it can be seen that there is misuse of either legitimate prescription opioids or those that have been illicitly acquired. The latter can be further divided into pharmaceutically derived opioids (i.e. theft or diversion of medicinal supplies) or those produced from non-pharmaceutical sources. Historically, illicit access to fentanyl would, at least at the outset of its introduction, typically have been through theft from pharmacies by criminal entities or by healthcare staff with direct access to the drug preparations. Later, the increasing availability of transdermal skin patches provided a much more accessible route to fentanyl as well as more options for their deliberate misuse. It has been estimated that used patches can contain 28–84 % of fentanyl at the time of removal and hence can provide an economically exploitable avenue for illicit recovery and misuse [23]. However, extraction of the residual SOp and its administration by smoking, chewing, snorting, inhalation or injection can lead to unmetered dosing which will inevitably increase the risk of overdose [24]. A study by the Australian Institute of Criminology (2019) sampling six darknet markets for illicit fentanyl found that patches were the predominant form and constituted 40 % of the listings (that included powders, tablets, sprays and solutions) [25,26].

4. Non pharmaceutical fentanyl

Although fentanyl originally destined for medicinal use can be diverted for abuse purposes, non-pharmaceutical fentanyl (NPF) produced by illicit means has been increasingly found as a component in street drugs [27–30]. It is typically used to fortify existing drugs (i.e white powder heroin) as a means of increasing their potency but, where its inclusion has not been disclosed or the resulting strength is unknown, there will be a substantial risk of overdose [31–33]. The intentional combination of opioids with stimulants is also common where the stimulants are often taken to counteract sedation or to enhance its effects [34,35]. A recent study by Hayahsi et al (2018) investigating a syringe service programme in Vancouver, Canada, found that the majority (75 %) of users providing a urine sample tested positive for both fentanyl in addition to amphetamine or methamphetamine [36]. Wagner et al (2023) found fentanyl in both powdered methamphetamine (12.5 %) and cocaine (14.8 %) samples [37]. In contrast, they also found 6.6 % of heroin in the powdered cocaine. The significance of this approach is highlighted by the work of O'Donnell (2021) where one third of deaths attributed to overdose were found to involve both opioids and stimulants [38].

5. Designer Drugs: Fentanyl analogues

The original synthesis of Fentanyl was attributed to Paul Janssen in 1960 [39,40] but chemical manipulation of its structural components has led to an extensive library of analogues (from both established pharmaceutical and illicit sources) with different characteristics such as speed of onset, duration of effect and potency. It has been estimated that there are some 1400 fentanyl analogues of which 200 have been characterised pharmacologically [41,42]. Whilst some have resulted in derivatives with clear therapeutic use, others have been used as "designer drugs" and have arisen to avoid legislative controls on named variants or have evolved to overcome restrictive controls on the supply of the key chemicals need for the production of opioid analogues [21,22]. The sudden release of an untested opioid in the illicit supply market can be especially problematic where the unfamiliarity of its characteristics – particularly its potency – can be fatal [43,44]. Carfentanil is a particularly apt example, with a potency in the region of 10,000 times that of morphine, and while it is licensed for veterinary use as a sedative for darting large wild animals, it has also made its way into street drugs [45,46]. As the potency of the fentanyl analogue increases, there also becomes a point at which it becomes a direct hazard – not simply to the users but, also to the first responders where inadvertent contact with even minute amounts of the powder could be fatal [47]. The extreme potency of some has led to their recognition as potential chemical weapons. Support for such classification arises from evidence arising from analysis of the blood and urine of survivors of the 2002 Moscow Theatre siege where it was reported that Russian security forces used carfentanil in aerosol form to subdue the terrorists [48].

6. Production to distribution

While clandestine laboratories producing fentanyl within the US arose periodically from the 1990 s through to the early 2000 s [49,50], NPF was, until late, sourced largely from China and India [51,52]. Both countries possess extensive chemical manufacturing industries from which the necessary precursors and the expertise needed to produce fentanyl are readily available. It has been postulated that some 70 % of illicit fentanyl arose from China and is regarded by the US government as the principal source of the SOp responsible for initially fuelling its opioid epidemic [21,22,51,53]. In the past, SOps were sent directly to the US. In recent years, China has been the world leading shipper of parcels (in 2022, China shipped more than 110 bn parcels) via air and sea cargo and through conventional mail services [54]. While the vast bulk of these packages has been attributed to e-commerce, it is easy to appreciate the difficulty of identifying illicit packages in what could be an ocean of legitimate consumer items. This is a major issue and there have been substantive efforts incentivise the development of technological solutions to aid detection within postal services. The US government in particular allocated US$ 1.5 m through its Opioid Detection Challenge.

In contrast to heroin or cocaine, the high potency to weight ratio of fentanyl or its analogues means that it is much more amenable to be trafficked via conventional postal and courier services and can be directly mailed to dealers throughout the world [51]. This also means that the SOp samples being mailed are liable to be of far greater purity and potency than conventional "street" drugs. Data from the US Sentencing Commission found that in 2019, of those convicted of SOp possession, only 2.3 % had received fentanyl that had been shipped directly from China. In contrast, those possessing a fentanyl analogue shipped from China were substantially more prevalent (20.2 %) [55].

In response to international pressure, the Chinese government has since placed tighter restrictions on the manufacture of fentanyl, its analogues and several of the precursor materials necessary for its production [22]. However, it has been noted that the governance framework in China is complex with multi-agency conflicts leading to enforcement ambiguities and inefficiency [21,21,53]. Despite such measures, there are many alternatives, and it is perhaps little surprise that clandestine labs switched methods accordingly. It has been suggested that, as a consequence of the restrictive access to chemical precursors along with increased scrutiny by Chinese authorities, drug traffickers responded by increasing output from India [22,51]. A study by Broadhurst et al. (2020) analysing the advertisements for fentanyl and analogues on the internet and darknet found that almost 15 % were for NPF and 36.4 % for 4-Fluoroisobutyr-fentanyl [25]. The US Drug Enforcement Agency (DEA) has since identified Mexico as an emerging production player and is evidenced by reports from Mexican law enforcement where approximately 1400 clandestine fentanyl labs were identified in 2022 [56]. It must be noted however, that any country with the required skill base, access to the appropriate chemical primers and production capabilities can, through the ready availability of efficient transportation and internet-based payment systems, easily become a source of supply.

7. Pill press mechanics

The synthetic processes required for the production of NPF or fentanyl analogues are typically much simpler and higher yielding than those associated with heroin and thereby provide a much more accessible and incentivised entry point for illicit manufacture. The proliferation of SOps has been linked to the increasing availability of counterfeit (or "pressed") pills [57–61]. These were originally designed to mimic the physical characteristics of authentic tablets. However, rather than the regulated active ingredient (i.e. oxycodone, alprazolam), they typically contain an unspecified amount of NPF or other novel SOp as well as different fillers. A 2019 analysis by US Sentencing Commission (USSC) found that of 886 offenders, 275 (31 %) sold or advertised fentanyl as another drug – principally as heroin (89.5 %) with 10 % passed off as a diverted prescription [55]. Similarly, of 233 fentanyl analogue offenders, 100 (42.9 %) sold the synthetic derivative as another drug – 68 % heroin, 31 % as a diverted prescription. In the case of both fentanyl and fentanyl analogues, the diverted prescription samples were counterfeit pills design to resemble oxycodone or alprazolam [55,58,59,61].

The extent of the pill problem is highlighted by figures from the U.S. DEA where 50.6 million NPF-laced counterfeit pills were confiscated in 2022 – double that seized in the previous year [62]. The unregulated nature of the NPF/SOps component has led to increasing challenges for public health where, in recent years, there has been a substantial rise in the proportion of pills containing potentially deadly amounts of NPF. While pill seizures in 2017 found 7 % to contain lethal doses of fentanyl, the proportion had grown dramatically to 60 % in 2022. It has been postulated that 2 mg of pure fentanyl is sufficient to constitute a lethal dose, though it must also be acknowledged that a much lower amount could equally be fatal for new or inexperienced users [63]. It is noteworthy, that 30 mg of heroin is typically regarded as a lethal dose. The DEA Fentanyl Profiling programme found that of tablet samples seized in 2022, the concentration range of fentanyl varied from 0.01 mg/tablet to 8 mg/tablet with some 45 % of those sampled containing a minimum of 2 mg [64].

Transforming the powder to pill format, at first glance, could be considered to be relatively easy as the dies, punches and presses are relatively inexpensive and there are few controls on their supply or use [20]. It must be noted however, that the production of robust pills is more complicated and will still require a degree of formulation expertise where binders are required to maintain mechanical integrity [65–68]. Presses are a central instrument of conventional pharmaceutical manufacturing processes employed for the supply of oral tablets. The first pill press device was patented in 1843 by William Brockedon [69,70] and, while the complexity may have increased since then, the basic principles remain unchanged. Their primary function is to compress powder, containing the active pharmaceutical ingredient (API) and suitable binders in a die (mold) which determines the size and shape of the tablet [65]. A series of punches are used to compress the powder within the die into the tablet form. The surface of the punches can also be patterned to imprint a specific identifier marking. The size of the pill press will vary depending on the scale of production – from simple handheld designs through to desktop devices producing 1000 s of tablets per hour all the way up to industrial scale systems providing anywhere between 100,000 and 1 million tablets per hour [71,72]. An example of a seized single station system [73] is shown in Fig. 1A and its step-wise operation is highlighted in Fig. 1B.

The single station system in Fig. 1A typically comprises a die and a pair of upper and lower punches where the rapid impact of the upper punch on the powder effects compression and pill formation. The bottom punch often remains stationary and serves to buttress the powder against the hammer action of the upper punch (Fig. 1B). The simplicity of the single punch system provides numerous advantages: its operation requires little expertise, it is mechanically robust, easily maintained and easily adaptable to different powders. Changing the die/punch arrangement is simple and can readily be exchanged to create custom pill motifs. The inexpensive nature of the equipment, small portable size and silent operation are particularly important from the perspective of small clandestine laboratories. Manually operated single station systems involving a lever assembly to lower the upper punch are widely available at very low cost but their operation would be too slow and laborious for those involved in organised crime entities whose requirement is for volume production. A second issue relates to the vagaries of manual compression where insufficient force could yield thicker, softer pills that retain a granular texture which is liable to fall apart upon handling or storage [65,67,68]. The addition of a motor, as indicated in Fig. 1A, to automate the punch mechanism would standardise the compression force, improving yield and quality and would greatly increase output. As such, the motorised single station system could be considered as the entry level system for mainstream illicit SOp pill production.

Significant boosts to pill production can be achieved through the adoption of rotary pill presses where, depending on the system configuration, 9000 to 234,000 tablets per hour could be produced. The process flow for a fully automated rotatory system (Fig. 2) is significantly more complex and, in contrast to the single punch operation detailed in Fig. 1B, both upper and lower punches are involved in the compression cycle. While the key benefit is a much greater output, the downsides relate to the expense of the system and the greater expertise needed to operate and maintain it. In contrast to the bench top system highlighted in Fig. 1A, the rotary system is less easy to conceal and is essentially an industrial device. Nevertheless, such systems have been employed by drug gangs where, in 2022, the US DEA, Department of Homeland Security and US Postal Inspection service seized a rotary pill press with a

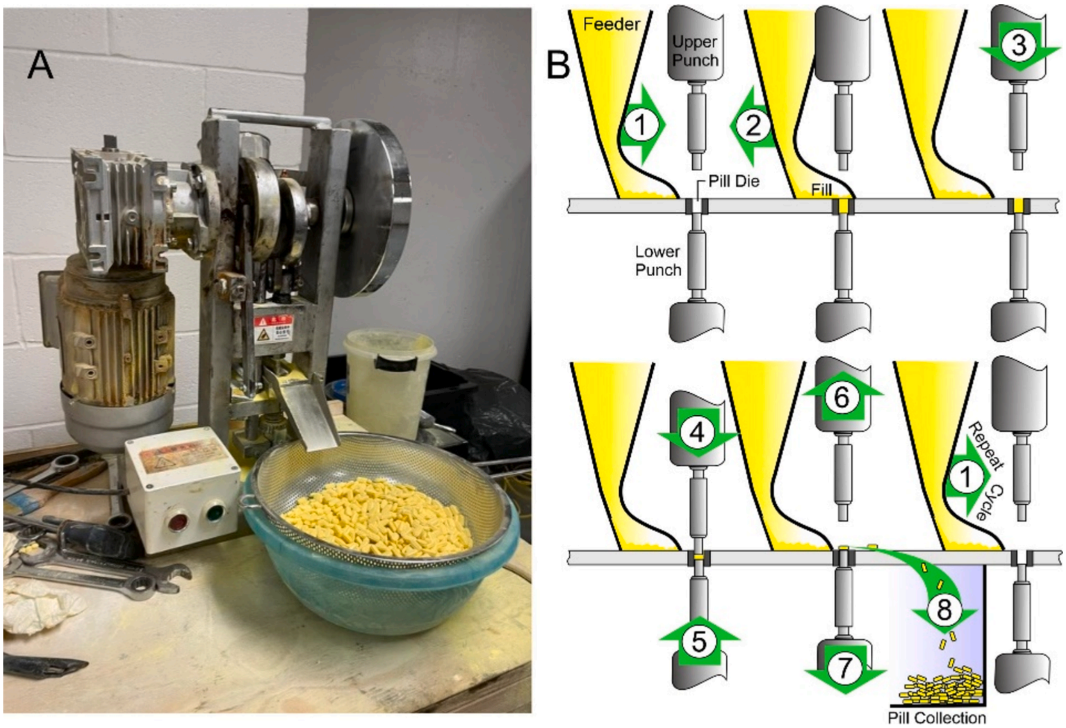

Fig. 1. (A) Automatic single station (punch) pill press and (B) its mode of operation. Photograph of the pill press is courtesy of the US Drug Enforcement Agency Media Gallery.

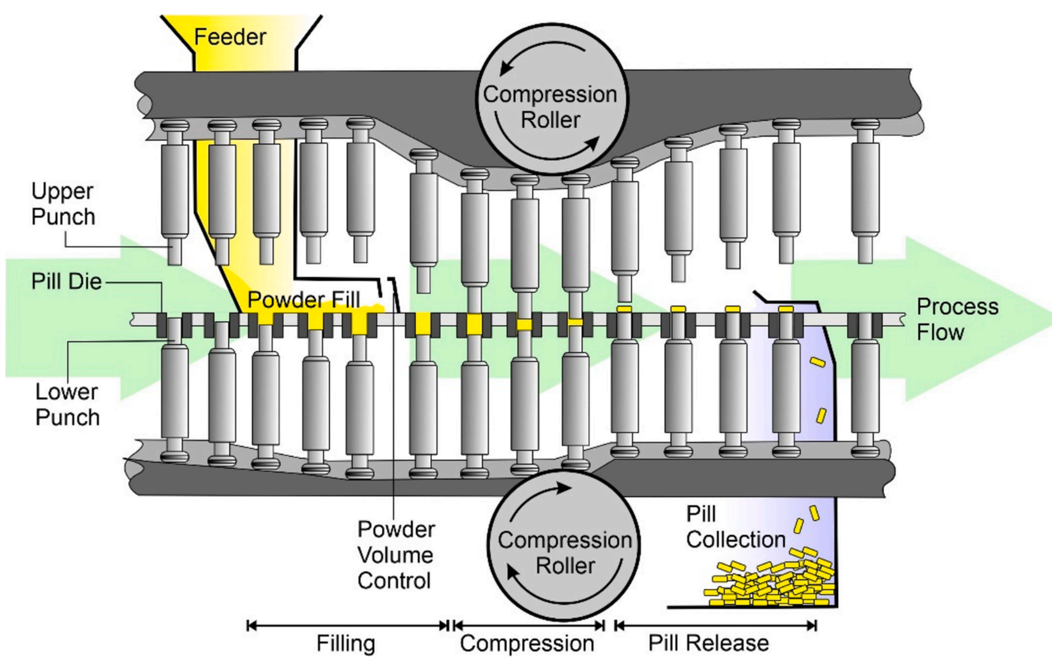

Fig. 2. Process flow for a rotary pill press (
adapted from [72]).

production capacity of 20,000 tablets per hour, trademarked dies, a range of bulk mixed powder and mixing equipment [73]. The automated systems (single or rotary) have the added advantage of providing precise control over the amount of powder applied (Metering) such that each tablet has a consistent weight. This is critical in pharmaceutical applications but especially so in illicit drug manufacture where an inadvertent excess of the active drug could easily be fatal should the pill be ingested.

It has been estimated that an illicit pill press converting 1 kg of fentanyl into pills (each containing 1 mg) would give rise to 1 million tablets which could easily translate to $20 m [52]. Depending on the accuracy of the embossing on the die, the resulting tablets can easily be formulated to resemble authentic prescription medicines, essentially being indistinguishable to casual inspection with their true identity only becoming apparent after chemical analysis.

8. Counter measures

Countering the illicit production and distribution of NPF based pills has required a multiagency approach on both national and international stages. Most countries, however, have adopted two core strategies aimed at severing the material and machinery supply chains that lead to domestic pill production. As of May 2023, more than 30 fentanyl-related substances, including precursors, are subject to international controls [74]. U.N. member states first subjected fentanyl precursors to international control in 2017. However, the manufacture of fentanyl and its analogues is not limited to a single pathway and traffickers have successfully used a number of synthetic solutions to refine the process – easing production and evading attempts at precursor controls [63]. This is highlighted by a report from the International Narcotics Control Board (INCB) who noted there are over 150 substances that, while having no significant or legitimate use, could allow those with the required expertise to illicitly synthesize thousands of potential fentanyl analogues [74].

An alternative approach, at least to countering supply, has been to remove the capability of illicit drug gangs to produce the pills. The availability of counterfeit pills that mimic legitimate products has been seen as a key strategy to hook potential users on drugs that they may never otherwise have considered. Restricting the supply of pill presses, dies and punches has garnered considerable interest, not least in the media, as a means of disarming traffickers and has led to numerous legislative measures aimed at rendering possession of such equipment illegal [20]. This has certainly been the route adopted by the US and Canada with import bans and sanctions but, while many other governments have noted their concern, this has seldom translated to firm action beyond briefings and committee musings.

The US Treasury Department imposed sanctions on a number of Chinese organisations in June 2023, for the alleged distribution of pill presses and associated equipment in Mexico and the U.S [75]. The prevalence of the pill press problem is highlighted through numerous domestic seizures across the US with data from the US Department of Homeland Security (DHS) highlighting the seizure of 3600 pill presses in 2023. In September 2023, U. S. Customs and Border Protection (CBP) under "Operation Artemis" seized 14 pill press die sets (from 5 shipments) at John F. Kennedy International Airport that arrived from China [76]. Examples of individual law enforcement successes include: two pill presses, 130,000 pills and 3 kg of fentanyl (New York, 6th April 2024); an electronic TDP 5 pill press with M−30 oxycodone dies and large quantity of counterfeit M−30 pills containing fentanyl (Louisville 31st January 2024) and two pill presses and over 80,000 fentanyl pills designed to mimic Xanax, oxycodone and MDMA (Mississippi 18th January 2024)[73]. Similar reports of pill seizures have been reported in the UK [77,78].

US Federal law requires any transactions relating to the sale or purchase of pill presses (or encapsulating machines) to be reported to the DEA. It is an offense, under the remit of the Controlled Substances Act (CSA) to possess, distribute, manufacture, import or export pill presses, encapsulating machines, chemicals or associate equipment with the knowledge, intent or even having a reasonable cause to believe that it could be used for the manufacture of a controlled substance [20]. The darknet has been accredited to the supply of precursors yet, the supply of pill press equipment has been in full, unrestricted view for many years and systems continue to be advertised on the internet and within common online retailers. However, eBay®, the premier internet auction platform, recently fell foul of the CSA and was fined $59 m where it was alleged that the site failed to comply with the CSA by allowing the sale of thousands of pill presses – many high capacity systems – along with counterfeit dies and punches [79]. It should be noted that it is still possible to purchase manual pill press systems from various online retailers.

9. Custom pill presses – Bypassing traditional supply Lines

Lassi (2023) has provided a detailed overview of US government approaches to pill presses and has recommended that pill press control should receive more legislative regulation and greater law enforcement attention in the U.S., China, and Mexico [20]. Such measures have already given rise to a considerable number of pill press seizures [73,76] and, it could be envisaged that they would help curb the import of commercial tableting machinery. However, the rise of domestic pill presses from non-registered sources could serve to undermine conventional restrictions and shipment surveillance. Previously, the production of pill presses, dies and punches would have been prohibitive from the perspective of the high degree of engineering expertise and metal machining / milling equipment infrastructure required. However, there has been a marked change in the nature and cost of manufacturing equipment in recent years where the need for fast prototyping has given rise to a new generation of bench top systems. This is perhaps best exemplified by the increasing the availability of lost cost, yet high specification computer numerical control (CNC) milling systems targeted at smaller enterprises and hobbyists [80]. Some of these are highlighted in Table 1.

It must be noted that CNC systems are a subtractive technique where the shape is milled from a solid block [80–82]. While this process can generate a lot of waste material as the molds, punches and gears are shaped [82], it is unlikely that this would be of much consequence to members of the illicit drug trade. The main drawback associated with the adoption of this approach is the expense associated with the starting

Table 1
Specifications of benchtop CNC milling machines.

CNC Milling Machine	Brand	Materials	Price
Twotrees TTC-450 CNC Router Machine	Twotrees	Aluminium	
		Brass Copper	£ 576
3030-PROVer MAX	Genmitsu	Aluminium	£899
		Brass Copper	
PROVerXL 4030 V2 Desktop CNC Router	Genmitsu	Aluminium	£1,064
		Brass Copper	
STEPCRAFT D.420	STEPCRAFT	Aluminium	€ 1,399
		Brass Copper	
CNC Router Machine Vasto	FoxAlien	Aluminium	$1,999
		Brass, Copper Low Carbon Steel	
Ghost Gunner 3-S	Ghost Gunner	Aluminium, Low Carbon Steel (1008, A36)	$2,500
		Stainless Steel (304, 17–4) Chromoly 4140 Brass,Copper	
Nomad 3 – Desktop CNC Mill	Carbide3D	Aluminium	$2,800
		Brass, Copper	
Bantam Tools Explorer™ CNC Milling Machine	Bantam Tools	6061 Aluminium	£3,047
		Brass, Copper	
Shapeoko 5 Pro	Carbide3D	Aluminium	$3,750
		Brass, Copper	
Pocket NC V2-10	Pocket NC	Aluminium	£7,500
		Low carbon Steel G5 titanium	

block and the expertise needed to programme the cutting tool. It must also be acknowledged that is not simply a case of acquiring a suitable digital design that can be fed to the CNC machine, successful translation to a high specification product (necessary for repeated mold/die operation) requires an engineering background with knowledge and experience of how the cutting tools interact with materials. The CNC machines can be defined by their axis number where, for a 3-axis system, the cutting tool can move in the x, y and z directions in order to mill. Such configurations are common to the lower cost instruments and could require considerable manipulation of the base material in order to create complex geometries [80,81]. A 5-axis system, however, can also rotate the material and, while this removes the need for manual repositioning and is more appropriate for rapid prototyping, its use comes with a higher cost and expertise overhead [81]. It could be argued that the creation of a simple single die mold/punch press via CNC machining is relatively straightforward but, the development of a multi-die or rotary system requiring gears with complex geometries would be much more demanding. This is a critical point, where there is a vast library of online resources available to the 3D printing community, CNC produced materials will invariably need to be designed from the bottom up.

In contrast to CNC machines, 3D printing has made considerable inroads to the domestic home. This can allow the latter to become the base of a highly versatile machine shop capable of yielding a spectrum of products without any requirement for the user to have a background in mechanical design or engineering. Designs can be readily downloaded from a large variety of internet sources, in most cases free of charge, and simply printed. While the capital outlay and steep learning curve associated with CNC milling machine could be seen as prohibitive for all but the largest gangs, small 3D printers can retail for very little (less than the cost of a smart phone) and hence are readily accessible. Moreover, their ubiquity as a hobby purchase is unlikely to register any alarms of nefarious intent. Current estimates suggest that manufacturers shipped 2.2 million 3D printers in 2021 – though it must be recognised that the number of users is liable to be smaller where individuals (or organisations) have more than one printer [83].

Third party models produced in computer aided design (CAD) software can often be rendered in 3D and translated to a stereolithography (STL) file which can be processed by the software used to control a 3D printer. It is perhaps little surprise that there are already many STL files pertaining to pill presses. Once the files are downloaded, the designs are transformed into a physical form through the printer and are assembled layer by layer. There are many different types of printers and a detailed description of the operation of each is beyond the remit of the present report. However, to summarise, they can be broken down into three broad categories – fused deposition modelling (FDM), stereolithography (SLA) and selective laser sintering (SLS) [84]. The first, FDM, heats a filament (typically a polymer though it can also be a metal) and extrudes it through a nozzle (sub mm diameter) which is moved in the horizontal x-y plane to trace the desired pattern. The baseplate (or nozzle) is then incremented in the vertical (z-axis) direction and the x-y processes repeated to build up the structure layer by layer. The SLA method involves immersing the baseplate in a bath of photopolymerisable resin which, when irradiated with light of a suitable wavelength (typically 405 nm) polymerises to leave a solid deposit. Instead of a movable nozzle, the pattern is determined by the position (pattern projection of an individual layer) of the light on the substrate/baseplate. As with FDM, the structure is built by incrementally raising the baseplate to allow layer by layer construction. While the SLA method operates on a liquid starting material, SLS systems use a higher energy laser to create parts from a finely powdered matrix. In this instance the laser energy is used to fuse the particles (polymer or metal) together with the resulting structures tending to be much stronger than their FDM or SLA equivalents.

Once an appropriate STL file has been obtained, the structure can usually be printed irrespective of the type of printer available. The association of 3D printing with crime is increasingly recognised and has received high profile exposure with the creation of printed guns [85]. The original report quickly spawned many replicas and there is a STL library of designs. The same is true of pill presses and some examples of the designs which are readily available on internet forums or STL repositories are highlighted in Fig. 3. In most cases, the design relates to a simple manual die-punch assembly (similar to the first design proposed by Brockedon (1843)) with the pill output determined more by the number of dies than the speed of the operation. The significance of such designs is not restricted to the hobbyist drug producer, and it must be noted that illicit pill production does not need the larger single station or rotary press systems to yield economically viable counterfeits. Fig. 4A details a manual – 9 pill die and punch assembly seized by US law enforcement in 2023 [76]. A similar 3D printable design obtained from a readily accessible STL repository, is compared in Fig. 4B. The key elements are the same and, while the stainless steel structure of the illicit press will undoubtedly last longer, it must be noted that replacing the 3D printed parts after signs of wear will come at a very small cost (few dollars) and will be achievable within a very short timeframe (minutes to a few hours depending on the printer). It is also important to emphasize the fact that, while the machined metal die is fixed in size, the dimensions of the 3D printed system can be rescaled and printed within minutes and thus can readily adapted to mimic different pill forms.

One of the core limitations in the pill press designs highlighted in Fig. 3 and Fig. 4 relates to the use of manual compression to form the pill. As noted previously, this will inevitably lead to variations in the applied force which could result in the production of soft/powdery tablets which will readily disintegrate on handling or storage [66,67,70]. In the case of the 3D printed polymer systems, it is also possible that the pressure, especially across the larger pill plates, will be uneven and the punch component could buckle reducing the quality of the final yield. In many respects, the designs highlighted in Fig. 3 are the first iteration and it is likely that the sophistication of the design will evolve. Evidence for this is already present where a much more robust pill press (Fig. 5) constructed from 3D printed parts is freely available online. The ready availability of such designs again contrasts the limited resources available to CNC systems. The assembly allows the production of 4 pills with fine control of the applied force and its distribution. At present, the system is still manually operated, however, it is worth noting that the first single station pill presses were also manual – but their automation followed swiftly and the same could easily be true of this design or its subsequent iterations.

The design obtained from the 4 pill STL file highlighted in Fig. 5 is a computer render with the material chosen to simulate metal. Printing the latter is more difficult than polymer systems and the printing equipment is more expensive as a result but, while such systems would once have been out of reach for all but large industries, advances in printer technology has seen the purchase costs of both metal FDM and SLS systems fall considerably. This is highlighted in Table 2 where entry level FDM printers capable of producing steel structures would clearly be a minor outlay when considering the vast sums that arise from the sale of the subsequent pill products. Metal 3D printed parts are regularly used to produce specialist components for the automotive and aerospace industries – providing mechanically robust parts designed to operate under demanding conditions. It could be anticipated that their application to the production of pill press systems would easily produce durable components that can also withstand the repeated punishment of the powder compression cycles. While the higher specification systems come at a cost, there is arguably little need for their enhanced resolution when it comes to a pill press and, therefore, systems at the lower cost scale could be more than sufficient for the purposes of producing equipment for illicit tablet manufacture.

While the design and production of the press via 3D printing could be viewed as relatively facile, could the durability of the structure through repeated compression cycles be a limitation? The answer to this lies in the design approach taken and the material employed. There is a significant contrast between CNC structures and those created via 3D

Fig. 3. Design available for 3D printed pill presses.

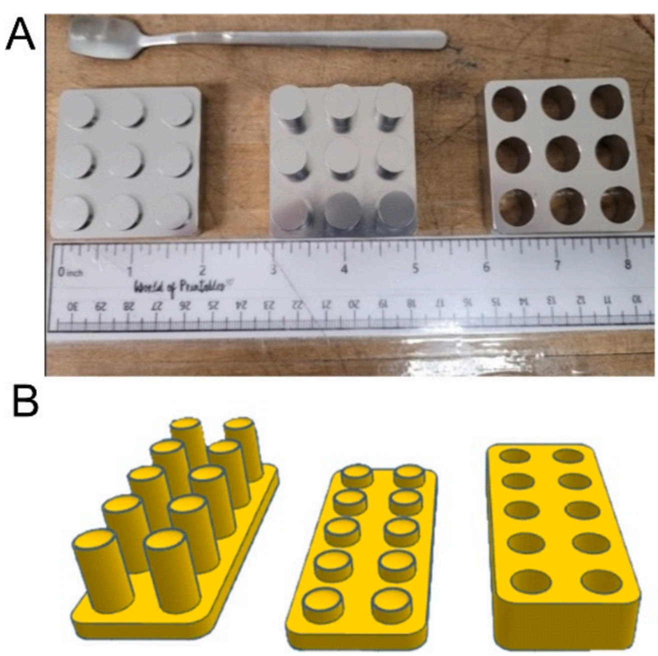

Fig. 4. (A) Manual pill press seized by US law enforcement in 2023 [76] and (B) A computer render of a readily available 3D printed manual pill press.

printing when considering the density of the model. In conventional model making, a 3D printer will typically print the "outside" of the shape with the mechanical integrity of latter supported by an internal frame ("Infill" or "hatch") rather than having solid blocks of polymer [86,87]. This provides a significant economic advantage over CNC methods [82] and can greatly lessen the time needed to print the structure but, it is easy to appreciate why a solid block milled from a CNC machine is liable to be stronger – especially where the powder is liable to be compressed under the action of the punch. The degree of infilling however can be adjusted to 100 % solid at the design stage through simple manipulation of the software and, in terms of a simple mold/die/punch configuration, can be comparable to that of a CNC product from similar material.

The surface of the final printed structure using FDM or SLS methods is typically rougher than that found with CNC milling [88,89] and it is inevitable that there will be frictional contact as the punch is inserted into the mold to compress the powder. While the consequences could be relatively small for small scale manual pressing, the impact of heat and wear would be greatly exacerbated under the high frequency reciprocating motion common to rotary systems (Fig. 2). There have been numerous studies on the wear characteristics of 3D printed materials (polymer [86–89], composites [90–93], alloy [94–96] and metals [93,97–99]) and their comparison with conventionally machined parts. As could be expected, the degree of wear is dependent on multiple factors (material and design and machine configuration) but, perhaps, a more immediate example of the wear resistance capability of composites is the increasing use of 3D printed materials in production of dental prothesis. The latter are regularly subject to compression and shear forces and it is notable that the the 3D printed systems have shown comparable or superior performance to the ceramics produced using conventional milling processes [100,101]. While metals may appear to be the material of choices it is important to note that there are many high-performance polymer/composite systems [86–93] that are readily accessible for domestic printing and, while wear is inevitable, their replacement could be relatively facile and simply a case of loading a file and printing the new component.

At present, those with an intent to produce pills are reliant on the use of relatively inferior/simple press designs similar to those highlighted in Fig. 3 and Fig. 4 which will restrict production considerably. It could be postulated that the acquisition of industrial rotary presses (small or large), despite the many advances in 3D printing technology, would be a much more reasonable option for organised crime. This is presently true as one critical factor is missing. The absence of the digital blueprint that allows the printing of a functioning rotary press is probably the main impediment to the efficient exploitation of 3D printing for illicit pill manufacture. However, it has already been noted that the four pill press specified in Fig. 5 represents a step change in design sophistication and, while it is not automatic, it is easy to speculate that this could be achieved in subsequent iterations. There is a possibility that a fully automated rotary system could arise not as a consequence of drug cartel influence but, rather from an enthusiastic hobbyist. A similar device design evolution has been seen with 3D printed weapons (knife or firearm). The danger is that once a rotary STL file has been created, preventing it is dissemination through a multitude of web repositories would be extremely difficult (*cf.* 3D printed guns). Once its practicality had been validated, this could markedly change the focus of the drug trade.

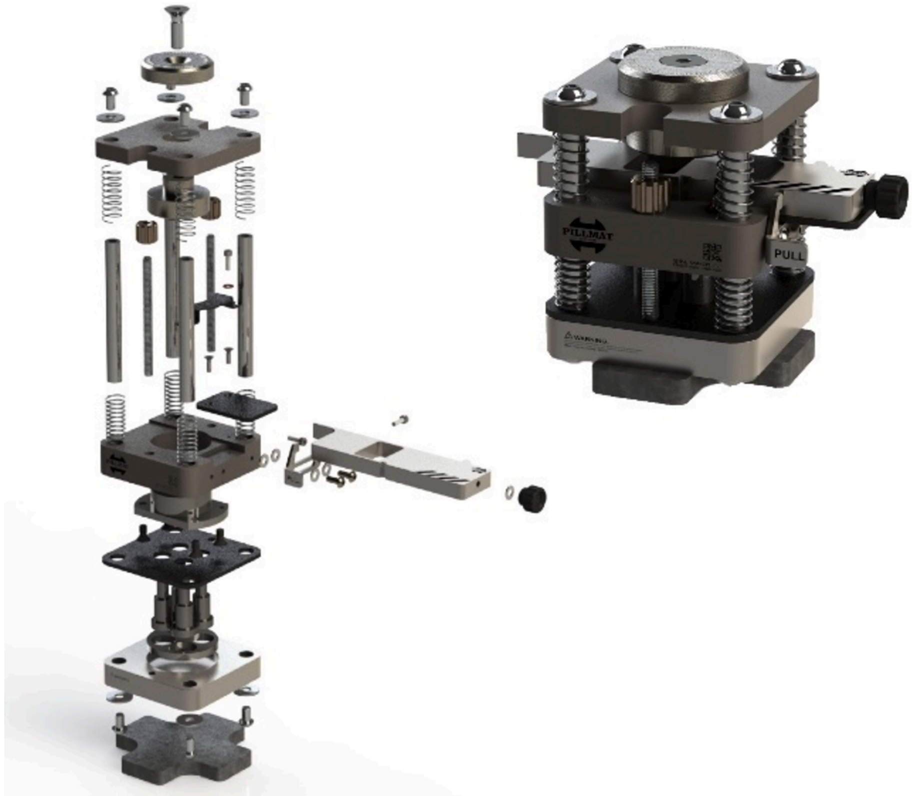

Fig. 5. Computer render a freely available 4-pill press STL file – before and after assembly of the component printed parts.

Table 2
Specifications of 3D printers capable of printing metal structures.

Metal 3D Printer	Brand	Technology	Printing Media	Materials	Price
Anycubic 4Max Metal	Anycubic	FDM	Filament	316L Stainless Steel	$899
Zortax M300 Dual with Full Metal Package	Zortax	FDM	Filament	316L Stainless Steel	£4,310
Ultimaker S5 with Metal Expansion Kit	Ultimaker	FDM	Filament	17–4 PH Stainless Steel	£7,884
BCN3D Epsilon W27 with Metal Pack	BCN3D	FDM	Filament	316L Stainless Steel	£7,540
Raise3D Forge1	Raise3D	FDM	Filament	17–4 PH Stainless Steel 316L Stainless Steel	£8,278
Markforged Metal X	Markforged	Bound Powder Filament	Bound Powder Filament	17–4 PH Stainless Steel 17–4 PH stainless steel	£108,000
One Click Metal Mprint+	One Click Metal	Laser Powder Bed Fusion	Powder	Copper H13 Tool Steel Inconel 625 A2 and D2 Tool Steel M300 Tool Steel	£110,000
HP Metal Jet S100	HP	Binder Jetting	Powder	316L Stainless Steel 17–4 PH Stainless Steel Ni-718 AlSi10MG TiAl6V4 316L Stainless Steel 17–4 PH Stainless Steel	$400,000

10. Conclusions

There has been great concern over the influx of counterfeit and designer drug pills with increased regulation of the drug precursors and pill making equipment having some successes. However, the illicit drug trade is counter responsive and clandestine laboratories are quick to adopt new chemicals and synthetic routes and methods of manufacture. The rise of 3D printing has been a boon to the hobbyist interested in design, however, it also offers a serendipitous opportunity for organised crime gangs to overcome current governmental bans on the supply and distribution of pill making equipment. While once only obtainable from industrial sources, a pill press can now be fabricated in the domestic home and there is an abundance of pill press designs available for download at no cost. At present, such designs are in their relative infancy but, it is clear that the field is evolving and could render a strategic law enforcement measure redundant. While the possession of a pill press (irrespective of origin) can still, in many countries, be considered illegal, preventing the domestic production of 3D printed of CNC milled systems is logistically impossible. Given the prevalence of hobbyist systems and an existing library of digital pill press designs, domestic production is clearly possible and probable. As these could be manufactured using off the shelf consumer filaments (i.e. PLA, ABS) it would be difficult to consider any means of enforcement. Fortunately, adoption is limited by the simplistic nature of the available design rendering their commercial (albeit illicit) production impracticable. The production of more sophisticated, high volume presses, however, will require a step change in expertise but, is still feasible and it is here that more cautionary measures could be implemented. While sales restrictions or registration regulations on 3D printers would be unworkable, especially where there can be legitimate second-hand sales, the metal printing system are much more niche as is the metal filament/powder. Key to the entire process however will be the availability and accessibility of the STL blueprint that can lead to the subsequent production of the press. While surveillance of the printer hardware or consumables may be unworkable, efforts to restrict or monitor the dissemination of the digital file (when it arises) may be more worthwhile.

CRediT authorship contribution statement

Victoria Gilpin: Methodology, Investigation, Writing – review & editing. **Robert B. Smith:** Conceptualization, Writing – review & editing. **Jason W. Birkett:** Conceptualization, Methodology, Writing – review & editing. **James Davis:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] E. Cheema, K. McGuinness, M.A. Hadi, V. Paudyal, M.H. Elnaem, A.A. Alhifany, M.E. Elrggal, A. Al Hamid, Causes, nature and toxicology of fentanyl-associated deaths: a systematic review of deaths reported in peer-reviewed literature, J. Pain Res. 13 (2020) 3281–3294, https://doi.org/10.2147/JPR.S280462.
[2] M. Cano, P. Timmons, M. Hooten, K. Sweeney, Drug supply measures and drug overdose mortality in the era of fentanyl and stimulants, Drug Alcohol Depend. Rep. 9 (2023) 100197, https://doi.org/10.1016/j.dadr.2023.100197.
[3] J. Patocka, W. Wu, P. Oleksak, R. Jelinkova, E. Nepovimova, L. Spicanova, P. Springerova, S. Alomar, M. Long, K. Kuca, Fentanyl and its derivatives: Pain-killers or man-killers? Heliyon 10 (2024) e28795 https://doi.org/10.1016/j.heliyon.2024.e28795.
[4] A. Weber, J. Trebach, M. Brenner, M. Thomas, N. Bormann, Managing opioid withdrawal symptoms during the fentanyl crisis: a review, Subst. Abuse Rehabil. 15 (2024) 59–71, https://doi.org/10.2147/SAR.S433358.
[5] T. Perdue, R. Carlson, R. Daniulaityte, S.M. Silverstein, R.N. Bluthenthal, A. Valdez, A. Cepeda, Characterizing prescription opioid, heroin, and fentanyl initiation trajectories: a qualitative study, Soc. Sci. Med. 340 (2024) 116441, https://doi.org/10.1016/j.socscimed.2023.116441.
[6] C. Florence, F. Luo, K. Rice, The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017, Drug Alcohol Depend. 218 (2021) 108350, https://doi.org/10.1016/j.drugalcdep.2020.108350.
[7] K. Humphreys, C.L. Shover, C.M. Andrews, A.S.B. Bohnert, M.L. Brandeau, J. P. Caulkins, J.H. Chen, M.-F. Cuéllar, Y.L. Hurd, D.N. Juurlink, H.K. Koh, E. E. Krebs, A. Lembke, S.C. Mackey, L. Larrimore Ouellette, B. Suffoletto, C. Timko, Responding to the opioid crisis in North America and beyond: recommendations of the Stanford-Lancet Commission, The Lancet 399 (2022) 555–604, https://doi.org/10.1016/S0140-6736(21)02252-2.
[8] M.R. Spencer, M.F. Garnett,, A.M. Minino, Drug Overdose Deaths in the United States, 2002–2022 NCHS Data Brief. No 491, (2024). https://stacks.cdc.gov/view/cdc/135849 (accessed December 6, 2024).
[9] K.L. Show, C. Ngamjarus, K. Kongwattanakul, S. Rattanakanokchai, C. Duangkum, M.A. Bohren, A.P. Betrán, M. Somjit, W.Y.H. Win, P. Lumbiganon, Fentanyl for labour pain management: a scoping review, BMC Pregnancy Childbirth 22 (2022) 846, https://doi.org/10.1186/s12884-022-05169-x.
[10] K. Sridharan, G. Sivaramakrishnan, Comparison of fentanyl, remifentanil, sufentanil and alfentanil in combination with propofol for general anesthesia: a systematic review and meta-analysis of randomized controlled trials, Curr. Clin. Pharmacol. 14 (2019) 116–124, https://doi.org/10.2174/1567201816666190313160438.
[11] Y. Aoki, H. Kato, N. Fujimura, Y. Suzuki, M. Sakuraya, M. Doi, Effects of fentanyl administration in mechanically ventilated patients in the intensive care unit: a systematic review and meta-analysis, BMC Anesthesiol. 22 (2022) 323, https://doi.org/10.1186/s12871-022-01871-7.
[12] R. Vallejo, Pharmacology of opioids in the treatment ofchronic pain syndromes, Pain Physician 4 (14) (2011) E343–E360, https://doi.org/10.36076/ppj.2011/14/E343.
[13] J.S. Ahn, J. Lin, S. Ogawa, Y. Chen, T. O'Brien, B. Le, A. Bothwell, H. Moon, Y. Hadjiat, A. Ganapathi, Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review, J. Pain Res. 10 (2017) 1963–1972, https://doi.org/10.2147/JPR.S140320.
[14] B. Bhagat, K. Bhate, N. Pandey, S.B. Bhagat, Transdermal fentanyl patch in long term postoperative pain management for oral submucous fibrosis: to be or not to be? Re: transdermal fentanyl patch versus standard analgesia in postoperative oral submucous fibrosis patients: a triple blinded, randomised control trial, Br. J. Oral Maxillofac. Surg. 61 (2023) 190, https://doi.org/10.1016/j.bjoms.2022.12.008.
[15] A.D. Kaye, B.L. Menard, K.P. Ehrhardt, S.A. Gennuso, E.C. Okereke, S. R. Tirumala, C.J. Fox, E.M. Cornett, Consensus perioperative management best practices for patients on transdermal fentanyl patches undergoing surgery, Curr. Pain Headache Rep. 23 (2019) 50, https://doi.org/10.1007/s11916-019-0780-2.
[16] N. Langford, Fentanyl patches: use and misuse, Acute Med (2020).
[17] E. Kelly, K. Sutcliffe, D. Cavallo, N. Ramos-Gonzalez, N. Alhosan, G. Henderson, The anomalous pharmacology of fentanyl, Br. J. Pharmacol. 180 (2023) 797–812, https://doi.org/10.1111/bph.15573.
[18] H. Gill, E. Kelly, G. Henderson, How the complex pharmacology of the fentanyls contributes to their lethality, Addiction 114 (2019) 1524–1525.
[19] M. Trivedi, S. Shaikh, C. Gwinnut, Pharmacology of opioids, Update Anaesth. (2007) 118–124.
[20] N. Lassi, Strengthening pill press control to combat fentanyl: Legislative and law enforcement imperatives, Explor. Res. Clin. Soc. Pharm. 11 (2023) 100321, https://doi.org/10.1016/j.rcsop.2023.100321.
[21] C. Wang, N. Lassi, From poppy to pill: a comprehensive strategy to combat illicit synthetic drug production in Southeast Asia, J. Int. Dev. 36 (2024) 710–727, https://doi.org/10.1002/jid.3835.
[22] C. Wang, N. Lassi, X. Zhang, V. Sharma, The evolving regulatory landscape for fentanyl: China, India, and global drug governance, Int. J. Environ. Res. Public. Health 19 (2022) 2074, https://doi.org/10.3390/ijerph19042074.
[23] K.A. Marquardt, R.S. Tharratt, N.A. Musallam, Fentanyl remaining in a transdermal system following three days of continuous use, Ann. Pharmacother. 29 (1995) 969–971, https://doi.org/10.1177/106002809502901O.
[24] S. Lucyk, L. Nelson, Consequences of unsafe prescribing of transdermal fentanyl, CMAJ 188 (2016) 638–639.
[25] R. Broadhurst, M. Ball, H. Trivedi, Fentanyl availability on darknet markets, Trends Issuesin Crime Crim. Justice (2020) 590.
[26] M. Ball, R. Broadhurst, H. Trivedi, How much fentanyl is available on the darknet?, (2019). https://aic.gov.au/publications/sb/sb18.
[27] S.G. Mars, D. Rosenblum, D. Ciccarone, Illicit fentanyls in the opioid street market: desired or imposed? Addiction 114 (2019) 774–780, https://doi.org/10.1111/add.14474.
[28] J.E. Zibbell, A. Alderidge, M. Grabenauer, D. Heller, S. Duhart Clarke, D. Pressley, H.S. McDonald, Associations between opioid overdose deaths and drugs confiscated by law enforcement and submitted to crime laboratories for analysis, United States, 2014–2019: an observational study, Lancet Reg. Health - Am. 25 (2023) 100569.
[29] O. Erinoso, R. Daugherty, M.R. Kirk, R.W. Harding, H. Etchart, A. Reyes, K. Page, P. Fiuty, K.D. Wagner, Safety strategies and harm reduction for methamphetamine users in the era of fentanyl contamination: a qualitative analysis, Int. J. Drug Policy 128 (2024) 104456, https://doi.org/10.1016/j.drugpo.2024.104456.
[30] V.W.L. Tsang, J.S.H. Wong, J.N. Westenberg, N.H. Ramadhan, H. Fadakar, M. Nikoo, V.W. Li, N. Mathew, P. Azar, K.L. Jang, R.M. Krausz, Systematic review on intentional non-medical fentanyl use among people who use drugs, Front. Psychiatry 15 (2024) 1347678, https://doi.org/10.3389/fpsyt.2024.1347678.
[31] A. Amlani, G. McKee, N. Khamis, G. Raghukumar, E. Tsang, J.A. Buxton, Why the FUSS (Fentanyl Urine Screen Study)? A cross-sectional survey to characterize an emerging threat to people who use drugs in British Columbia, Canada, Harm. Reduct. J. 12 (2015) 54, https://doi.org/10.1186/s12954-015-0088-4.
[32] D. Ciccarone, J. Ondocsin, S.G. Mars, Heroin uncertainties: exploring users' perceptions of fentanyl-adulterated and -substituted 'heroin', Int. J. Drug Policy 46 (2017) 146–155, https://doi.org/10.1016/j.drugpo.2017.06.004.
[33] N. Baldwin, R. Gray, A. Goel, E. Wood, J.A. Buxton, L.M. Rieb, Fentanyl and heroin contained in seized illicit drugs and overdose-related deaths in British Columbia, Canada: an observational analysis, Drug Alcohol Depend. 185 (2018) 322–327, https://doi.org/10.1016/j.drugalcdep.2017.12.032.
[34] S.N. Glick, K.S. Klein, J. Tinsley, M.R. Golden, Increasing heroin-methamphetamine (goofball) use and related morbidity among seattle area people who inject drugs, Am. J. Addict. 30 (2021) 183–191, https://doi.org/10.1111/ajad.13115.

[35] H.J. Elder, N.B. Varshneya, D.M. Walentiny, P.M. Beardsley, Amphetamines modulate fentanyl-depressed respiration in a bidirectional manner, Drug Alcohol Depend. 243 (2023) 109740, https://doi.org/10.1016/j.drugalcdep.2022.109740.
[36] K. Hayashi, M.-J. Milloy, M. Lysyshyn, K. DeBeck, E. Nosova, E. Wood, T. Kerr, Substance use patterns associated with recent exposure to fentanyl among people who inject drugs in Vancouver, Canada: a cross-sectional urine toxicology screening study, Drug Alcohol Depend. 183 (2018) 1–6, https://doi.org/10.1016/j.drugalcdep.2017.10.020.
[37] K.D. Wagner, Prevalence of fentanyl in methamphetamine and cocaine samples collected by community-based drug checking services, Drug Alcohol Depend (2023).
[38] J. O'Donnell, L.J. Tanz, R.M. Gladden, N.L. Davis, J. Bitting, Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyls — United States, 2019–2020, MMWR Morb Mortal Wkly Rep 70 (2021) 1740–1746.
[39] P.A. Janssen, Pirinitramide (R 3365), a potent analgesic with unusual chemical structure, J. Pharm. Pharmacol. 13 (1961) 513–530.
[40] P.A. Janssen, B.E. Nathan, Compounds related to pethidine-IV. New general chemical methods of increasing the analgesic activity of pethidine, J. Med. Pharm. Chem. 2 (1960) 31–45.
[41] UNODC, Global Smart Update 17. Fentanyl and its analogues - 50 years on., (2017). https://www.unodc.org/documents/scientific/Global_SMART_Update_17_web.pdf.
[42] P. Armenian, K.T. Vo, J. Barr-Walker, K.L. Lynch, Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review, Neuropharmacology 134 (2018) 121–132, https://doi.org/10.1016/j.neuropharm.2017.10.016.
[43] M.J. Lozier, M. Boyd, C. Stanley, L. Ogilvie, E. King, C. Martin, L. Lewis, Acetyl fentanyl, a novel fentanyl analog, causes 14 overdose deaths in Rhode Island, March–May 2013, J. Med. Toxicol. 11 (2015) 208–217, https://doi.org/10.1007/s13181-015-0477-9.
[44] S. Sofalvi, E.S. Lavins, I.T. Brooker, C.K. Kaspar, J. Kucmanic, C.D. Mazzola, C. L. Mitchell-Mata, C.L. Clyde, R.N. Rico, L.G. Apollonio, C. Goggin, B. Marshall, D. Moore, T.P. Gilson, Unique structural/stereo-isomer and isobar analysis of novel fentanyl analogues in postmortem and DUID whole blood by UHPLC–MS-MS, J. Anal. Toxicol. 43 (2019) 673–687, https://doi.org/10.1093/jat/bkz056.
[45] E. Kiely, M. Juhascik, Fentanyl, acetylfentanyl and carfentanil in impaired driving cases: a review of 270 cases, J. Anal. Toxicol. 45 (2021) 913–917, https://doi.org/10.1093/jat/bkab085.
[46] D. Salani, M. Mckay, M. Zdanowicz, The deadly trio: heroin, FentaNYL, and carfentanil, J. Emerg. Nurs. 46 (2020) 26–33, https://doi.org/10.1016/j.jen.2019.08.005.
[47] A. Adams, C. Maloy, B.J. Warrick, Does occupational exposure to fentanyl cause illness? A systematic review, Clin. Toxicol. 61 (2023) 631–638, https://doi.org/10.1080/15563650.2023.2259087.
[48] J.R. Riches, R.W. Read, R.M. Black, N.J. Cooper, C.M. Timperley, Analysis of clothing and urine from moscow theatre siege casualties reveals carfentanil and remifentanil use, J. Anal. Toxicol. 36 (2012) 647–656, https://doi.org/10.1093/jat/bks078.
[49] V. Felbab-Brown, Fentanyl and Geopolitics: Controlling Opioid Supply from China, (2020). https://www.brookings.edu/research/fentanyl-and-geopolitics-controlling-opioid-supply-from-china/ (accessed June 21, 2024).
[50] P.J. Jannetto, A. Helander, U. Garg, G.C. Janis, B. Goldberger, H. Ketha, The fentanyl epidemic and evolution of fentanyl analogs in the United States and the European Union, Clin. Chem. 65 (2019) 242–253, https://doi.org/10.1373/clinchem.2017.281626.
[51] DEA, DEA Intelligence Report: Fentanyl Flow to the United States. DEA-DCT-DIR-008-20, (2020). https://www.dea.gov/sites/default/files/2020-03/DEA_GOV_DIR-008-20%20Fentanyl%20Flow%20in%20the%20United%20States_0.pdf.
[52] DEA, Counterfeit Prescription Pills Containing Fentanyls: A Global Threat, (2016).
[53] C. Wang, N. Lassi, Combating illicit fentanyl: will increased Chinese regulation generate a public health crisis in India? Front. Public Health 10 (2022) 969395 https://doi.org/10.3389/fpubh.2022.969395.
[54] Statistica, China Leads the World in Posted Packages, (2022). https://www.statista.com/chart/25936/number-of-parcels-shipped-worldwide/.
[55] K.M. Tennyson, C.S. Ray, K.T. Maass, Fentanyl and Fentanyl Analogues: Federal Trends and Trafficking Patterns, U. S. Sentencing Comm. (2021). https://www.ussc.gov/research/research-reports/fentanyl-and-fentanyl-analogues-federal-trends-and-trafficking-patterns.
[56] NBC News, Mexico asks China for help on fentanyl and slams U.S. critics, (2023). https://www.nbcnews.com/news/world/mexico-asks-china-help-fentanyl-slams-us-critics-rcna78269.
[57] J.J. Palamar, D. Ciccarone, C. Rutherford, K.M. Keyes, T.H. Carr, L.B. Cottler, Trends in seizures of powders and pills containing illicit fentanyl in the United States, 2018 through 2021, Drug Alcohol Depend. 234 (2022) 109398, https://doi.org/10.1016/j.drugalcdep.2022.109398.
[58] R. Daniulaityte, K. Sweeney, S. Ki, B.N. Doebbeling, N. Mendoza, "They say it's fentanyl, but they honestly look like Perc 30s": initiation and use of counterfeit fentanyl pills, Harm. Reduct. J. 19 (2022) 52, https://doi.org/10.1186/s12954-022-00634-4.
[59] S. Arya, S. Nagappala, N. Krawczyk, Y. Gu, M.C. Meacham, A.M. Bunting, Fentanyl in pressed oxycodone pills: a qualitative analysis of online community experiences with an emerging drug trend, Subst. Use Misuse 57 (2022) 1940–1945, https://doi.org/10.1080/10826084.2022.2120365.
[60] J. Friedman, M. Godvin, C. Molina, R. Romero, A. Borquez, T. Avra, D. Goodman-Meza, S. Strathdee, P. Bourgois, C.L. Shover, Fentanyl, heroin, and methamphetamine-based counterfeit pills sold at tourist-oriented pharmacies in Mexico: an ethnographic and drug checking study, Drug Alcohol Depend. 249 (2023) 110819, https://doi.org/10.1016/j.drugalcdep.2023.110819.
[61] F.R. Lamy, R. Daniulaityte, S. Dudley, "Pressed OXY M30 Pills, great press, potent, fast shipping!!!": availability of counterfeit and pharmaceutical oxycodone pills on one major cryptomarket, J. Psychoactive Drugs 56 (2024) 1–7, https://doi.org/10.1080/02791072.2023.2176954.
[62] DEA, Drug Enforcement Administration Announces the Seizure of Over 379 million Deadly Doses of Fentanyl in 2022, (2022). https://www.dea.gov/press-releases/2022/12/20/drug-enforcement-administration-announces-seizure-over-379-million-deadly.
[63] UNODC, Global Smart Update 23. An expanding synthetic drugs market – Implications for precursor control Research 2020, (2020). https://www.unodc.org/documents/scientific/Global_SMART_23_web2.pdf.
[64] DEA, Fentanyl Profiling Program Report 2021, (2022). https://www.dea.gov/documents/2022/2022-08/2022-08-22/cy-2021-fentanyl-profiling-program-fpp.
[65] M. Sohail Arshad, S. Zafar, B. Yousef, Y. Alyassin, R. Ali, A. AlAsiri, M.-W. Chang, Z. Ahmad, A. Ali Elkordy, A. Faheem, K. Pitt, A review of emerging technologies enabling improved solid oral dosage form manufacturing and processing, Adv. Drug Deliv. Rev. 178 (2021) 113840, https://doi.org/10.1016/j.addr.2021.113840.
[66] S.S. Gaikwad, S.J. Kshirsagar, Review on tablet in tablet techniques, Beni-Suef Univ. J. Basic Appl. Sci. 9 (2020) 1, https://doi.org/10.1186/s43088-019-0027-7.
[67] V.D. Patel, D.B. Patel, J.C. Sturgis, K. Queensen, R. Sedlock, R.V. Haware, Assessing the impact of punch geometries on tablet capping using a newly proposed capping index, Pharm. Res. 40 (2023) 2935–2945, https://doi.org/10.1007/s11095-023-03555-4.
[68] A. Abaci, C. Gedeon, A. Kuna, M. Guvendiren, Additive manufacturing of oral tablets: technologies, Materials and Printed Tablets, Pharmaceutics 13 (2021) 156, https://doi.org/10.3390/pharmaceutics13020156.
[69] W. Brockedon, Shaping Pills, Lozenges and Black Lead by Pressure in Dies, (1843).
[70] A. Helmstaedter, Controlling the quality of tablets: from their invention to the dissolution test, Pharm. Hist. 50 (2020) 53–58.
[71] SaintyCo, Pill Press Machine: The Ultimate FAQ Guide, (2021). https://capsulefiller.com/pill-press-machine/.
[72] IPharmachine, Exploring the Working Principle of a Rotary Tablet Press, (2023). https://www.ipharmachine.com/rotary-tablet-press-working-principle.
[73] DEA, Recent DEA Seizures of Pill Presses, (2024). https://www.dea.gov/stories/2024/2024-04/2024-04-09/recent-dea-seizures-pill-presses.
[74] United Nations, Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances, (2023).
[75] US Department of the Treasury, Treasury Sanctions China- and Mexico-Based Enablers of Counterfeit, Fentanyl-Laced Pill Production, (2023). https://home.treasury.gov/news/press-releases/jy1507.
[76] US CBP, CBP's Operation Artemis at JFK Seize Pill Press Die Sets from China, (2023). https://www.cbp.gov/newsroom/local-media-release/cbp-s-operation-artemis-jfk-seize-pill-press-die-sets-china-0.
[77] Northumbria Police UK, Suspected drug dealers due in court after pill press scheme uncovered, (2024). https://www.northumbria.police.uk/news/northumbria/news/gateshead/suspected-dealers-due-in-court-after-pill-press-scheme-uncovered/#:~:text=Two%20men%20were%20arrested%20as,thousands%20more%20tablets%20were%20found.
[78] Cheshire Police UK, Encrochat drug dealer jailed for supplying thousands of pounds worth of class A and B drugs in Chester and Ellesmere Port, (2024). https://www.cheshire.police.uk/news/cheshire/news/articles/2024/5/encrochat-drug-dealer-jailed-for-supplying-thousands-of-pounds-worth-of-class-a-and-b-drugs-in-chester-and-ellesmere-port/#:~:text=Jay%20Roberts%2C%20of%20Nelson%20Road,and%20possession%20of%20criminal%20property.
[79] US Office of Public Affairs, eBay to Pay $59 Million to Settle Controlled Substances Act Allegations Related to Pill Presses Sold Through its Website, (2024). https://www.justice.gov/opa/pr/ebay-pay-59-million-settle-controlled-substances-act-allegations-related-pill-presses-sold.
[80] Z.A. Rahman, S.B. Mohamed, M. Minhat, Z.A. Rahman, Design and development of 3-axis benchtop CNC milling machine for educational purpose, Int. J. Integrated Eng. 15 (2023) 145–160.
[81] Protolabs Network, "What is CNC Machining", https://www.hubs.com/knowledge-base/what-is-cnc-milling/. Accessed 10/10/24.
[82] A. Mecheter, F. Tarlochan, M. Kucukvar, A review of conventional versus additive manufacturing for metals: life-cycle environmental and economic analysis, Sustainability 15 (2023) 12299.
[83] S. Joshi, 3D Printing Statistics: 69 Facts and Trends to Follow in 2023, (2023). https://learn.g2.com/3d-printing-statistics#:~:text=In%202021%2C%20close%20to%202.2,Desktop%20Metal%2C%20and%20Proto%20Labs.
[84] 3D Printing Industry, Beginner's Guide, (2024). https://3dprintingindustry.com/3d-printing-basics-free-beginners-guide.
[85] A. Daly, M. Mann, P. Squires, R. Walters, 3D printing, policing and crime, Polic. Soc. 31 (2021) 37–51, https://doi.org/10.1080/10439463.2020.1730835.
[86] M.K. Razaviye, R.A. Tafti, M. Khajehmohammadi, An investigation on mechanical properties of PA12 parts produced by a SLS 3D printer: an experimental approach, CIRP J. Manuf. Sci. Technol. 38 (2022) 760–768.

[87] A. Phogat, D. Chhabra, V. Sindhu, A. Ahlawat, Analysis of wear assessment of FDM printed specimens with PLA, multi-material and ABS via hybrid algorithms, Mater. Today Proc. 62 (2022) 37–43.
[88] S. Petzold, J. Klett, A. Schauer, T.A. Osswald, Surface roughness of polyamide 12 parts manufactured using selective laser Sintering, Polym. Test. 80 (2019) 106094.
[89] P. Zhang, Z. Hu, H. Xie, G.-H. Lee, C.-H. Lee, Friction and wear characteristics of polylactic acid (PLA) for 3D printing under reciprocating sliding condition, Ind. Lubr. Tribol. 72 (2020) 533–539.
[90] M.E. Imanian, F. r., Biglari Modeling and prediction of surface roughness and dimensional accuracy in SLS 3D printing of PVA/CB composite using the central composite design, J. Manuf. Process. 75 (2022) 154–169.
[91] M. Subramaniyan, S. Karuppan, K. Radhakrishnan, R.R. Kumar, K.S. Kumar, Investigation of wear properties of 3D-printed PLA components using sandwich structure – a review, Mater. Today Proc. 66 (2022) 1112–1119.
[92] L.A. Chavez, P. Ibave, M.S. Hassan, S.E. Hall-Sanchez, K.M.M. Billah, A. Leyva, C. Marquez, D. Espalin, S. Torres, T. Robison, Y. Lin, Low-temperature selective laser sintering 3D printing of PEEK-Nylon blends: Impact of thermal post-processing on mechanical properties and thermal stability, J Appl Polym Sci. 139 (2022) e52290.
[93] R. Kumar, M. Antonov, U. Beste, D. Goljandin, Assessment of 3D printed steels and composites intended for wear applications in abrasive, dry or slurry erosive conditions, Int. J. Refract Metal Hard Mater. 86 (2020) 105126.
[94] M. Marquer, P. Laheurte, L. Faure, S. Philippon, Influence of 3D-printing on the behaviour of Ti6Al4V in high-speed friction, Tribol. Int. 152 (2020) 106557.
[95] Peter Renner, Swarn Jha, Yan Chen, Ajinkya Raut, Siddhi G. Mehta, Hong Liang, A review on corrosion and wear of additively manufactured alloys, J. Tribol. 143 (2021) 050802.
[96] I. Karagiannidis, D. Tzanis A. Drees, L. Lopes, G. Chondrakis, M.M. Dardavila, E. Georgiou, A. Koutsomichalis, Friction and wear behavior of 3D-printed inconel 718 alloy under dry sliding conditions, Coatings 14 (2024) 1029.
[97] F.R. Andreacola, I. Capasso, A. Langella, G. Brando, 3D-printed metals: process parameters effects on mechanical properties of 17–4 P H stainless steel, Heliyon. 9 (2023) e17698.
[98] H. Jayawardane, I.J. Davies, J.R. Gamage, M. John, W.K. Biswas, Investigating the 'techno-eco-efficiency' performance of pump impellers: metal 3D printing vs, CNC Machining, the International Journal of Advanced Manufacturing Technology 121 (2022) 6811–6836.
[99] Z. Wei, S. Attarilar, M. Ebrahimi, J. Li, Corrosion and wear behavior of additively manufactured metallic parts in biomedical applications, Metals 14 (2024) 96.
[100] E. Prause, J. Hey, F. Beuer, F. Schmidt, Wear resistance of 3D-printed materials: a systematic review, Dentistry Review 2 (2022) 100051.
[101] M.A. Alghauli, A.Y. Alqutaibi, D-printed intracoronal restorations, occlusal and laminate veneers: clinical relevance, properties, and behavior compared to milled restorations; a systematic review and meta-analysis, J Esthet Restor Dent. 36 (2024) 1153–1170.